Regulation of proteasome assembly and activity in health and disease

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Regulation of proteasome assembly and activity in health and disease

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Abstract

The proteasome degrades most cellular proteins in a controlled and tightly regulated manner and thereby controls many processes including cell cycle, transcription, signalling, trafficking and protein quality control. Proteasomal degradation is vital in all cells and organisms and dysfunction or failure of proteasomal degradation is associated with diverse human diseases, including cancer and neurodegeneration. Target selection is an important and well-established way to control protein degradation. In addition, mounting evidence indicates that cells adjust proteasome-mediated degradation to their needs by regulating proteasome abundance through the coordinated expression of proteasome subunits and assembly chaperones. Central to the regulation of proteasome assembly is TORC1, which is the master regulator of cell growth and stress. This Review discusses how proteasome assembly and the regulation of proteasomal degradation are integrated with cellular physiology, including the interplay between the proteasome and autophagy pathways. Understanding these mechanisms has potential implications for disease therapy, as the misregulation of proteasome function contributes to human diseases such as cancer and neurodegeneration.

[~7,060 words]

[H1] Introduction

Thousands of proteins are required to execute the diverse cellular functions essential to maintain cell and organismal viability. Proteins are in a dynamic equilibrium defined by the balance between protein synthesis and protein degradation[1]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a11khcpa047","properties":{"formattedCitation":"{\\rtf \\super 1\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":96,"uris":["http://zotero.org/users/4604651/items/UWDPHHHM"],"uri":["http://zotero.org/users/4604651/items/UWDPHHHM"],"itemData":{"id":96,"type":"book","title":"The dynamic state of body constituents","collection-title":"Harvard university monographs in medicine and public health.no. 3","publisher":"Harvard university press","publisher-place":"Cambridge, Mass.","number-of-pages":"x p., 3 L., [3]-78 p., 2 L.","source":"Hathi Trust","event-place":"Cambridge, Mass.","URL":"https//catalog.hathitrust.org/Record/001554011","author":[{"family":"Schoenheimer","given":"Rudolf"},{"family":"Clarke","given":"Hans Thacher"}],"issued":{"date-parts":[["1942"]]},"accessed":{"date-parts":[["2017",8,14]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a7turi04r3","properties":{"formattedCitation":"{\\rtf \\super 1\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":96,"uris":["http://zotero.org/users/4604651/items/UWDPHHHM"],"uri":["http://zotero.org/users/4604651/items/UWDPHHHM"],"itemData":{"id":96,"type":"book","title":"The dynamic state of body constituents","collection-title":"Harvard university monographs in medicine and public health.no. 3","publisher":"Harvard university

press","publisher-place":"Cambridge, Mass.","number-of-pages":"x p., 3 L., [3]-78 p., 2 L.","source":"Hathi Trust","event-place":"Cambridge, Mass.","URL":"https//catalog.hathitrust.org/Record/001554011","author":[{"family":"Schoenheimer","given":"Rudolf"},{"family":"Clarke","given":"Hans Thacher"}],"issued":{"date-parts":[["1942"]]},"accessed":{"date-parts":[["2017",8,14]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Cellular protein levels depend on protein synthesis, folding and degradation, and failure to accurately regulate and coordinate these processes leads to disease. During cell and organismal growth, protein synthesis exceeds degradation, whereas during unfavourable conditions such as lack of nutrients, degradation may exceed synthesis. Under normal conditions, dietary amino acids constitute only about 20% of the amino acid supply to build the proteins that an adult human synthetizes daily to maintain an essentially constant body weight[2]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1c1ehrmsg0","properties":{"formattedCitation":"{\\rtf \\super 2\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":95,"uris":["http://zotero.org/users/4604651/items/G78KJM8T"],"uri":["http://zotero.org/users/4604651/items/G78KJM8T"],"itemData":{"id":95,"type":"article-journal","title":"Total human body protein synthesis in relation to protein requirements at various ages","container-title":"Nature","page":"192-194","volume":"253","issue":"5488","source":"PubMed","ISSN":"0028-0836","note":"PMID: 1110767","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Young","given":"V. R."},{"family":"Steffee","given":"W. P."},{"family":"Pencharz","given":"P. B."},{"family":"Winterer","given":"J. C."},{"family":"Scrimshaw","given":"N. S."}],"issued":{"date-parts":[["1975",1,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2ln1uqiuep","properties":{"formattedCitation":"{\\rtf \\super 2\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":95,"uris":["http://zotero.org/users/4604651/items/G78KJM8T"],"uri":["http://zotero.org/users/4604651/items/G78KJM8T"],"itemData":{"id":95,"type":"article-journal","title":"Total human body protein synthesis in relation to protein requirements at various ages","container-title":"Nature","page":"192-194","volume":"253","issue":"5488","source":"PubMed","ISSN":"0028-0836","note":"PMID: 1110767","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Young","given":"V. R."},{"family":"Steffee","given":"W. P."},{"family":"Pencharz","given":"P. B."},{"family":"Winterer","given":"J. C."},{"family":"Scrimshaw","given":"N. S."}],"issued":{"date-parts":[["1975",1,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The remaining ~80% of amino acids comes from the recycling of amino acids following protein degradation.

In cells, protein degradation is achieved by two systems: the ubiquitin-proteasome system (UPS) (Fig. 1) and the autophagy-lysosome system. Autophagy is a self-eating process by which cells degrade often large cellular components, such as organelles or protein aggregates, by engulfing them in a double-membrane compartment, the autophagosome, which fuses with lysosomes[3]{ ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"a110573ubhr","properties":{"formattedCitation":"{\\rtf \\super 3\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":94,"uris":["http://zotero.org/users/4604651/items/HXYKJCFI"],"uri":["http://zotero.org/users/4604651/items/HXYKJCFI"],"itemData":{"id":94,"type":"article-journal","title":"Dynamics and diversity in autophagy mechanisms: lessons from yeast","container-title":"Nature Reviews. Molecular Cell Biology","page":"458-467","volume":"10","issue":"7","source":"PubMed","abstract":"Autophagy is a fundamental function of eukaryotic cells and is well conserved from yeast to humans. The most remarkable feature of autophagy is the synthesis of double membrane-bound compartments that sequester materials to be degraded in lytic compartments, a process that seems to be mechanistically distinct from conventional membrane traffic. The discovery of autophagy in yeast and the genetic tractability of this organism have allowed us to identify genes that are responsible for this process, which has led to the explosive growth of this research field seen today. Analyses of autophagy-related (Atg) proteins have unveiled dynamic and diverse aspects of mechanisms that underlie membrane formation during autophagy.","DOI":"10.1038/nrm2708","ISSN":"1471-0080","note":"PMID: 19491929","shortTitle":"Dynamics and diversity in autophagy mechanisms","journalAbbreviation":"Nat. Rev. Mol. Cell Biol.","language":"eng","author":[{"family":"Nakatogawa","given":"Hitoshi"},{"family":"Suzuki","given":"Kuninori"},{"family":"Kamada","given":"Yoshiaki"},{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-parts":[["2009",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . This is the major form of autophagy, also known as macroautophagy to which we refer in this Review. Other forms of autophagy, such as microautophagy **[G]** and chaperone-mediated autophagy **[G]** won't be discussed. The cellular levels of autophagy vary considerably depending on the conditions: this was discovered in yeast and also applies in mammals with autophagy being induced by nutrient starvation[3]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"apm9j17tnv","properties":{"formattedCitation":"{\\rtf \\super 3\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":94,"uris":["http://zotero.org/users/4604651/items/HXYKJCFI"],"uri":["http://zotero.org/users/4604651/items/HXYKJCFI"],"itemData":{"id":94,"type":"article-journal","title":"Dynamics and diversity in autophagy mechanisms: lessons from yeast","container-title":"Nature Reviews. Molecular Cell Biology","page":"458-467","volume":"10","issue":"7","source":"PubMed","abstract":"Autophagy is a fundamental function of eukaryotic cells and is well conserved from yeast to humans. The most remarkable feature of autophagy is the synthesis of double membrane-bound compartments that sequester materials to be degraded in lytic compartments, a process that seems to be mechanistically distinct from conventional membrane traffic. The discovery of autophagy in yeast and the genetic tractability of this organism have allowed us to identify genes that are responsible for this process, which has led to the explosive growth of this research field seen today. Analyses of autophagy-related (Atg) proteins have unveiled dynamic and diverse aspects of mechanisms that underlie membrane formation during autophagy.","DOI":"10.1038/nrm2708","ISSN":"1471-0080","note":"PMID: 19491929","shortTitle":"Dynamics and diversity in autophagy mechanisms","journalAbbreviation":"Nat. Rev. Mol. Cell Biol.","language":"eng","author":[{"family":"Nakatogawa","given":"Hitoshi"},{"family":"Suzuki","given":"Kuninori"},{"family":"Kamada","given":"Yoshiaki"},{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-

parts":[["2009",7]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2705ir12iu","properties":{"formattedCitation":"{\\rtf \\super 3\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":94,"uris":["http://zotero.org/users/4604651/items/HXYKJCFI"],"uri":["http://zotero.org/users/4604651/items/HXYKJCFI"],"itemData":{"id":94,"type":"article-journal","title":"Dynamics and diversity in autophagy mechanisms: lessons from yeast","container-title":"Nature Reviews. Molecular Cell Biology","page":"458-467","volume":"10","issue":"7","source":"PubMed","abstract":"Autophagy is a fundamental function of eukaryotic cells and is well conserved from yeast to humans. The most remarkable feature of autophagy is the synthesis of double membrane-bound compartments that sequester materials to be degraded in lytic compartments, a process that seems to be mechanistically distinct from conventional membrane traffic. The discovery of autophagy in yeast and the genetic tractability of this organism have allowed us to identify genes that are responsible for this process, which has led to the explosive growth of this research field seen today. Analyses of autophagy-related (Atg) proteins have unveiled dynamic and diverse aspects of mechanisms that underlie membrane formation during autophagy.","DOI":"10.1038/nrm2708","ISSN":"1471-0080","note":"PMID: 19491929","shortTitle":"Dynamics and diversity in autophagy mechanisms","journalAbbreviation":"Nat. Rev. Mol. Cell Biol.","language":"eng","author":[{"family":"Nakatogawa","given":"Hitoshi"},{"family":"Suzuki","given":"Kuninori"},{"family":"Kamada","given":"Yoshiaki"},{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-parts":[["2009",7]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Autophagy increases in response to starvation in order to recycle intracellular components into nutrients, particularly amino acids, to sustain protein synthesis and thereby enables cells to survive this challenge[5]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a6vpdub9l6","properties":{"formattedCitation":"{\\rtf \\super 5\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":93,"uris":["http://zotero.org/users/4604651/items/7DQWEMYV"],"uri":["http://zotero.org/users/4604651/items/7DQWEMYV"],"itemData":{"id":93,"type":"article-journal","title":"Autophagy is required for maintenance of amino acid levels and protein synthesis under nitrogen starvation","container-title":"The Journal of Biological Chemistry","page":"31582-31586","volume":"280","issue":"36","source":"PubMed","abstract":"Autophagy is a transport system of cytoplasmic components to the lysosome/vacuole for degradation well conserved in eukaryotes. Autophagy is strongly induced by nutrient starvation. Several specific proteins, including amino acid synthesis enzymes and vacuolar enzymes, are increased during nitrogen starvation in wild-type cells but not in autophagy-defective delta atg7 cells despite similar mRNA levels. We further examined deficiencies in these cells. Bulk protein synthesis was substantially reduced in delta atg7 cells under nitrogen starvation compared with wild-type cells. The total intracellular amino acid pool was reduced in delta atg7 cells, and the levels of several amino acids fell below critical values. In contrast, wild-type cells maintained amino acid levels compatible with life. Autophagy-defective cells fail to maintain physiologic amino acid levels, and their inability to synthesize new proteins may explain most phenotypes associated with autophagy mutants at least partly.","DOI":"10.1074/jbc.M506736200","ISSN":"0021-9258","note":"PMID: 16027116","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Onodera","given":"Jun"},{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-parts":[["2005",9,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

When nutrients are abundant, cells can survive without autophagy, and mutations or deletions in autophagy genes, which encode components of the autophagy machinery and its regulation, do not compromise cell viability[6]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a21kikaf0gq","properties":{"formattedCitation":"{\\rtf \\super 6\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":367,"uris":["http://zotero.org/users/4604651/items/8AERMCI5"],"uri":["http://zotero.org/users/4604651/items/8AERMCI5"],"itemData":{"id":367,"type":"article-journal","title":"Historical landmarks of autophagy research","container-title":"Cell Research","page":"9-23","volume":"24","issue":"1","source":"PubMed","abstract":"The year of 2013 marked the 50th anniversary of C de Duve's coining of the term \"autophagy\" for the degradation process of cytoplasmic constituents in the lysosome/vacuole. This year we regretfully lost this great scientist, who contributed much during the early years of research to the field of autophagy. Soon after the discovery of lysosomes by de Duve, electron microscopy revealed autophagy as a means of delivering intracellular components to the lysosome. For a long time after the discovery of autophagy, studies failed to yield any significant advances at a molecular level in our understanding of this fundamental pathway of degradation. The first breakthrough was made in the early 1990s, as autophagy was discovered in yeast subjected to starvation by microscopic observation. Next, a genetic effort to address the poorly understood problem of autophagy led to the discovery of many autophagy-defective mutants. Subsequent identification of autophagy-related genes in yeast revealed unique sets of molecules involved in membrane dynamics during autophagy. ATG homologs were subsequently found in various organisms, indicating that the fundamental mechanism of autophagy is well conserved among eukaryotes. These findings brought revolutionary changes to research in this field. For instance, the last 10 years have seen remarkable progress in our understanding of autophagy, not only in terms of the molecular mechanisms of autophagy, but also with regard to its broad physiological roles and relevance to health and disease. Now our knowledge of autophagy is dramatically expanding day by day. Here, the historical landmarks underpinning the explosion of autophagy research are described with a particular focus on the contribution of yeast as a model organism.","DOI":"10.1038/cr.2013.169","ISSN":"1748-7838","note":"PMID: 24366340\nPMCID: PMC3879711","journalAbbreviation":"Cell Res.","language":"eng","author":[{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-parts":[["2014",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a22a6rmgiuf","properties":{"formattedCitation":"{\\rtf \\super 5\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":93,"uris":["http://zotero.org/users/4604651/items/7DQWEMYV"],"uri":["http://zotero.org/users/4604651/items/7DQWEMYV"],"itemData":{"id":93,"type":"article-journal","title":"Autophagy is required for maintenance of amino acid levels and protein synthesis under nitrogen starvation","container-title":"The Journal of Biological Chemistry","page":"31582-31586","volume":"280","issue":"36","source":"PubMed","abstract":"Autophagy is a transport system of cytoplasmic components to the lysosome/vacuole for degradation well conserved in eukaryotes. Autophagy is strongly induced by nutrient starvation. Several specific proteins, including amino acid synthesis enzymes and vacuolar enzymes, are increased during nitrogen starvation in wild-type cells but not in autophagy-defective delta atg7 cells despite similar mRNA levels. We further examined deficiencies in these cells. Bulk protein synthesis was substantially reduced in delta atg7 cells under nitrogen starvation compared with wild-type cells. The total intracellular amino acid pool was reduced in delta atg7 cells, and the levels of several amino acids fell below critical values. In contrast, wild-type cells maintained amino acid levels compatible with life. Autophagy-defective cells fail to maintain physiologic amino acid levels, and their inability to synthesize new

proteins may explain most phenotypes associated with autophagy mutants at least partly.","DOI":"10.1074/jbc.M506736200","ISSN":"0021-9258","note":"PMID: 16027116","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Onodera","given":"Jun"},{"family":"Ohsumi","given":"Yoshinori"}],"issued":{"date-parts":[["2005",9,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . In contrast to autophagy genes, the vast majority of genes encoding proteasome subunits are essential[7]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2p4eua0383","properties":{"formattedCitation":"{\\rtf \\super 7\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , because the turnover of proteins mediated by the UPS is high even when nutrients are abundant. The UPS is thought to degrade thousands of short-lived and regulatory proteins, as well as damaged and misfolded proteins, to regulate various cellular functions including cell cycle, cell survival, apoptosis, cell metabolism and

protein quality control[8–11]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2dkqoujg0k","properties":{"formattedCitation":"{\\rtf \\super 8\\uc0\\u8211{}11\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":92,"uris":["http://zotero.org/users/4604651/items/WF25YE7S"],"uri":["http://zotero.org/users/4604651/items/WF25YE7S"],"itemData":{"id":92,"type":"article-journal","title":"Regulated protein degradation","container-title":"Trends in Biochemical Sciences","page":"283-286","volume":"30","issue":"6","source":"PubMed","DOI":"10.1016/j.tibs.2005.04.005","ISSN":"0968-0004","note":"PMID: 15950869","journalAbbreviation":"Trends Biochem. Sci.","language":"eng","author":[{"family":"Varshavsky","given":"Alexander"}],"issued":{"date-parts":[["2005",6]]}}},{"id":91,"uris":["http://zotero.org/users/4604651/items/8FRDSMVU"],"uri":["http://zotero.org/users/4604651/items/8FRDSMVU"],"itemData":{"id":91,"type":"article-journal","title":"Intracellular protein degradation: From a vague idea thru the lysosome and the ubiquitin–proteasome system and onto human diseases and drug targeting","container-title":"Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics","collection-title":"Proteolysis 50 years after the discovery of lysosome","page":"3-13","volume":"1824","issue":"1","source":"ScienceDirect","abstract":"Between the 1950s and 1980s, scientists were focusing mostly on how the genetic code was transcribed to RNA and translated to proteins, but how proteins were degraded had remained a neglected research area. With the discovery of the lysosome by Christian de Duve it was assumed that cellular proteins are degraded within this organelle. Yet, several independent lines of experimental evidence strongly suggested that intracellular proteolysis was largely non-lysosomal, but the mechanisms involved have remained obscure. The discovery of the ubiquitin–proteasome system resolved the enigma. We now recognize that degradation of intracellular proteins is involved in regulation of a broad array of cellular processes, such as cell cycle and division, regulation of transcription factors, and assurance of the cellular quality control. Not surprisingly, aberrations in the system have been implicated in the pathogenesis of human disease, such as malignancies and neurodegenerative disorders, which led subsequently to an increasing effort to develop mechanism-based drugs. This article is part of a Special Issue entitled: Proteolysis 50 years after the discovery of lysosome.","DOI":"10.1016/j.bbapap.2011.03.007","ISSN":"1570-9639","shortTitle":"Intracellular protein degradation","journalAbbreviation":"Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics","author":[{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2012",1]]}}},{"id":90,"uris":["http://zotero.org/users/4604651/items/LR4M88KA"],"uri":["http://zotero.org/users/4604651/items/LR4M88KA"],"itemData":{"id":90,"type":"article-journal","title":"The proteasome: Overview of structure and functions","container-title":"Proceedings of the Japan Academy. Series B, Physical and Biological Sciences","page":"12-36","volume":"85","issue":"1","source":"PubMed Central","abstract":"The proteasome is a highly sophisticated protease complex designed to carry out selective, efficient and processive hydrolysis of client proteins. It is known to collaborate with ubiquitin, which polymerizes to form a marker for regulated proteolysis in eukaryotic cells. The highly organized proteasome plays a prominent role in the control of a diverse array of basic cellular activities by rapidly and unidirectionally catalyzing biological reactions. Studies of the proteasome during the past quarter of a century have provided profound insights into its structure and functions, which has appreciably contributed to our understanding of cellular life. Many questions, however, remain to be elucidated.","DOI":"10.2183/pjab.85.12","ISSN":"0386-2208","note":"PMID: 19145068\nPMCID: PMC3524306","shortTitle":"The proteasome","journalAbbreviation":"Proc Jpn Acad Ser B Phys Biol

Sci","author":[{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",1]]}},{"id":89,"uris":["http://zotero.org/users/4604651/items/2E9IKRM9"],"uri":["http://zotero.org/users/4604651/items/2E9IKRM9"],"itemData":{"id":89,"type":"article-journal","title":"The ubiquitin system","container-title":"Annual Review of Biochemistry","page":"425-479","volume":"67","source":"PubMed","abstract":"The selective degradation of many short-lived proteins in eukaryotic cells is carried out by the ubiquitin system. In this pathway, proteins are targeted for degradation by covalent ligation to ubiquitin, a highly conserved small protein. Ubiquitin-mediated degradation of regulatory proteins plays important roles in the control of numerous processes, including cell-cycle progression, signal transduction, transcriptional regulation, receptor down-regulation, and endocytosis. The ubiquitin system has been implicated in the immune response, development, and programmed cell death. Abnormalities in ubiquitin-mediated processes have been shown to cause pathological conditions, including malignant transformation. In this review we discuss recent information on functions and mechanisms of the ubiquitin system. Since the selectivity of protein degradation is determined mainly at the stage of ligation to ubiquitin, special attention is focused on what we know, and would like to know, about the mode of action of ubiquitin-protein ligation systems and about signals in proteins recognized by these systems.","DOI":"10.1146/annurev.biochem.67.1.425","ISSN":"0066-4154","note":"PMID: 9759494","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Hershko","given":"A."},{"family":"Ciechanover","given":"A."}],"issued":{"date-parts":[["1998"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The proteasome is also essential for amino acid homeostasis[12]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ah5h0a9n5","properties":{"formattedCitation":"{\\rtf \\super 12\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":97,"uris":["http://zotero.org/users/4604651/items/8GWU56TD"],"uri":["http://zotero.org/users/4604651/items/8GWU56TD"],"itemData":{"id":97,"type":"article-journal","title":"Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition","container-title":"Molecular Cell","page":"242-253","volume":"48","issue":"2","source":"ScienceDirect","abstract":"The ubiquitin-proteasome system targets many cellular proteins for degradation and thereby controls most cellular processes. Although it is well established that proteasome inhibition is lethal, the underlying mechanism is unknown. Here, we show that proteasome inhibition results in a lethal amino acid shortage. In yeast, mammalian cells, and flies, the deleterious consequences of proteasome inhibition are rescued by amino acid supplementation. In all three systems, this rescuing effect occurs without noticeable changes in the levels of proteasome substrates. In mammalian cells, the amino acid scarcity resulting from proteasome inhibition is the signal that causes induction of both the integrated stress response and autophagy, in an unsuccessful attempt to replenish the pool of intracellular amino acids. These results reveal that cells can tolerate protein waste, but not the amino acid scarcity resulting from proteasome inhibition.","DOI":"10.1016/j.molcel.2012.08.003","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Suraweera","given":"Amila"},{"family":"Münch","given":"Christian"},{"family":"Hanssum","given":"Ariane"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2012",10,26]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. In order to achieve these crucial functions, the activity of the UPS must be tightly regulated.

Two types of signal target proteins for degradation by the proteasome: ubiquitylation, usually in the form of Lysine 48-linked polyubiquitin chains[7,13–15]{ ADDIN ZOTERO_ITEM

CSL_CITATION {"citationID":"ai2cu0sfa","properties":{"formattedCitation":"{\\rtf \\super 7,13\\uc0\\u8211{}15\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}},{"id":88,"uris":["http://zotero.org/users/4604651/items/UJAUYTXE"],"uri":["http://zotero.org/users/4604651/items/UJAUYTXE"],"itemData":{"id":88,"type":"article-journal","title":"The ubiquitin code","container-title":"Annual Review of Biochemistry","page":"203-229","volume":"81","source":"PubMed","abstract":"The posttranslational modification with ubiquitin, a process referred to as ubiquitylation, controls almost every process in cells. Ubiquitin can be attached to substrate proteins as a single moiety or in the form of polymeric chains in which successive ubiquitin molecules are connected through specific isopeptide bonds. Reminiscent of a code, the various ubiquitin modifications adopt distinct conformations and lead to different outcomes in cells. Here, we discuss the structure, assembly, and function of this ubiquitin code.","DOI":"10.1146/annurev-biochem-060310-170328","ISSN":"1545-4509","note":"PMID: 22524316","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Komander","given":"David"},{"family":"Rape","given":"Michael"}],"issued":{"date-parts":[["2012"]]}}},{"id":12,"uris":["http://zotero.org/users/4604651/items/4V75P44H"],"uri":["http://zotero.org/users/4604651/items/4V75P44H"],"itemData":{"id":12,"type":"article-journal","title":"Recognition of Client Proteins by the Proteasome","container-title":"Annual Review of Biophysics","page":"149-173","volume":"46","source":"PubMed","abstract":"The ubiquitin proteasome system controls the concentrations of regulatory proteins and removes damaged and misfolded proteins from cells. Proteins are targeted to the protease at the center of this system, the proteasome, by ubiquitin tags, but ubiquitin is also used as a signal in other cellular processes. Specificity is conferred by the size and structure of the ubiquitin tags, which are recognized by receptors associated with the different cellular processes. However, the ubiquitin code remains ambiguous, and the same ubiquitin tag can target different proteins to different fates. After binding substrate protein at the ubiquitin tag, the proteasome initiates degradation at a disordered region in the substrate. The proteasome has pronounced preferences for the initiation site, and its recognition represents a second component of the degradation signal.","DOI":"10.1146/annurev-biophys-070816-

033719","ISSN":"1936-1238","note":"PMID: 28301771","journalAbbreviation":"Annu Rev Biophys","language":"eng","author":[{"family":"Yu","given":"Houqing"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2017",5,22]]}},{"id":86,"uris":["http://zotero.org/users/4604651/items/7MB84V5S"],"uri":["http://zotero.org/users/4604651/items/7MB84V5S"],"itemData":{"id":86,"type":"article-journal","title":"Ubiquitin recognition by the proteasome","container-title":"The Journal of Biochemistry","page":"113-124","volume":"161","issue":"2","source":"academic.oup.com","abstract":"The 26S proteasome is a 2.5-MDa complex responsible for the selective, ATP-dependent degradation of ubiquitylated proteins in eukaryotic cells. Substrates in hundreds cellular pathways are timely ubiquitylated and converged to the proteasome by direct recognition or by multiple shuttle factors. Engagement of substrate protein triggers conformational changes of the proteasome, which drive substrate unfolding, deubiquitylation and translocation of substrates to proteolytic sites. Recent studies have challenged the previous paradigm that Lys48-linked tetraubiquitin is a minimal degradation signal: in addition, monoubiquitylation or multiple short ubiquitylations can serve as the targeting signal for proteasomal degradation. In this review, I highlight recent advances in our understanding of the proteasome structure, the ubiquitin topology in proteasome targeting, and the cellular factors that regulate proteasomal degradation.","DOI":"10.1093/jb/mvw091","ISSN":"0021-924X","journalAbbreviation":"J Biochem","author":[{"family":"Saeki","given":"Yasushi"}],"issued":{"date-parts":[["2017",2,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}, and the presence of an unstructured region in proteins, which serves as an initiator for degradation[16,17]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2f5lbm8pqc","properties":{"formattedCitation":"{\\rtf \\super 16,17\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":78,"uris":["http://zotero.org/users/4604651/items/ERUTYSWW"],"uri":["http://zotero.org/users/4604651/items/ERUTYSWW"],"itemData":{"id":78,"type":"article-journal","title":"An unstructured initiation site is required for efficient proteasome-mediated degradation","container-title":"Nature Structural & Molecular Biology","page":"830-837","volume":"11","issue":"9","source":"PubMed","abstract":"The proteasome is the main ATP-dependent protease in eukaryotic cells and controls the concentration of many regulatory proteins in the cytosol and nucleus. Proteins are targeted to the proteasome by the covalent attachment of polyubiquitin chains. The ubiquitin modification serves as the proteasome recognition element but by itself is not sufficient for efficient degradation of folded proteins. We report that proteolysis of tightly folded proteins is accelerated greatly when an unstructured region is attached to the substrate. The unstructured region serves as the initiation site for degradation and is hydrolyzed first, after which the rest of the protein is digested sequentially. These results identify the initiation site as a novel component of the targeting signal, which is required to engage the proteasome unfolding machinery efficiently. The proteasome degrades a substrate by first binding to its ubiquitin modification and then initiating unfolding at an unstructured region.","DOI":"10.1038/nsmb814","ISSN":"1545-9993","note":"PMID: 15311270","journalAbbreviation":"Nat. Struct. Mol. Biol.","language":"eng","author":[{"family":"Prakash","given":"Sumit"},{"family":"Tian","given":"Lin"},{"family":"Ratliff","given":"Kevin S."},{"family":"Lehotzky","given":"Rebecca E."},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2004",9]]}},{"id":8,"uris":["http://zotero.org/users/4604651/items/GUTBWCCE"],"uri":["http://zotero.org/users/4604651/items/GUTBWCCE"],"itemData":{"id":8,"type":"article-journal","title":"Paradigms of protein degradation by the proteasome","container-title":"Current Opinion in Structural Biology","page":"156-164","volume":"24","source":"PubMed","abstract":"The proteasome is the main proteolytic machine in the cytosol and nucleus of eukaryotic cells where it degrades hundreds of regulatory proteins, removes damaged

proteins, and produces peptides that are presented by MHC complexes. New structures of the proteasome particle show how its subunits are arranged and provide insights into how the proteasome is regulated. Proteins are targeted to the proteasome by tags composed of several ubiquitin moieties. The structure of the tags tunes the order in which proteins are degraded. The proteasome itself edits the ubiquitin tags and drugs that interfere in this process can enhance the clearance of toxic proteins from cells. Finally, the proteasome initiates degradation at unstructured regions within its substrates and this step contributes to substrate selection.","DOI":"10.1016/j.sbi.2014.02.002","ISSN":"1879-033X","note":"PMID: 24632559\nPMCID: PMC4010099","journalAbbreviation":"Curr. Opin. Struct. Biol.","language":"eng","author":[{"family":"Inobe","given":"Tomonao"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2014",2]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } (Fig. 1). Ubiquitylation, which involves a complex interplay of ubiquitylating and deubiquitylating enzymes (DUBs) is an important element of control of the UPS[7,13,14,18]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2av3qo81c7","properties":{"formattedCitation":"{\\rtf \\super 7,13,14,18\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}},{"id":88,"uris":["http://zotero.org/users/4604651/items/UJAUYTXE"],"uri":["http://zotero.org/users/4604651/items/UJAUYTXE"],"itemData":{"id":88,"type":"article-journal","title":"The ubiquitin code","container-title":"Annual Review of Biochemistry","page":"203-229","volume":"81","source":"PubMed","abstract":"The posttranslational modification with ubiquitin, a process referred to as ubiquitylation, controls almost every process in cells. Ubiquitin can be attached to substrate proteins as a single moiety or in the form of polymeric chains in which successive ubiquitin molecules are connected through specific isopeptide bonds. Reminiscent of a code, the various ubiquitin modifications adopt distinct conformations and lead to different outcomes in cells. Here, we discuss the structure, assembly, and function of this ubiquitin code.","DOI":"10.1146/annurev-biochem-060310-170328","ISSN":"1545-4509","note":"PMID: 22524316","journalAbbreviation":"Annu. Rev.

Biochem.","language":"eng","author":[{"family":"Komander","given":"David"},{"family":"Rape","given":"Michael"}],"issued":{"date-parts":[["2012"]]}}},{"id":12,"uris":["http://zotero.org/users/4604651/items/4V75P44H"],"uri":["http://zotero.org/users/4604651/items/4V75P44H"],"itemData":{"id":12,"type":"article-journal","title":"Recognition of Client Proteins by the Proteasome","container-title":"Annual Review of Biophysics","page":"149-173","volume":"46","source":"PubMed","abstract":"The ubiquitin proteasome system controls the concentrations of regulatory proteins and removes damaged and misfolded proteins from cells. Proteins are targeted to the protease at the center of this system, the proteasome, by ubiquitin tags, but ubiquitin is also used as a signal in other cellular processes. Specificity is conferred by the size and structure of the ubiquitin tags, which are recognized by receptors associated with the different cellular processes. However, the ubiquitin code remains ambiguous, and the same ubiquitin tag can target different proteins to different fates. After binding substrate protein at the ubiquitin tag, the proteasome initiates degradation at a disordered region in the substrate. The proteasome has pronounced preferences for the initiation site, and its recognition represents a second component of the degradation signal.","DOI":"10.1146/annurev-biophys-070816-033719","ISSN":"1936-1238","note":"PMID: 28301771","journalAbbreviation":"Annu Rev Biophys","language":"eng","author":[{"family":"Yu","given":"Houqing"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2017",5,22]]}}},{"id":369,"uris":["http://zotero.org/users/4604651/items/GEWPQKH7"],"uri":["http://zotero.org/users/4604651/items/GEWPQKH7"],"itemData":{"id":369,"type":"article-journal","title":"Drugging the undruggables: exploring the ubiquitin system for drug development","container-title":"Cell Research","page":"484","volume":"26","issue":"4","source":"www.nature.com","abstract":"Drugging the undruggables: exploring the ubiquitin system for drug development","DOI":"10.1038/cr.2016.31","ISSN":"1748-7838","shortTitle":"Drugging the undruggables","language":"En","author":[{"family":"Huang","given":"Xiaodong"},{"family":"Dixit","given":"Vishva M."}],"issued":{"date-parts":[["2016",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}.

In addition to selectively targeting proteins to the proteasome, cells have another way of regulating proteasomal degradation, which consists in adjusting proteasome abundance. Recent findings have revealed that proteasome abundance is controlled at the level of proteasome assembly, which is a highly regulated process that is finely tuned to cellular metabolism. In this Review, we describe the different steps of proteasome assembly and their regulation, the interplay between proteasomal degradation and autophagy and how these mechanisms are integrated with cellular physiology. We also discuss how the misregulation of proteasome assembly and activity can contribute to human disease.

[H1] Components of the 26S proteasome

The eukaryotic 26S proteasome is a 2.5 MDa proteolytic complex that consists of two different subcomplexes: the 20S core particle (CP) and the 19S regulatory particle (RP)[19–23]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2a846aruag","properties":{"formattedCitation":"{\\rtf \\super 19\\uc0\\u8211{}23\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":77,"uris":["http://zotero.org/users/4604651/items/MFCA9SZR"],"uri":["http://zotero.org/users/4604651/items/MFCA9SZR"],"itemData":{"id":77,"type":"article-journal","title":"Regulation of

proteasome activity in health and disease","container-title":"Biochimica et biophysica acta","volume":"1843","issue":"1","source":"PubMed Central","abstract":"The ubiquitin-proteasome system (UPS) is the primary selective degradation system in the nuclei and cytoplasm of eukaryotic cells, required for the turnover of myriad soluble proteins. The hundreds of factors that comprise the UPS include an enzymatic cascade that tags proteins for degradation via the covalent attachment of a poly-ubiquitin chain, and a large multimeric enzyme that degrades ubiquitinated proteins, the proteasome. Protein degradation by the UPS regulates many pathways and is a crucial component of the cellular proteostasis network. Dysfunction of the ubiquitination machinery or the proteolytic activity of the proteasome is associated with numerous human diseases. In this review we discuss the contributions of the proteasome to human pathology, describe mechanisms that regulate the proteolytic capacity of the proteasome, and discuss strategies to modulate proteasome function as a therapeutic approach to ameliorate diseases associated with altered UPS function.","URL":"http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858528/","DOI":"10.1016/j.bbamcr.2013.08.012","ISSN":"0006-3002","note":"PMID: 23994620\nPMCID: PMC3858528","journalAbbreviation":"Biochim Biophys Acta","author":[{"family":"Schmidt","given":"Marion"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2014",1]]},"accessed":{"date-parts":[["2017",6,26]]}},{"id":84,"uris":["http://zotero.org/users/4604651/items/6D759M67"],"uri":["http://zotero.org/users/4604651/items/6D759M67"],"itemData":{"id":84,"type":"article-journal","title":"The Logic of the 26S Proteasome","container-title":"Cell","page":"792-806","volume":"169","issue":"5","source":"www.cell.com","DOI":"10.1016/j.cell.2017.04.023","ISSN":"0092-8674, 1097-4172","note":"PMID: 28525752","journalAbbreviation":"Cell","language":"English","author":[{"family":"Collins","given":"Galen Andrew"},{"family":"Goldberg","given":"Alfred L."}],"issued":{"date-parts":[["2017",5,18]]}},{"id":76,"uris":["http://zotero.org/users/4604651/items/D2R2QDAY"],"uri":["http://zotero.org/users/4604651/items/D2R2QDAY"],"itemData":{"id":76,"type":"article-journal","title":"Molecular mechanisms of proteasome assembly","container-title":"Nature Reviews Molecular Cell Biology","page":"104-115","volume":"10","issue":"2","source":"www.nature.com","abstract":"The 26S proteasome is a highly conserved protein degradation machine that consists of the 20S proteasome and 19S regulatory particles, which include 14 and 19 different polypeptides, respectively. How the proteasome components are assembled is a fundamental question towards understanding the process of protein degradation and its functions in diverse biological processes. Several proteasome-dedicated chaperones are involved in the efficient and correct assembly of the 20S proteasome. These chaperones help the initiation and progression of the assembly process by transiently associating with proteasome precursors. By contrast, little is known about the assembly of the 19S regulatory particles, but several hints have emerged.","DOI":"10.1038/nrm2630","ISSN":"1471-0072","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Murata","given":"Shigeo"},{"family":"Yashiroda","given":"Hideki"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",2]]}},{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated

substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}},{"id":2,"uris":["http://zotero.org/users/4604651/items/UGYILVCT"],"uri":["http://zotero.org/users/4604651/items/UGYILVCT"],"itemData":{"id":2,"type":"article-journal","title":"Proteasome Structure and Assembly","container-title":"Journal of Molecular Biology","page":"3500-3524","volume":"429","issue":"22","source":"PubMed","abstract":"The eukaryotic 26S proteasome is a large multisubunit complex that degrades the majority of proteins in the cell under normal conditions. The 26S proteasome can be divided into two subcomplexes: the 19S regulatory particle and the 20S core particle. Most substrates are first covalently modified by ubiquitin, which then directs them to the proteasome. The function of the regulatory particle is to recognize, unfold, deubiquitylate, and translocate substrates into the core particle, which contains the proteolytic sites of the proteasome. Given the abundance and subunit complexity of the proteasome, the assembly of this ~2.5MDa complex must be carefully orchestrated to ensure its correct formation. In recent years, significant progress has been made in the understanding of proteasome assembly, structure, and function. Technical advances in cryo-electron microscopy have resulted in a series of atomic cryo-electron microscopy structures of both human and yeast 26S proteasomes. These structures have illuminated new intricacies and dynamics of the proteasome. In this review, we focus on the mechanisms of proteasome assembly, particularly in light of recent structural information.","DOI":"10.1016/j.jmb.2017.05.027","ISSN":"1089-8638","note":"PMID: 28583440\nPMCID: PMC5675778","journalAbbreviation":"J. Mol. Biol.","language":"eng","author":[{"family":"Budenholzer","given":"Lauren"},{"family":"Cheng","given":"Chin Leng"},{"family":"Li","given":"Yanjie"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2017",11,10]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Fig. 1). The CP is flanked at one or both ends by the RP to form the singly- (RP_1-CP) and doubly- (RP_2-CP) capped proteasome, respectively (FIG. 1). Currently, the functional significance of singly or doubly capped proteasomes is unknown. Additional regulatory complexes can substitute the RP to assemble alternative forms of the proteasome. The function of these alternative regulatory particles, including proteasome activator PA200 in mammals (Bml10 in yeast) [19,24,25]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ifgqn8pvh","properties":{"formattedCitation":"{\\rtf \\super 19,24,25\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":81,"uris":["http://zotero.org/users/4604651/items/KA4CKH3A"],"uri":[

"http://zotero.org/users/4604651/items/KA4CKH3A"],"itemData":{"id":81,"type":"article-journal","title":"Formation of alternative proteasomes: Same lady, different cap?","container-title":"FEBS Letters","page":"389-393","volume":"587","issue":"5","source":"ScienceDirect","abstract":"The 26S proteasome is thought to be a homogenous complex, consisting of a 20S proteolytic core and a 19S regulatory particle that is required for its activation.\nTwo groups have recently reported the activation of archeal 20S by a p97-related double-ring AAA+ ATPase complex, in a similar fashion to that reported for 19S. Since p97 is found in eukaryotes, the existence of a parallel setting in higher organisms is intriguing. Herein, we present supporting data and hypothesize that in eukaryotes, p97 and CSN form a promiscuous, hence hard-to-detect, “alternative cap”, enabling the prompt and precise elimination of particular substrates.","DOI":"10.1016/j.febslet.2013.01.014","ISSN":"0014-5793","shortTitle":"Formation of alternative proteasomes","journalAbbreviation":"FEBS Letters","author":[{"family":"Pick","given":"Elah"},{"family":"Berman","given":"Tali S."}],"issued":{"date-parts":[["2013",3,1]]}}},{"id":77,"uris":["http://zotero.org/users/4604651/items/MFCA9SZR"],"uri":["http://zotero.org/users/4604651/items/MFCA9SZR"],"itemData":{"id":77,"type":"article-journal","title":"Regulation of proteasome activity in health and disease","container-title":"Biochimica et biophysica acta","volume":"1843","issue":"1","source":"PubMed Central","abstract":"The ubiquitin-proteasome system (UPS) is the primary selective degradation system in the nuclei and cytoplasm of eukaryotic cells, required for the turnover of myriad soluble proteins. The hundreds of factors that comprise the UPS include an enzymatic cascade that tags proteins for degradation via the covalent attachment of a poly-ubiquitin chain, and a large multimeric enzyme that degrades ubiquitinated proteins, the proteasome. Protein degradation by the UPS regulates many pathways and is a crucial component of the cellular proteostasis network. Dysfunction of the ubiquitination machinery or the proteolytic activity of the proteasome is associated with numerous human diseases. In this review we discuss the contributions of the proteasome to human pathology, describe mechanisms that regulate the proteolytic capacity of the proteasome, and discuss strategies to modulate proteasome function as a therapeutic approach to ameliorate diseases associated with altered UPS function.","URL":"http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858528/","DOI":"10.1016/j.bbamcr.2013.08.012","ISSN":"0006-3002","note":"PMID: 23994620\nPMCID: PMC3858528","journalAbbreviation":"Biochim Biophys Acta","author":[{"family":"Schmidt","given":"Marion"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2014",1]]},"accessed":{"date-parts":[["2017",6,26]]}}},{"id":79,"uris":["http://zotero.org/users/4604651/items/UV7QAVP2"],"uri":["http://zotero.org/users/4604651/items/UV7QAVP2"],"itemData":{"id":79,"type":"article-journal","title":"Proteasome Activators","container-title":"Molecular Cell","page":"8-19","volume":"41","issue":"1","source":"www.cell.com","abstract":"Proteasomes degrade a multitude of protein substrates in the cytosol and nucleus, and thereby are essential for many aspects of cellular function. Because the proteolytic sites are sequestered in a closed barrel-shaped structure, activators are required to facilitate substrate access. Structural and biochemical studies of two activator families, 11S and Blm10, have provided insights to proteasome activation mechanisms, although the biological functions of these factors remain obscure. Recent advances have improved our understanding of the third activator family, including the 19S activator, which targets polyubiquitylated proteins for degradation. Here we present a structural perspective on how proteasomes are activated and how substrates are delivered to the proteolytic sites.","DOI":"10.1016/j.molcel.2010.12.020","ISSN":"1097-2765","note":"PMID: 21211719","journalAbbreviation":"Molecular Cell","language":"English","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Hill","given":"Christopher

P."}],"issued":{"date-parts":[["2011",1,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }

{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2552565f5v","properties":{"formattedCitation":"{\\rtf \\super 19,24,25\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":81,"uris":["http://zotero.org/users/4604651/items/KA4CKH3A"],"uri":["http://zotero.org/users/4604651/items/KA4CKH3A"],"itemData":{"id":81,"type":"article-journal","title":"Formation of alternative proteasomes: Same lady, different cap?","container-title":"FEBS Letters","page":"389-393","volume":"587","issue":"5","source":"ScienceDirect","abstract":"The 26S proteasome is thought to be a homogenous complex, consisting of a 20S proteolytic core and a 19S regulatory particle that is required for its activation.\nTwo groups have recently reported the activation of archeal 20S by a p97-related double-ring AAA+ ATPase complex, in a similar fashion to that reported for 19S. Since p97 is found in eukaryotes, the existence of a parallel setting in higher organisms is intriguing. Herein, we present supporting data and hypothesize that in eukaryotes, p97 and CSN form a promiscuous, hence hard-to-detect, “alternative cap”, enabling the prompt and precise elimination of particular substrates.","DOI":"10.1016/j.febslet.2013.01.014","ISSN":"0014-5793","shortTitle":"Formation of alternative proteasomes","journalAbbreviation":"FEBS Letters","author":[{"family":"Pick","given":"Elah"},{"family":"Berman","given":"Tali S."}],"issued":{"date-parts":[["2013",3,1]]}}},{"id":77,"uris":["http://zotero.org/users/4604651/items/MFCA9SZR"],"uri":["http://zotero.org/users/4604651/items/MFCA9SZR"],"itemData":{"id":77,"type":"article-journal","title":"Regulation of proteasome activity in health and disease","container-title":"Biochimica et biophysica acta","volume":"1843","issue":"1","source":"PubMed Central","abstract":"The ubiquitin-proteasome system (UPS) is the primary selective degradation system in the nuclei and cytoplasm of eukaryotic cells, required for the turnover of myriad soluble proteins. The hundreds of factors that comprise the UPS include an enzymatic cascade that tags proteins for degradation via the covalent attachment of a poly-ubiquitin chain, and a large multimeric enzyme that degrades ubiquitinated proteins, the proteasome. Protein degradation by the UPS regulates many pathways and is a crucial component of the cellular proteostasis network. Dysfunction of the ubiquitination machinery or the proteolytic activity of the proteasome is associated with numerous human diseases. In this review we discuss the contributions of the proteasome to human pathology, describe mechanisms that regulate the proteolytic capacity of the proteasome, and discuss strategies to modulate proteasome function as a therapeutic approach to ameliorate diseases associated with

altered UPS function.","URL":"http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858528/","DOI":"10.1016/j.bbamcr.2013.08.012","ISSN":"0006-3002","note":"PMID: 23994620\nPMCID: PMC3858528","journalAbbreviation":"Biochim Biophys Acta","author":[{"family":"Schmidt","given":"Marion"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2014",1]]},"accessed":{"date-parts":[["2017",6,26]]}},{"id":79,"uris":["http://zotero.org/users/4604651/items/UV7QAVP2"],"uri":["http://zotero.org/users/4604651/items/UV7QAVP2"],"itemData":{"id":79,"type":"article-journal","title":"Proteasome Activators","container-title":"Molecular Cell","page":"8-19","volume":"41","issue":"1","source":"www.cell.com","abstract":"Proteasomes degrade a multitude of protein substrates in the cytosol and nucleus, and thereby are essential for many aspects of cellular function. Because the proteolytic sites are sequestered in a closed barrel-shaped structure, activators are required to facilitate substrate access. Structural and biochemical studies of two activator families, 11S and Blm10, have provided insights to proteasome activation mechanisms, although the biological functions of these factors remain obscure. Recent advances have improved our understanding of the third activator family, including the 19S activator, which targets polyubiquitylated proteins for degradation. Here we present a structural perspective on how proteasomes are activated and how substrates are delivered to the proteolytic sites.","DOI":"10.1016/j.molcel.2010.12.020","ISSN":"1097-2765","note":"PMID: 21211719","journalAbbreviation":"Molecular Cell","language":"English","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Hill","given":"Christopher P."}],"issued":{"date-parts":[["2011",1,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} and the 11S regulator complex PA28 or REG in mammals is less clear than the function of RP[7]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a29p5khjq07","properties":{"formattedCitation":"{\\rtf \\super 7\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-

coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Three types of PA28 subunits have been described, the α- and β-subunits forming the PA28α/β heteroheptamer (with a stoichiometry of $\alpha_4\beta_3$) and the γ-subunits induced by interferon-γ and forming a homoheptamer [26–28]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a16e8536q3e","properties":{"formattedCitation":"{\\rtf \\super 26\\uc0\\u8211{}28\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":374,"uris":["http://zotero.org/users/4604651/items/T6PGHBPS"],"uri":["http://zotero.org/users/4604651/items/T6PGHBPS"],"itemData":{"id":374,"type":"article-journal","title":"Functions of the proteasome: from protein degradation and immune surveillance to cancer therapy","container-title":"Biochemical Society Transactions","page":"12-17","volume":"35","issue":"Pt 1","source":"PubMed","abstract":"This review focuses on recent insights into the mechanisms and the biological functions of the proteasome. This large ATP-dependent proteolytic complex is the main site for protein degradation in mammalian cells and catalyses the rapid degradation of ubiquitinated proteins, and is the source of most antigenic peptides used by the immune system to screen for viruses and cancer. ATP is required to unfold globular proteins to open the gated channel into the 20S proteasome and to facilitate protein translation into it. Inhibitors of its proteolytic activity are widely used as research tools and have proven effective in cancer therapy.","DOI":"10.1042/BST0350012","ISSN":"0300-5127","note":"PMID: 17212580","shortTitle":"Functions of the proteasome","journalAbbreviation":"Biochem. Soc. Trans.","language":"eng","author":[{"family":"Goldberg","given":"A. L."}],"issued":{"date-parts":[["2007",2]]}}},{"id":415,"uris":["http://zotero.org/users/4604651/items/VEEEC2QC"],"uri":["http://zotero.org/users/4604651/items/VEEEC2QC"],"itemData":{"id":415,"type":"article-journal","title":"PA28αβ: the enigmatic magic ring of the proteasome?","container-title":"Biomolecules","page":"566-584","volume":"4","issue":"2","source":"PubMed","abstract":"PA28αβ is a γ-interferon-induced 11S complex that associates with the ends of the 20S proteasome and stimulates in vitro breakdown of small peptide substrates, but not proteins or ubiquitin-conjugated proteins. In cells, PA28 also exists in larger complexes along with the 19S particle, which allows ATP-dependent degradation of proteins; although in vivo a large fraction of PA28 is present as PA28αβ-20S particles whose exact biological functions are largely unknown. Although several lines of evidence strongly indicate that PA28αβ plays a role in MHC class I antigen presentation, the exact molecular mechanisms of this activity are still poorly understood. Herein, we review current knowledge about the biochemical and biological properties of PA28αβ and discuss recent findings concerning its role in modifying the spectrum of proteasome's peptide products, which are important to better understand the molecular mechanisms and biological consequences of PA28αβ

activity.","DOI":"10.3390/biom4020566","ISSN":"2218-273X","note":"PMID: 24970231\nPMCID: PMC4101498","shortTitle":"PA28αβ","journalAbbreviation":"Biomolecules","language":"eng","author":[{"family":"Cascio","given":"Paolo"}],"issued":{"date-parts":[["2014",6,19]]}},{"id":413,"uris":["http://zotero.org/users/4604651/items/YS83X9H7"],"uri":["http://zotero.org/users/4604651/items/YS83X9H7"],"itemData":{"id":413,"type":"article-journal","title":"The Mammalian Proteasome Activator PA28 Forms an Asymmetric α4β3Complex","container-title":"Structure (London, England: 1993)","page":"1473-1480.e3","volume":"25","issue":"10","source":"PubMed","abstract":"The heptameric proteasome activator (PA) 28αβ is known to modulate class I antigen processing by docking onto 20S proteasome core particles (CPs). The exact stoichiometry and arrangement of its α and β subunits, however, is still controversial. Here we analyzed murine PA28 complexes regarding structure and assembly. Strikingly, PA28α, PA28β, and PA28αβ preparations form heptamers, but solely PA28α and PA28αβ associate with CPs. Co-expression of α and β yields one unique PA28αβ species with an unchangeable subunit composition. Structural data on PA28α, PA28β, and PA28αβ up to 2.9 Å resolution reveal a PA28α4β3complex with an alternating subunit arrangement and a single α-α interface. Differential scanning fluorimetry experiments and activity assays classify PA28α4β3as most stable and most active, indicating that this assembly might represent the physiologically relevant species. Together, our data resolve subunit composition and arrangement of PA28αβ and clarify how an asymmetric heptamer can be assembled from two highly homologous subunits.","DOI":"10.1016/j.str.2017.07.013","ISSN":"1878-4186","note":"PMID: 28867616","journalAbbreviation":"Structure","language":"eng","author":[{"family":"Huber","given":"Eva M."},{"family":"Groll","given":"Michael"}],"issued":{"date-parts":[["2017",10,3]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Because one or two regulatory particles can be bound to the CP, this creates a number of possible hybrid proteasome assemblies the functions of which remain to be elucidated. We will use the standardized nomenclature and the yeast and human subunit names are listed in table 1.

[H2] The 20S core particle

Protein degradation occurs inside the narrow proteolytic chamber of the CP, a barrel-shaped cylinder composed of α- and β-subunits arranged in four stacked hetero-heptameric rings with a stoichiometry of $\alpha_{1\text{-}7}\beta_{1\text{-}7}\beta_{1\text{-}7}\alpha_{1\text{-}7}$[10,29–31]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2ph1n2ekdi","properties":{"formattedCitation":"{\\rtf \\super 10,29\\uc0\\u8211{}31\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":90,"uris":["http://zotero.org/users/4604651/items/LR4M88KA"],"uri":["http://zotero.org/users/4604651/items/LR4M88KA"],"itemData":{"id":90,"type":"article-journal","title":"The proteasome: Overview of structure and functions","container-title":"Proceedings of the Japan Academy. Series B, Physical and Biological Sciences","page":"12-36","volume":"85","issue":"1","source":"PubMed Central","abstract":"The proteasome is a highly sophisticated protease complex designed to carry out selective, efficient and processive hydrolysis of client proteins. It is known to collaborate with ubiquitin, which polymerizes to form a marker for regulated proteolysis in eukaryotic cells. The highly organized proteasome plays a prominent role in the control of a diverse array of basic cellular activities by rapidly and unidirectionally catalyzing biological reactions.

Studies of the proteasome during the past quarter of a century have provided profound insights into its structure and functions, which has appreciably contributed to our understanding of cellular life. Many questions, however, remain to be elucidated.","DOI":"10.2183/pjab.85.12","ISSN":"0386-2208","note":"PMID: 19145068\nPMCID: PMC3524306","shortTitle":"The proteasome","journalAbbreviation":"Proc Jpn Acad Ser B Phys Biol Sci","author":[{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",1]]}},{"id":75,"uris":["http://zotero.org/users/4604651/items/JVBW5TU6"],"uri":["http://zotero.org/users/4604651/items/JVBW5TU6"],"itemData":{"id":75,"type":"article-journal","title":"Structure and functions of the 20S and 26S proteasomes","container-title":"Annual Review of Biochemistry","page":"801-847","volume":"65","source":"PubMed","abstract":"The proteasome is an essential component of the ATP-dependent proteolytic pathway in eukaryotic cells and is responsible for the degradation of most cellular proteins. The 20S (700-kDa) proteasome contains multiple peptidase activities that function through a new type of proteolytic mechanism involving a threonine active site. The 26S (2000-kDa) complex, which degrades ubiquitinated proteins, contains in addition to the 20S proteasome a 19S regulatory complex composed of multiple ATPases and components necessary for binding protein substrates. The proteasome has been highly conserved during eukaryotic evolution, and simpler forms are even found in archaebacteria and eubacteria. Major advances have been achieved recently in our knowledge about the molecular organization of the 20S and 19S particles, their subunits, the proteasome's role in MHC-class 1 antigen presentation, and regulators of its activities. This article focuses on recent progress concerning the biochemical mechanisms and intracellular functions of the 20S and 26S proteasomes.","DOI":"10.1146/annurev.bi.65.070196.004101","ISSN":"0066-4154","note":"PMID: 8811196","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Coux","given":"O."},{"family":"Tanaka","given":"K."},{"family":"Goldberg","given":"A. L."}],"issued":{"date-parts":[["1996"]]}},{"id":74,"uris":["http://zotero.org/users/4604651/items/6CHLFDIX"],"uri":["http://zotero.org/users/4604651/items/6CHLFDIX"],"itemData":{"id":74,"type":"article-journal","title":"Structure and Function of the 20S Proteasome and of Its Regulatory Complexes","container-title":"Cold Spring Harbor Symposia on Quantitative Biology","page":"515-524","volume":"60","source":"symposium.cshlp.org","abstract":"Excerpt\nProteasomes are ubiquitous, multisubunit proteases with highly conserved structures (for review, see Lupas et al. 1993). The 26S proteasome, an ATP-dependent enzyme of about 2000 kD, is the central protease of the ubiquitin- dependent pathway of protein degradation (for review, see Hochstrasser 1995). Detected so far only in eukaryotes, it plays a central role in a variety of cellular processes, including cell cycle (Glotzer et al. 1991; Ghislain et al. 1993; Gordon et al. 1993), transcriptional regulation (Dubiel et al. 1993, 1994; DeMartino et al. 1994), and antigen presentation (for review, see Gaczynska et al. 1993). The core of the 26S complex is formed by the 20S proteasome, an ATP-independent, barrel-shaped protease of about 700 kD, which is found in all three kingdoms of life.\nTHE 20S PROTEASOME\nOccurrence\nThe 20S proteasome was first described by Hase et al. (1980) in carp muscle and by Wilk and Orlowski (1980) in...","DOI":"10.1101/SQB.1995.060.01.055","ISSN":"0091-7451, 1943-4456","note":"PMID: 8824424","journalAbbreviation":"Cold Spring Harb Symp Quant Biol","language":"en","author":[{"family":"Lupas","given":"A."},{"family":"Zwickl","given":"P."},{"family":"Wenzel","given":"T."},{"family":"Seemüller","given":"E."},{"family":"Baumeister","given":"W."}],"issued":{"date-parts":[["1995",1,1]]}},{"id":72,"uris":["http://zotero.org/users/4604651/items/JK6UXJIS"],"uri":["http://zotero.org/users/4604651/items/JK6UXJIS"],"itemData":{"id":72,"type":"article-journal","title":"Assembly of the 20S proteasome","container-title":"Biochimica Et

Biophysica Acta","page":"2-12","volume":"1843","issue":"1","source":"PubMed","abstract":"The proteasome is a cellular protease responsible for the selective degradation of the majority of the intracellular proteome. It recognizes, unfolds, and cleaves proteins that are destined for removal, usually by prior attachment to polymers of ubiquitin. This macromolecular machine is composed of two subcomplexes, the 19S regulatory particle (RP) and the 20S core particle (CP), which together contain at least 33 different and precisely positioned subunits. How these subunits assemble into functional complexes is an area of active exploration. Here we describe the current status of studies on the assembly of the 20S proteasome (CP). The 28-subunit CP is found in all three domains of life and its cylindrical stack of four heptameric rings is well conserved. Though several CP subunits possess self-assembly properties, a consistent theme in recent years has been the need for dedicated assembly chaperones that promote on-pathway assembly. To date, a minimum of three accessory factors have been implicated in aiding the construction of the 20S proteasome. These chaperones interact with different assembling proteasomal precursors and usher subunits into specific slots in the growing structure. This review will focus largely on chaperone-dependent CP assembly and its regulation. This article is part of a Special Issue entitled: Ubiquitin-Proteasome System. Guest Editors: Thomas Sommer and Dieter H. Wolf.","DOI":"10.1016/j.bbamcr.2013.03.008","ISSN":"0006-3002","note":"PMID: 23507199\nPMCID: PMC3752329","journalAbbreviation":"Biochim. Biophys. Acta","language":"eng","author":[{"family":"Kunjappu","given":"Mary J."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2014",1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The two outer α–rings function as a gate that prevents uncontrolled access to the proteolytic chamber inside the two β–rings. The gate is formed by the tightly interweaved N-terminal tails of the α-subunits that block substrate entry[7]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2pijirsgba","properties":{"formattedCitation":"{\\rtf \\super 7\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-

parts":[["2009"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Gate opening controls the access of substrates inside the catalytic chamber of the proteasome and has an important role in the regulation of proteasomal degradation[7]. Among the seven β-subunits, only β1, β2 and β5 have proteolytic activities, which are known as caspase-like activity, trypsin-like activity and chymotrypsin-like activity, respectively[32–34]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1sm6665eae","properties":{"formattedCitation":"{\\rtf \\super 32\\uc0\\u8211{}34\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":71,"uris":["http://zotero.org/users/4604651/items/P7WQ3M7N"],"uri":["http://zotero.org/users/4604651/items/P7WQ3M7N"],"itemData":{"id":71,"type":"article-journal","title":"Structure of 20S proteasome from yeast at 2.4 A resolution","container-title":"Nature","page":"463-471","volume":"386","issue":"6624","source":"PubMed","abstract":"The crystal structure of the 20S proteasome from the yeast Saccharomyces cerevisiae shows that its 28 protein subunits are arranged as an (alpha1...alpha7, beta1...beta7)2 complex in four stacked rings and occupy unique locations. The interior of the particle, which harbours the active sites, is only accessible by some very narrow side entrances. The beta-type subunits are synthesized as proproteins before being proteolytically processed for assembly into the particle. The proforms of three of the seven different beta-type subunits, beta1/PRE3, beta2/PUP1 and beta5/PRE2, are cleaved between the threonine at position 1 and the last glycine of the pro-sequence, with release of the active-site residue Thr 1. These three beta-type subunits have inhibitor-binding sites, indicating that PRE2 has a chymotrypsin-like and a trypsin-like activity and that PRE3 has peptidylglutamyl peptide hydrolytic specificity. Other beta-type subunits are processed to an intermediate form, indicating that an additional nonspecific endopeptidase activity may exist which is important for peptide hydrolysis and for the generation of ligands for class I molecules of the major histocompatibility complex.","DOI":"10.1038/386463a0","ISSN":"0028-0836","note":"PMID: 9087403","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Groll","given":"M."},{"family":"Ditzel","given":"L."},{"family":"Löwe","given":"J."},{"family":"Stock","given":"D."},{"family":"Bochtler","given":"M."},{"family":"Bartunik","given":"H. D."},{"family":"Huber","given":"R."}],"issued":{"date-parts":[["1997",4,3]]}}},{"id":73,"uris":["http://zotero.org/users/4604651/items/3T4EYIRC"],"uri":["http://zotero.org/users/4604651/items/3T4EYIRC"],"itemData":{"id":73,"type":"article-journal","title":"The structure of the mammalian 20S proteasome at 2.75 A resolution","container-title":"Structure (London, England: 1993)","page":"609-618","volume":"10","issue":"5","source":"PubMed","abstract":"The 20S proteasome is the catalytic portion of the 26S proteasome. Constitutively expressed mammalian 20S proteasomes have three active subunits, beta 1, beta 2, and beta 5, which are replaced in the immunoproteasome by interferon-gamma-inducible subunits beta 1i, beta 2i, and beta 5i, respectively. Here we determined the crystal structure of the bovine 20S proteasome at 2.75 A resolution. The structures of alpha 2, beta 1, beta 5, beta 6, and beta 7 subunits of the bovine enzyme were different from the yeast enzyme but enabled the bovine proteasome to accommodate either the constitutive or the inducible subunits. A novel N-terminal nucleophile hydrolase activity was proposed for the beta 7 subunit. We also determined the site of the nuclear localization signals in the molecule. A model of the immunoproteasome was predicted from this constitutive structure.","ISSN":"0969-2126","note":"PMID: 12015144","journalAbbreviation":"Structure","language":"eng","author":[{"family":"Unno","given":"Masaki"},{"family":"Mizushima","gi

ven":"Tsunehiro"},{"family":"Morimoto","given":"Yukio"},{"family":"Tomisugi","given":"Yoshikazu"},{"family":"Tanaka","given":"Keiji"},{"family":"Yasuoka","given":"Noritake"},{"family":"Tsukihara","given":"Tomitake"}],"issued":{"date-parts":[["2002",5]]}},{"id":70,"uris":["http://zotero.org/users/4604651/items/HLB95LTA"],"uri":["http://zotero.org/users/4604651/items/HLB95LTA"],"itemData":{"id":70,"type":"article-journal","title":"Identification of the yeast 20S proteasome catalytic centers and subunit interactions required for active-site formation","container-title":"Proceedings of the National Academy of Sciences of the United States of America","page":"7156-7161","volume":"94","issue":"14","source":"PubMed","abstract":"The proteasome is responsible for degradation of substrates of the ubiquitin pathway. 20S proteasomes are cylindrical particles with subunits arranged in a stack of four heptameric rings. The outer rings are composed of alpha subunits, and the inner rings are composed of beta subunits. A well-characterized archaeal proteasome has a single type of each subunit, and the N-terminal threonine of the beta subunit is the active-site nucleophile. Yeast proteasomes have seven different beta subunits and exhibit several distinct peptidase activities, which were proposed to derive from disparate active sites. We show that mutating the N-terminal threonine in the yeast Pup1 beta subunit eliminates cleavage after basic residues in peptide substrates, and mutating the corresponding threonine of Pre3 prevents cleavage after acidic residues. Surprisingly, neither mutation has a strong effect on cell growth, and they have at most minor effects on ubiquitin-dependent proteolysis. We show that Pup1 interacts with Pup3 in each beta subunit ring. Our data reveal that different proteasome active sites contribute very differently to protein breakdown in vivo, that contacts between particular subunits in each beta subunit ring are critical for active-site formation, and that active sites in archaea and different eukaryotes are highly similar.","ISSN":"0027-8424","note":"PMID: 9207060\nPMCID: PMC23776","journalAbbreviation":"Proc. Natl. Acad. Sci. U.S.A.","language":"eng","author":[{"family":"Arendt","given":"C. S."},{"family":"Hochstrasser","given":"M."}],"issued":{"date-parts":[["1997",7,8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Three additional β-subunits, β1i, β2i and β5i, are induced by treatment with interferon-γ in mammals and replace their constitutive counterparts to form the immunoproteasome[35,36]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"amo6rrqlvu","properties":{"formattedCitation":"{\\rtf \\super 35,36\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":69,"uris":["http://zotero.org/users/4604651/items/EGKGVXMR"],"uri":["http://zotero.org/users/4604651/items/EGKGVXMR"],"itemData":{"id":69,"type":"article-journal","title":"Immunoproteasome Assembly: Cooperative Incorporation of Interferon γ (IFN-γ)–inducible Subunits","container-title":"Journal of Experimental Medicine","page":"97-104","volume":"187","issue":"1","source":"jem.rupress.org","abstract":"LMP2, LMP7, and MECL are interferon γ–inducible catalytic subunits of vertebrate 20S proteasomes, which can replace constitutive catalytic subunits (delta, X, and Z, respectively) during proteasome biogenesis. We demonstrate that MECL requires LMP2 for efficient incorporation into preproteasomes, and preproteasomes containing LMP2 and MECL require LMP7 for efficient maturation. The latter effect depends on the presequence of LMP7, but not on LMP7 catalytic activity. This cooperative mechanism favors the assembly of homogeneous “immunoproteasomes” containing all three inducible subunits, suggesting that these subunits act in concert to enhance proteasomal generation of major histocompatibility complex class I–binding peptides.","DOI":"10.1084/jem.187.1.97","ISSN":"0022-1007, 1540-9538","note":"PMID: 9419215","shortTitle":"Immunoproteasome Assembly","language":"en","author":[{"family":"Griffin","given":"Thomas A."},{"family":"Nandi","given":"Dipankar"},{"family":"Cruz","given":"Miguel"},{"family":"Fehling","given":"Hans Jörg"},{"family":"Kaer","given":"Luc Van"},{"family":"Monaco","given":"John J."},{"family":"Colbert","given":"Robert

A."}],"issued":{"date-parts":[["1998",1,5]]}},{"id":58,"uris":["http://zotero.org/users/4604651/items/8MY7BYTZ"],"uri":["http://zotero.org/users/4604651/items/8MY7BYTZ"],"itemData":{"id":58,"type":"article-journal","title":"IFN-gamma-induced immune adaptation of the proteasome system is an accelerated and transient response","container-title":"Proceedings of the National Academy of Sciences of the United States of America","page":"9241-9246","volume":"102","issue":"26","source":"PubMed","abstract":"Peptide generation by the proteasome is rate-limiting in MHC class I-restricted antigen presentation in response to IFN-gamma. IFN-gamma-induced de novo formation of immunoproteasomes, therefore, essentially supports the rapid adjustment of the mammalian immune system. Here, we report that the molecular interplay between the proteasome maturation protein (POMP) and the proteasomal beta5i subunit low molecular weight protein 7 (LMP7) has a key position in this immune adaptive program. IFN-gamma-induced coincident biosynthesis of POMP and LMP7 and their direct interaction essentially accelerate immunoproteasome biogenesis compared with constitutive 20S proteasome assembly. The dynamics of this process is determined by rapid LMP7 activation and the immediate LMP7-dependent degradation of POMP. Silencing of POMP expression impairs recruitment of both beta5 subunits into the proteasome complex, resulting in decreased proteasome activity, reduced MHC class I surface expression, and induction of apoptosis. Furthermore, our data reveal that immunoproteasomes exhibit a considerably shortened half-life, compared with constitutive proteasomes. In consequence, our studies demonstrate that the cytokine-induced rapid immune adaptation of the proteasome system is a tightly regulated and transient response allowing cells to return rapidly to a normal situation once immunoproteasome function is no longer required.","DOI":"10.1073/pnas.0501711102","ISSN":"0027-8424","note":"PMID: 15944226\nPMCID: PMC1166598","journalAbbreviation":"Proc. Natl. Acad. Sci. U.S.A.","language":"eng","author":[{"family":"Heink","given":"Sylvia"},{"family":"Ludwig","given":"Daniela"},{"family":"Kloetzel","given":"Peter-M."},{"family":"Krüger","given":"Elke"}],"issued":{"date-parts":[["2005",6,28]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Box 1). Other tissue-specific subunits, β5t and α4s, have been reported to be part of the thymoproteasome and the testis-specific proteasome, respectively[37,38]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"at2ljqpoki","properties":{"formattedCitation":"{\\rtf \\super 37,38\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":334,"uris":["http://zotero.org/users/4604651/items/9BDKI3DV"],"uri":["http://zotero.org/users/4604651/items/9BDKI3DV"],"itemData":{"id":334,"type":"article-journal","title":"Activity-based profiling reveals reactivity of the murine thymoproteasome-specific subunit beta5t","container-title":"Chemistry & Biology","page":"795-801","volume":"17","issue":"8","source":"PubMed","abstract":"Epithelial cells of the thymus cortex express a unique proteasome particle involved in positive T cell selection. This thymoproteasome contains the recently discovered beta5t subunit that has an uncharted activity, if any. We synthesized fluorescent epoxomicin probes that were used in a chemical proteomics approach, entailing activity-based profiling, affinity purification, and LC-MS

identification, to demonstrate that the beta5t subunit is catalytically active in the murine thymus. A panel of established proteasome inhibitors showed that the broad-spectrum inhibitor epoxomicin blocks the beta5t activity and that the subunit-specific antagonists bortezomib and NC005 do not inhibit beta5t. We show that beta5t has a substrate preference distinct from beta5/beta5i that might explain how the thymoproteasome generates the MHC class I peptide repertoire needed for positive T cell selection.","DOI":"10.1016/j.chembiol.2010.05.027","ISSN":"1879-1301","note":"PMID: 20797608\nPMCID: PMC3039300","journalAbbreviation":"Chem. Biol.","language":"eng","author":[{"family":"Florea","given":"Bogdan I."},{"family":"Verdoes","given":"Martijn"},{"family":"Li","given":"Nan"},{"family":"Linden","given":"Wouter A.","non-dropping-particle":"van der"},{"family":"Geurink","given":"Paul P."},{"family":"Elst","given":"Hans","non-dropping-particle":"van den"},{"family":"Hofmann","given":"Tanja"},{"family":"Ru","given":"Arnoud","non-dropping-particle":"de"},{"family":"Veelen","given":"Peter A.","non-dropping-particle":"van"},{"family":"Tanaka","given":"Keiji"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Murata","given":"Shigeo"},{"family":"Dulk","given":"Hans","non-dropping-particle":"den"},{"family":"Brouwer","given":"Jaap"},{"family":"Ossendorp","given":"Ferry A."},{"family":"Kisselev","given":"Alexei F."},{"family":"Overkleeft","given":"Herman S."}],"issued":{"date-parts":[["2010",8,27]]}}},{"id":342,"uris":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"uri":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"itemData":{"id":342,"type":"article-journal","title":"Ontogeny of thymic cortical epithelial cells expressing the thymoproteasome subunit β5t","container-title":"European Journal of Immunology","page":"1278-1287","volume":"41","issue":"5","source":"PubMed","abstract":"Proteasomes are responsible for generating peptides presented by class I MHC molecules of the immune system. β5t, a recently identified proteasome component, is specifically expressed in thymic cortical epithelial cells (cTECs) and plays a pivotal role in generating an immunocompetent repertoire of class I MHC-restricted CD8(+) T cells. Here, we report that β5t is detectable in the thymus as early as E12.5 mouse embryos. We also found that β5t expression in cTECs was detectable in mice deficient for RelB or Rag2, indicating that β5t in cTECs is expressed in the absence of thymic medulla formation or thymocyte development beyond the CD4(-) CD8(-) stage. β5t expression in the embryonic thymus was not detectable in Foxn1-deficient nude mice, although

its expression was not reduced in mice deficient for both CCR7 and CCR9, in which fetal thymus colonization by leukocytes is defective. These results indicate that β5t expression in cTECs is dependent on Foxn1 but independent of thymocyte crosstalk or thymic medulla formation.","DOI":"10.1002/eji.201041375","ISSN":"1521-4141","note":"PMID: 21469133","journalAbbreviation":"Eur. J. Immunol.","language":"eng","author":[{"family":"Ripen","given":"Adiratna Mat"},{"family":"Nitta","given":"Takeshi"},{"family":"Murata","given":"Shigeo"},{"family":"Tanaka","given":"Keiji"},{"family":"Takahama","given":"Yousuke"}],"issued":{"date-parts":[["2011",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } (Box1).

[H2] The 19S regulatory particle

The RP has the crucial functions of controlling substrate recognition, unfolding and translocation into the narrow CP after opening the gates formed by the α-ring[7,20,39]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a439saa3si","properties":{"formattedCitation":"{\\rtf \\super 7,20,39\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":84,"uris":["http://zotero.org/users/4604651/items/6D759M67"],"uri":["http://zotero.org/users/4604651/items/6D759M67"],"itemData":{"id":84,"type":"article-journal","title":"The Logic of the 26S Proteasome","container-title":"Cell","page":"792-806","volume":"169","issue":"5","source":"www.cell.com","DOI":"10.1016/j.cell.2017.04.023","ISSN":"0092-8674, 1097-4172","note":"PMID: 28525752","journalAbbreviation":"Cell","language":"English","author":[{"family":"Collins","given":"Galen Andrew"},{"family":"Goldberg","given":"Alfred L."}],"issued":{"date-parts":[["2017",5,18]]}}},{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev.

Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}},{"id":68,"uris":["http://zotero.org/users/4604651/items/ZD3EP9NC"],"uri":["http://zotero.org/users/4604651/items/ZD3EP9NC"],"itemData":{"id":68,"type":"article-journal","title":"Regulated protein turnover: snapshots of the proteasome in action","container-title":"Nature Reviews Molecular Cell Biology","page":"122-133","volume":"15","issue":"2","source":"www.nature.com","abstract":"The ubiquitin proteasome system (UPS) is the main ATP-dependent protein degradation pathway in the cytosol and nucleus of eukaryotic cells. At its centre is the 26S proteasome, which degrades regulatory proteins and misfolded or damaged proteins. In a major breakthrough, several groups have determined high-resolution structures of the entire 26S proteasome particle in different nucleotide conditions and with and without substrate using cryo-electron microscopy combined with other techniques. These structures provide some surprising insights into the functional mechanism of the proteasome and will give invaluable guidance for genetic and biochemical studies of this key regulatory system.\nView full text","DOI":"10.1038/nrm3741","ISSN":"1471-0072","shortTitle":"Regulated protein turnover","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Bhattacharyya","given":"Sucharita"},{"family":"Yu","given":"Houqing"},{"family":"Mim","given":"Carsten"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2014",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The RP consists of two subcomplexes, the base and the lid. The base is composed of six distinct but related AAA^+-ATPase subunits which are referred to as regulatory particle triple-A protein 1 (Rpt1-Rpt6). These six AAA^+-ATPase proteins form a hetero-hexameric ring that directly contacts the surface of the outer α–ring of the CP. The base has four additional non-ATPase subunits: regulatory particle non-ATPase 1 (Rpn1), Rpn2, Rpn10 and Rpn13[40,41]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1dsrlp3o05","properties":{"formattedCitation":"{\\rtf \\super 40,41\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":57,"uris":["http://zotero.org/users/4604651/items/YTBPXLCK"],"uri":["http://zotero.org/users/4604651/items/YTBPXLCK"],"itemData":{"id":57,"type":"article-journal","title":"Assembly, Structure and Function of the 26S proteasome","container-title":"Trends in cell biology","page":"391-401","volume":"20","issue":"7","source":"PubMed Central","abstract":"The 26S proteasome is a large multi-protein complex involved in the regulated degradation of ubiquitinated proteins in the cell. The 26S proteasome has been shown to control an increasing number of essential biochemical mechanisms of the cellular lifecycle including DNA synthesis, repair, transcription, translation and cell signal transduction. Concurrently, it is increasingly seen that malfunction of the ubiquitin proteasome system contributes to the pathogenesis of disease. The recent identification of four molecular chaperones, in addition to five previously identified chaperones, have provided mechanistic insight into how this cellular megastructure is assembled in the cell. These data, together with new insights into the structure and function of the proteasome, provide a much better understanding of this complex protease.","DOI":"10.1016/j.tcb.2010.03.007","ISSN":"0962-8924","note":"PMID: 20427185\nPMCID: PMC2902798","journalAbbreviation":"Trends Cell Biol","author":[{"family":"Bedford","given":"Lynn"},{"family":"Paine","given":"Simon"},{"family":"Sheppard","given":"Paul W."},{"family":"Mayer","given":"R. John"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2010",7]]}}},{"id":67,"uris":["http://zotero.org/users/4604651/items/8C2R5GW6"],"uri":["http://zotero.org/users/4604651/items/8

C2R5GW6"],"itemData":{"id":67,"type":"article-journal","title":"Molecular architecture and assembly of the eukaryotic proteasome","container-title":"Annual review of biochemistry","page":"415-445","volume":"82","source":"NCBI PubMed","abstract":"The eukaryotic ubiquitin-proteasome system is responsible for most aspects of regulatory and quality-control protein degradation in cells. Its substrates, which are usually modified by polymers of ubiquitin, are ultimately degraded by the 26S proteasome. This 2.6-MDa protein complex is separated into a barrel-shaped proteolytic 20S core particle (CP) of 28 subunits capped on one or both ends by a 19S regulatory particle (RP) comprising at least 19 subunits. The RP coordinates substrate recognition, removal of substrate polyubiquitin chains, and substrate unfolding and translocation into the CP for degradation. Although many atomic structures of the CP have been determined, the RP has resisted high-resolution analysis. Recently, however, a combination of cryo-electron microscopy, biochemical analysis, and crystal structure determination of several RP subunits has yielded a near-atomic-resolution view of much of the complex. Major new insights into chaperone-assisted proteasome assembly have also recently emerged. Here we review these novel findings.","DOI":"10.1146/annurev-biochem-060410-150257","ISSN":"1545-4509","note":"PMID: 23495936 \nPMCID: PMC3827779","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Tomko","given":"Robert J"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . The lid is composed of nine non-ATPase subunits: Rpn3, Rpn5-9, Rpn11-12 and Sem1. Rpn10 was thought to be important for base-lid association[42]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ok182g3a5","properties":{"formattedCitation":"{\\rtf \\super 42\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":66,"uris":["http://zotero.org/users/4604651/items/SWCI2KBY"],"uri":["http://zotero.org/users/4604651/items/SWCI2KBY"],"itemData":{"id":66,"type":"article-journal","title":"A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome and eIF3","container-title":"Cell","page":"615-623","volume":"94","issue":"5","source":"PubMed","abstract":"The proteasome consists of a 20S proteolytic core particle (CP) and a 19S regulatory particle (RP), which selects ubiquitinated substrates for translocation into the CP. An eight-subunit subcomplex of the RP, the lid, can be dissociated from proteasomes prepared from a deletion mutant for Rpn10, an RP subunit. A second subcomplex, the base, contains all six proteasomal ATPases and links the RP to the CP. The base is sufficient to activate the CP for degradation of peptides or a nonubiquitinated protein, whereas the lid is required for ubiquitin-dependent degradation. By electron microscopy, the base and the lid correspond to the proximal and distal masses of the RP, respectively. The lid subunits share sequence motifs with components of the COP9/signalosome complex and eIF3, suggesting that these functionally diverse particles have a common evolutionary ancestry.","ISSN":"0092-8674","note":"PMID: 9741626","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Glickman","given":"M. H."},{"family":"Rubin","given":"D. M."},{"family":"Coux","given":"O."},{"family":"Wefes","given":"I."},{"family":"Pfeifer","given":"G."},{"family":"Cjeka","given":"Z."},{"family":"Baumeister","given":"W."},{"family":"Fried","given":"V. A."},{"family":"Finley","given":"D."}],"issued":{"date-parts":[["1998",9,4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . However, recent cryo-EM structures revealed that other base subunits interact with the lid{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"afvjufcqh6","properties":{"formattedCitation":"{\\rtf \\super

22,43\\uc0\\u8211{}45\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}},{"id":493,"uris":["http://zotero.org/users/4604651/items/SHIRM54M"],"uri":["http://zotero.org/users/4604651/items/SHIRM54M"],"itemData":{"id":493,"type":"article-journal","title":"Atomic structure of the 26S proteasome lid reveals the mechanism of deubiquitinase inhibition","container-title":"eLife","page":"e13027","volume":"5","source":"elifesciences.org","abstract":"Within the isolated lid sub-complex of the proteasome, a finely tuned network of interactions maintains the deubiquitinase in an inhibited conformation; dramatic rearrangements of the lid subunits upon incorporation into the holoenzyme lead to the deubiquitinase's activation.","DOI":"10.7554/eLife.13027","ISSN":"2050-084X","journalAbbreviation":"eLife Sciences","language":"en","author":[{"family":"Dambacher","given":"Corey M."},{"family":"Worden","given":"Evan J."},{"family":"Jr","given":"Mark A.

Herzik"},{"family":"Martin","given":"Andreas"},{"family":"Lander","given":"Gabriel C."}],"issued":{"date-parts":[["2016",1,8]]}},{"id":507,"uris":["http://zotero.org/users/4604651/items/FZAL836K"],"uri":["http://zotero.org/users/4604651/items/FZAL836K"],"itemData":{"id":507,"type":"article-journal","title":"Structure of the human 26S proteasome at a resolution of 3.9 Å","container-title":"Proceedings of the National Academy of Sciences","page":"7816-7821","volume":"113","issue":"28","source":"www.pnas.org","abstract":"Protein degradation in eukaryotic cells is performed by the Ubiquitin-Proteasome System (UPS). The 26S proteasome holocomplex consists of a core particle (CP) that proteolytically degrades polyubiquitylated proteins, and a regulatory particle (RP) containing the AAA-ATPase module. This module controls access to the proteolytic chamber inside the CP and is surrounded by non-ATPase subunits (Rpns) that recognize substrates and deubiquitylate them before unfolding and degradation. The architecture of the 26S holocomplex is highly conserved between yeast and humans. The structure of the human 26S holocomplex described here reveals previously unidentified features of the AAA-ATPase heterohexamer. One subunit, Rpt6, has ADP bound, whereas the other five have ATP in their binding pockets. Rpt6 is structurally distinct from the other five Rpt subunits, most notably in its pore loop region. For Rpns, the map reveals two main, previously undetected, features: the C terminus of Rpn3 protrudes into the mouth of the ATPase ring; and Rpn1 and Rpn2, the largest proteasome subunits, are linked by an extended connection. The structural features of the 26S proteasome observed in this study are likely to be important for coordinating the proteasomal subunits during substrate processing.","DOI":"10.1073/pnas.1608050113","ISSN":"0027-8424, 1091-6490","note":"PMID: 27342858","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Schweitzer","given":"Andreas"},{"family":"Aufderheide","given":"Antje"},{"family":"Rudack","given":"Till"},{"family":"Beck","given":"Florian"},{"family":"Pfeifer","given":"Günter"},{"family":"Plitzko","given":"Jürgen M."},{"family":"Sakata","given":"Eri"},{"family":"Schulten","given":"Klaus"},{"family":"Förster","given":"Friedrich"},{"family":"Baumeister","given":"Wolfgang"}],"issued":{"date-parts":[["2016",7,12]]}},"locator":"9"},{"id":526,"uris":["http://zotero.org/users/4604651/items/VHIGJWYQ"],"uri":["http://zotero.org/users/4604651/items/VHIGJWYQ"],"itemData":{"id":526,"type":"article-journal","title":"Molecular model of the human 26S proteasome","container-title":"Molecular Cell","page":"54-66","volume":"46","issue":"1","source":"PubMed","abstract":"The 26S proteasome plays a

fundamental role in eukaryotic homeostasis by undertaking the highly controlled degradation of a wide range of proteins, including key cellular regulators such as those controlling cell-cycle progression and apoptosis. Here we report the structure of the human 26S proteasome determined by cryo-electron microscopy and single-particle analysis, with secondary structure elements identified both in the 20S proteolytic core region and in the 19S regulatory particle. We have used this information together with crystal structures, homology models, and other biochemical information to construct a molecular model of the complete 26S proteasome. This model allows for a detailed description of the 20S core within the 26S proteasome and redefines the overall assignment of subunits within the 19S regulatory particle. The information presented here provides a strong basis for a mechanistic understanding of the 26S proteasome.","DOI":"10.1016/j.molcel.2012.03.026","ISSN":"1097-4164","note":"PMID: 22500737","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Fonseca","given":"Paula C. A.","non-dropping-particle":"da"},{"family":"He","given":"Jun"},{"family":"Morris","given":"Edward P."}],"issued":{"date-parts":[["2012",4,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, indicating that base-lid association mostly relies on the lid subunits Rpn3, Rpn7, Rpn8 and Rpn11 that make extensive contacts with base subunits including Rpt3/Rpt6 pair and Rpn2[22,43–45]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1uippv4hu7","properties":{"formattedCitation":"{\\rtf \\super 22,43\\uc0\\u8211{}45\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":493,"uris":["http://zotero.org/users/4604651/items/SHIRM54M"],"uri":["http://zotero.org/users/4604651/items/SHIRM54M"],"itemData":{"id":493,"type":"article-journal","title":"Atomic structure of the 26S proteasome lid reveals the mechanism of deubiquitinase inhibition","container-title":"eLife","page":"e13027","volume":"5","source":"elifesciences.org","abstract":"Within the isolated lid sub-complex of the proteasome, a finely tuned network of interactions maintains the deubiquitinase in an inhibited conformation; dramatic rearrangements of the lid subunits upon incorporation into the holoenzyme lead to the deubiquitinase’s activation.","DOI":"10.7554/eLife.13027","ISSN":"2050-084X","journalAbbreviation":"eLife Sciences","language":"en","author":[{"family":"Dambacher","given":"Corey M."},{"family":"Worden","given":"Evan J."},{"family":"Jr","given":"Mark A. Herzik"},{"family":"Martin","given":"Andreas"},{"family":"Lander","given":"Gabriel C."}],"issued":{"date-

parts":[["2016",1,8]]}},{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}},{"id":526,"uris":["http://zotero.org/users/4604651/items/VHIGJWYQ"],"uri":["http://zotero.org/users/4604651/items/VHIGJWYQ"],"itemData":{"id":526,"type":"article-journal","title":"Molecular model of the human 26S proteasome","container-title":"Molecular Cell","page":"54-66","volume":"46","issue":"1","source":"PubMed","abstract":"The 26S proteasome plays a fundamental role in eukaryotic homeostasis by undertaking the highly controlled degradation of a wide range of proteins, including key cellular regulators such as those controlling cell-cycle progression and apoptosis. Here we report the structure of the human 26S proteasome determined by cryo-electron microscopy and single-particle analysis, with secondary structure elements identified both in the 20S proteolytic core region and in the 19S regulatory particle. We have used this information together with crystal structures, homology models, and other biochemical information to construct a molecular model of the complete 26S proteasome. This

model allows for a detailed description of the 20S core within the 26S proteasome and redefines the overall assignment of subunits within the 19S regulatory particle. The information presented here provides a strong basis for a mechanistic understanding of the 26S proteasome.","DOI":"10.1016/j.molcel.2012.03.026","ISSN":"1097-4164","note":"PMID: 22500737","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Fonseca","given":"Paula C. A.","non-dropping-particle":"da"},{"family":"He","given":"Jun"},{"family":"Morris","given":"Edward P."}],"issued":{"date-parts":[["2012",4,13]]}},{"id":507,"uris":["http://zotero.org/users/4604651/items/FZAL836K"],"uri":["http://zotero.org/users/4604651/items/FZAL836K"],"itemData":{"id":507,"type":"article-journal","title":"Structure of the human 26S proteasome at a resolution of 3.9 Å","container-title":"Proceedings of the National Academy of Sciences","page":"7816-7821","volume":"113","issue":"28","source":"www.pnas.org","abstract":"Protein degradation in eukaryotic cells is performed by the Ubiquitin-Proteasome System (UPS). The 26S proteasome holocomplex consists of a core particle (CP) that proteolytically degrades polyubiquitylated proteins, and a regulatory particle (RP) containing the AAA-ATPase module. This module controls access to the proteolytic chamber inside the CP and is surrounded by non-ATPase subunits (Rpns) that recognize substrates and deubiquitylate them before unfolding and degradation. The architecture of the 26S holocomplex is highly conserved between yeast and humans. The structure of the human 26S holocomplex described here reveals previously unidentified features of the AAA-ATPase heterohexamer. One subunit, Rpt6, has ADP bound, whereas the other five have ATP in their binding pockets. Rpt6 is structurally distinct from the other five Rpt subunits, most notably in its pore loop region. For Rpns, the map reveals two main, previously undetected, features: the C terminus of Rpn3 protrudes into the mouth of the ATPase ring; and Rpn1 and Rpn2, the largest proteasome subunits, are linked by an extended connection. The structural features of the 26S proteasome observed in this study are likely to be important for coordinating the proteasomal subunits during substrate processing.","DOI":"10.1073/pnas.1608050113","ISSN":"0027-8424, 1091-6490","note":"PMID: 27342858","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Schweitzer","given":"Andreas"},{"family":"Aufderheide","given":"Antje"},{"family":"Rudack","given":"Till"},{"family":"Beck","given":"Florian"},{"family":"Pfeifer","given":"Günter"},{"family":"Plitzko","given":"Jürgen M."},{"family":"Sakata","given":"Eri"},{"family":"Schulten","given":"Klaus"},{"family":"F

örster","given":"Friedrich"},{"family":"Baumeister","given":"Wolfgang"}],"issued":{"date-parts":[["2016",7,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**.

[H1] Mechanisms of core particle assembly

CP assembly is a complex process that can be divided in three different steps in eukaryotes: α–ring formation, β–ring formation and half-proteasome dimerization and maturation (FIG. 2). All these steps are assisted by five proteasome assembly chaperones named proteasome biogenesis-associated 1 (Pba1)-Pba4 in yeast (proteasome assembly chaperone 1 (PAC1)-PAC4 in human) and underpinning maturation of proteasome 1 (Ump1) (proteasome maturation protein (POMP) in human)[21,31,46]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aolejqhi11","properties":{"formattedCitation":"{\\rtf \\super 21,31,46\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":76,"uris":["http://zotero.org/users/4604651/items/D2R2QDAY"],"uri":["http://zotero.org/users/4604651/items/D2R2QDAY"],"itemData":{"id":76,"type":"article-journal","title":"Molecular mechanisms of proteasome assembly","container-title":"Nature Reviews Molecular Cell Biology","page":"104-115","volume":"10","issue":"2","source":"www.nature.com","abstract":"The 26S proteasome is a highly conserved protein degradation machine that consists of the 20S proteasome and 19S regulatory particles, which include 14 and 19 different polypeptides, respectively. How the proteasome components are assembled is a fundamental question towards understanding the process of protein degradation and its functions in diverse biological processes. Several proteasome-dedicated chaperones are involved in the efficient and correct assembly of the 20S proteasome. These chaperones help the initiation and progression of the assembly process by transiently associating with proteasome precursors. By contrast, little is known about the assembly of the 19S regulatory particles, but several hints have emerged.","DOI":"10.1038/nrm2630","ISSN":"1471-0072","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Murata","given":"Shigeo"},{"family":"Yashiroda","given":"Hideki"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",2]]}},{"id":72,"uris":["http://zotero.org/users/4604651/items/JK6UXJIS"],"uri":["http://zotero.org/users/4604651/items/JK6UXJIS"],"itemData":{"id":72,"type":"article-journal","title":"Assembly of the 20S proteasome","container-title":"Biochimica Et Biophysica Acta","page":"2-12","volume":"1843","issue":"1","source":"PubMed","abstract":"The proteasome is a cellular protease responsible for the selective degradation of the majority of the intracellular proteome. It recognizes, unfolds, and cleaves proteins that are destined for removal, usually by prior attachment to polymers of ubiquitin. This macromolecular machine is composed of two subcomplexes, the 19S regulatory particle (RP) and the 20S core particle (CP), which together contain at least 33 different and precisely positioned subunits. How these subunits assemble into functional complexes is an area of active exploration. Here we describe the current status of studies on the assembly of the 20S proteasome (CP). The 28-subunit CP is found in all three domains of life and its cylindrical stack of four heptameric rings is well conserved. Though several CP subunits possess self-assembly properties, a consistent theme in recent years has been the need for dedicated assembly chaperones that promote on-pathway assembly. To date, a minimum of three accessory factors have been implicated in aiding the construction

of the 20S proteasome. These chaperones interact with different assembling proteasomal precursors and usher subunits into specific slots in the growing structure. This review will focus largely on chaperone-dependent CP assembly and its regulation. This article is part of a Special Issue entitled: Ubiquitin-Proteasome System. Guest Editors: Thomas Sommer and Dieter H. Wolf.","DOI":"10.1016/j.bbamcr.2013.03.008","ISSN":"0006-3002","note":"PMID: 23507199\nPMCID: PMC3752329","journalAbbreviation":"Biochim. Biophys. Acta","language":"eng","author":[{"family":"Kunjappu","given":"Mary J."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2014",1]]}}},{"id":65,"uris":["http://zotero.org/users/4604651/items/QF6S3CIY"],"uri":["http://zotero.org/users/4604651/items/QF6S3CIY"],"itemData":{"id":65,"type":"article-journal","title":"Characterisation of the newly identified human Ump1 homologue POMP and analysis of LMP7(β5i) incorporation into 20 S proteasomes11Edited by R. Huber","container-title":"Journal of Molecular Biology","page":"1-9","volume":"301","issue":"1","source":"ScienceDirect","abstract":"Biogenesis of mammalian 20 S proteasomes occurs via precursor complexes containing α and unprocessed β subunits. A human homologue of the yeast proteasome maturation factor Ump1 was identified in 2D gels of 16 S precursor preparations and designated as POMP (proteasome maturation protein). We show that POMP is detected only in precursor fractions and not in fractions containing mature 20 S proteasome. Northern blot experiments revealed that expression of POMP is induced after treatment with interferon γ. To analyse the role of the β5 propeptide for proper maturation and incorporation of the β5 subunit into the complex, human T2 cells, which highly express derivatives of the β5i subunit (LMP7), were studied. In contrast to yeast, the presence of the β5 propeptide is not essential for incorporation of LMP7 into the proteasome complex. Mutated LMP7 subunits either carrying the prosequence of β2i (LMP2) or containing a mutation in the active threonine site are incorporated like wild-type LMP7, while a LMP7 derivative lacking the prosequence completely is incorporated to a lesser extent. Although the absence of the prosequence does not affect incorporation of LMP7, its deletion leads to delayed proteasome maturation and thereby to an accumulation of precursor complexes. As a result of the precursor accumulation, an increased amount of the POMP protein can be detected in these cells.","DOI":"10.1006/jmbi.2000.3959","ISSN":"0022-2836","journalAbbreviation":"Journal of Molecular Biology","author":[{"family":"Witt","given":"Elke"},{"family":"Zantopf","given":"Daniela"},{"family":"Schmidt","given":"Marion"},{"family":"Kraft","given":"Regine"},{"family":"Kloetzel","given":"Peter-M"},{"family":"Krüger","given":"Elke"}],"issued":{"date-parts":[["2000",8,4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] α–ring formation

Among the five proteasome assembly chaperones, four are dedicated to the assembly of the α–ring, suggesting that the arrangement of the seven different α–subunits into a heptameric ring is a crucial step in CP assembly. These four assembly chaperones form two heterodimers, Pba1-Pba2[47]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mp4g4bbt9","properties":{"formattedCitation":"{\\rtf \\super 47\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":64,"uris":["http://zotero.org/users/4604651/items/JVV4QB2Z"],"uri":["http://zotero.org/users/4604651/items/JVV4QB2Z"],"itemData":{"id":64,"type":"article-journal","title":"A heterodimeric complex that promotes the assembly of mammalian 20S proteasomes","container-title":"Nature","page":"1381-1385","volume":"437","issue":"7063","source":"PubMed","abstract":"The 26S proteasome is a multisubunit protease responsible for

regulated proteolysis in eukaryotic cells. It comprises one catalytic 20S proteasome and two axially positioned 19S regulatory complexes. The 20S proteasome is composed of 28 subunits arranged in a cylindrical particle as four heteroheptameric rings, alpha1-7beta1-7beta1-7alpha1-7 (refs 4, 5), but the mechanism responsible for the assembly of such a complex structure remains elusive. Here we report two chaperones, designated proteasome assembling chaperone-1 (PAC1) and PAC2, that are involved in the maturation of mammalian 20S proteasomes. PAC1 and PAC2 associate as heterodimers with proteasome precursors and are degraded after formation of the 20S proteasome is completed. Overexpression of PAC1 or PAC2 accelerates the formation of precursor proteasomes, whereas knockdown by short interfering RNA impairs it, resulting in poor maturation of 20S proteasomes. Furthermore, the PAC complex provides a scaffold for alpha-ring formation and keeps the alpha-rings competent for the subsequent formation of half-proteasomes. Thus, our results identify a mechanism for the correct assembly of 20S proteasomes.","DOI":"10.1038/nature04106","ISSN":"1476-4687","note":"PMID: 16251969","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Hirano","given":"Yuko"},{"family":"Hendil","given":"Klavs B."},{"family":"Yashiroda","given":"Hideki"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Nagane","given":"Ryoichi"},{"family":"Hioki","given":"Yusaku"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2005",10,27]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } and Pba3-Pba4[48,49]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1oi80f75st","properties":{"formattedCitation":"{\\rtf \\super 48,49\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":63,"uris":["http://zotero.org/users/4604651/items/DD59CFJ9"],"uri":["http://zotero.org/users/4604651/items/DD59CFJ9"],"itemData":{"id":63,"type":"article-journal","title":"Cooperation of Multiple Chaperones Required for the Assembly of Mammalian 20S Proteasomes","container-title":"Molecular Cell","page":"977-984","volume":"24","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe 20S proteasome is a catalytic core of the 26S proteasome, a central enzyme in the degradation of ubiquitin-conjugated proteins. It is composed of 14 distinct gene products that form four stacked rings of seven subunits each, α1–7β1–7β1–7α1–7. It is reported that the biogenesis of mammalian 20S proteasomes is assisted by proteasome-specific chaperones, named PAC1, PAC2, and hUmp1, but the details are still unknown. Here, we report the identification of a chaperone, designated PAC3, as a component of α rings. Although it can intrinsically bind directly to both α and β subunits, PAC3 dissociates before the formation of half-proteasomes, a process coupled with the recruitment of β subunits and hUmp1. Knockdown of PAC3 impaired α ring formation. Further, PAC1/2/3 triple knockdown resulted in the accumulation of disorganized half-proteasomes that are incompetent for dimerization. Our results describe a cooperative system of multiple chaperones involved in the correct assembly of mammalian 20S proteasomes.","DOI":"10.1016/j.molcel.2006.11.015","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Hirano","given":"Yuko"},{"family":"Hayashi","given":"Hidemi"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Hendil","given":"Klavs B."},{"family":"Niwa","given":"Shin-ichiro"},{"family":"Kishimoto","given":"Toshihiko"},{"family":"Kasahara","given":"Masanori"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2006",12,28]]}}},{"id":62,"uris":["http://zotero.org/users/4604651/items/4PC9UAUZ"],"uri":["http://zotero.org/users/4604651/items/4PC9UAUZ"],"itemData":{"id":62,"type":"article-journal","title":"20S proteasome assembly is orchestrated by two distinct pairs of chaperones in yeast and in mammals","container-title":"Molecular Cell","page":"660-

674","volume":"27","issue":"4","source":"PubMed","abstract":"The 20S proteasome is the catalytic core of the 26S proteasome, a central enzyme in the ubiquitin-proteasome system. Its assembly proceeds in a multistep and orderly fashion. Ump1 is the only well-described chaperone dedicated to the assembly of the 20S proteasome in yeast. Here, we report a phenotype related to the DNA damage response that allowed us to isolate four other chaperones of yeast 20S proteasomes, which we named Poc1-Poc4. Poc1/2 and Poc3/4 form two pairs working at different stages in early 20S proteasome assembly. We identify PAC1, PAC2, the recently described PAC3, and an uncharacterized protein that we named PAC4 as functional mammalian homologs of yeast Poc factors. Hence, in yeast as in mammals, proteasome assembly is orchestrated by two pairs of chaperones acting upstream of the half-proteasome maturase Ump1. Our findings provide evidence for a remarkable conservation of a pairwise chaperone-assisted proteasome assembly throughout evolution.","DOI":"10.1016/j.molcel.2007.06.025","ISSN":"1097-2765","note":"PMID: 17707236","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Le Tallec","given":"Benoît"},{"family":"Barrault","given":"Marie-Bénédicte"},{"family":"Courbeyrette","given":"Régis"},{"family":"Guérois","given":"Raphaël"},{"family":"Marsolier-Kergoat","given":"Marie-Claude"},{"family":"Peyroche","given":"Anne"}],"issued":{"date-parts":[["2007",8,17]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . The Pba1-Pba2 complex ensures the appropriate incorporation of α5 and α6 subunits of the α–ring and has been shown to prevent premature binding of the RP to the α–ring[50,51]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a6a7re428q","properties":{"formattedCitation":"{\\rtf \\super 50,51\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":422,"uris":["http://zotero.org/users/4604651/items/BC3FG8WL"],"uri":["http://zotero.org/users/4604651/items/BC3FG8WL"],"itemData":{"id":422,"type":"article-journal","title":"Maturation of the proteasome core particle induces an affinity switch that controls regulatory particle association","container-title":"Nature Communications","page":"6384","volume":"6","source":"PubMed","abstract":"Proteasome assembly is a complex process, requiring 66 subunits distributed over several subcomplexes to associate in a coordinated fashion. Ten proteasome-specific chaperones have been identified that assist in this process. For two of these, the Pba1-Pba2 dimer, it is well established that they only bind immature core particles (CPs) in vivo. In contrast, the regulatory particle (RP) utilizes the same binding surface but only interacts with the mature CP in vivo. It is unclear how these binding events are regulated. Here, we show that Pba1-Pba2 binds tightly to the immature CP, preventing RP binding. Changes in the CP that occur on maturation significantly reduce its affinity for Pba1-Pba2, enabling the RP to displace the chaperone. Mathematical modelling indicates that this 'affinity switch' mechanism has likely evolved to improve assembly efficiency by preventing the accumulation of stable, non-productive intermediates. Our work thus provides mechanistic insights into a crucial step in proteasome

biogenesis.","DOI":"10.1038/ncomms7384","ISSN":"2041-1723","note":"PMID: 25812915\nPMCID: PMC4380239","journalAbbreviation":"Nat Commun","language":"eng","author":[{"family":"Wani","given":"Prashant S."},{"family":"Rowland","given":"Michael A."},{"family":"Ondracek","given":"Alex"},{"family":"Deeds","given":"Eric J."},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2015",3,16]]}},{"id":424,"uris":["http://zotero.org/users/4604651/items/5WLRBJRL"],"uri":["http://zotero.org/users/4604651/items/5WLRBJRL"],"itemData":{"id":424,"type":"article-journal","title":"Structure of a Proteasome Pba1-Pba2 Complex IMPLICATIONS FOR PROTEASOME ASSEMBLY, ACTIVATION, AND BIOLOGICAL FUNCTION","container-title":"Journal of Biological Chemistry","page":"37371-37382","volume":"287","issue":"44","source":"www.jbc.org","abstract":"The 20S proteasome is an essential, 28-subunit protease that sequesters proteolytic sites within a central chamber, thereby repressing substrate degradation until proteasome activators open the entrance/exit gate. Two established activators, Blm10 and PAN/19S, induce gate opening by binding to the pockets between proteasome α-subunits using C-terminal HbYX (hydrophobic-tyrosine-any residue) motifs. Equivalent HbYX motifs have been identified in Pba1 and Pba2, which function in proteasome assembly. Here, we demonstrate that Pba1-Pba2 proteins form a stable heterodimer that utilizes its HbYX motifs to bind mature 20S proteasomes in vitro and that the Pba1-Pba2 HbYX motifs are important for a physiological function of proteasomes, the maintenance of mitochondrial function. Other factors that contribute to proteasome assembly or function also act in the maintenance of mitochondrial function and display complex genetic interactions with one another, possibly revealing an unexpected pathway of mitochondrial regulation involving the Pba1-Pba2 proteasome interaction. Our determination of a proteasome Pba1-Pba2 crystal structure reveals a Pba1 HbYX interaction that is superimposable with those of known activators, a Pba2 HbYX interaction that is different from those reported previously, and a gate structure that is disrupted but not sufficiently open to allow entry of even small peptides. These findings extend understanding of proteasome interactions with HbYX motifs and suggest multiple roles for Pba1-Pba2 interactions throughout proteasome assembly and function.","DOI":"10.1074/jbc.M112.367003","ISSN":"0021-9258, 1083-351X","note":"PMID: 22930756","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Kish-

Trier","given":"Erik"},{"family":"Ferrell","given":"Katherine"},{"family":"Petersen","given":"Charisse
N."},{"family":"Robinson","given":"Howard"},{"family":"Myszka","given":"David
G."},{"family":"Eckert","given":"Debra
M."},{"family":"Formosa","given":"Tim"},{"family":"Hill","given":"Christopher
P."}],"issued":{"date-parts":[["2012",10,26]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (FIG. 2). In human, in addition to preventing premature association with the RP, the binding of PAC1-PAC2 heterodimer to the α–ring intermediate also prevents aberrant dimerization of α–rings[47,50–52]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ak5972e50n","properties":{"formattedCitation":"{\\rtf \\super 47,50\\uc0\\u8211{}52\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":424,"uris":["http://zotero.org/users/4604651/items/5WLRBJRL"],"uri":["http://zotero.org/users/4604651/items/5WLRBJRL"],"itemData":{"id":424,"type":"article-journal","title":"Structure of a Proteasome Pba1-Pba2 Complex IMPLICATIONS FOR PROTEASOME ASSEMBLY, ACTIVATION, AND BIOLOGICAL FUNCTION","container-title":"Journal of Biological Chemistry","page":"37371-37382","volume":"287","issue":"44","source":"www.jbc.org","abstract":"The 20S proteasome is an essential, 28-subunit protease that sequesters proteolytic sites within a central chamber, thereby repressing substrate degradation until proteasome activators open the entrance/exit gate. Two established activators, Blm10 and PAN/19S, induce gate opening by binding to the pockets between proteasome α-subunits using C-terminal HbYX (hydrophobic-tyrosine-any residue) motifs. Equivalent HbYX motifs have been identified in Pba1 and Pba2, which function in proteasome assembly. Here, we demonstrate that Pba1-Pba2 proteins form a stable heterodimer that utilizes its HbYX motifs to bind mature 20S proteasomes in vitro and that the Pba1-Pba2 HbYX motifs are important for a physiological function of proteasomes, the maintenance of mitochondrial function. Other factors that contribute to proteasome assembly or function also act in the maintenance of mitochondrial function and display complex genetic interactions with one another, possibly revealing an unexpected pathway of mitochondrial regulation involving the Pba1-Pba2 proteasome interaction. Our determination of a proteasome Pba1-Pba2 crystal structure reveals a Pba1 HbYX interaction that is superimposable with those of known activators, a Pba2 HbYX interaction that is different from those reported previously, and a gate structure that is disrupted but not sufficiently open to allow entry of even small peptides. These findings extend understanding of proteasome interactions with HbYX motifs and suggest multiple roles for Pba1-Pba2 interactions throughout proteasome assembly and function.","DOI":"10.1074/jbc.M112.367003","ISSN":"0021-9258, 1083-351X","note":"PMID: 22930756","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Kish-Trier","given":"Erik"},{"family":"Ferrell","given":"Katherine"},{"family":"Petersen","given":"Charisse N."},{"family":"Robinson","given":"Howard"},{"family":"Myszka","given":"David G."},{"family":"Eckert","given":"Debra M."},{"family":"Formosa","given":"Tim"},{"family":"Hill","given":"Christopher P."}],"issued":{"date-parts":[["2012",10,26]]}}},{"id":422,"uris":["http://zotero.org/users/4604651/items/BC3FG8WL"],"uri":["http://zotero.org/users/4604651/items/BC3FG8WL"],"itemData":{"id":422,"type":"article-journal","title":"Maturation of the proteasome core particle induces an affinity switch that controls regulatory particle association","container-title":"Nature

Communications","page":"6384","volume":"6","source":"PubMed","abstract":"Proteasome assembly is a complex process, requiring 66 subunits distributed over several subcomplexes to associate in a coordinated fashion. Ten proteasome-specific chaperones have been identified that assist in this process. For two of these, the Pba1-Pba2 dimer, it is well established that they only bind immature core particles (CPs) in vivo. In contrast, the regulatory particle (RP) utilizes the same binding surface but only interacts with the mature CP in vivo. It is unclear how these binding events are regulated. Here, we show that Pba1-Pba2 binds tightly to the immature CP, preventing RP binding. Changes in the CP that occur on maturation significantly reduce its affinity for Pba1-Pba2, enabling the RP to displace the chaperone. Mathematical modelling indicates that this 'affinity switch' mechanism has likely evolved to improve assembly efficiency by preventing the accumulation of stable, non-productive intermediates. Our work thus provides mechanistic insights into a crucial step in proteasome biogenesis.","DOI":"10.1038/ncomms7384","ISSN":"2041-1723","note":"PMID: 25812915\nPMCID: PMC4380239","journalAbbreviation":"Nat Commun","language":"eng","author":[{"family":"Wani","given":"Prashant S."},{"family":"Rowland","given":"Michael A."},{"family":"Ondracek","given":"Alex"},{"family":"Deeds","given":"Eric J."},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2015",3,16]]}}},{"id":64,"uris":["http://zotero.org/users/4604651/items/JVV4QB2Z"],"uri":["http://zotero.org/users/4604651/items/JVV4QB2Z"],"itemData":{"id":64,"type":"article-journal","title":"A heterodimeric complex that promotes the assembly of mammalian 20S proteasomes","container-title":"Nature","page":"1381-1385","volume":"437","issue":"7063","source":"PubMed","abstract":"The 26S proteasome is a multisubunit protease responsible for regulated proteolysis in eukaryotic cells. It comprises one catalytic 20S proteasome and two axially positioned 19S regulatory complexes. The 20S proteasome is composed of 28 subunits arranged in a cylindrical particle as four heteroheptameric rings, alpha1-7beta1-7beta1-7alpha1-7 (refs 4, 5), but the mechanism responsible for the assembly of such a complex structure remains elusive. Here we report two chaperones, designated proteasome assembling chaperone-1 (PAC1) and PAC2, that are involved in the maturation of mammalian 20S proteasomes. PAC1 and PAC2 associate as heterodimers with proteasome precursors and are degraded after formation of the 20S proteasome is completed. Overexpression of PAC1 or PAC2 accelerates the formation of precursor proteasomes, whereas knockdown by short interfering RNA impairs it, resulting in poor maturation of 20S proteasomes. Furthermore, the PAC complex provides a scaffold for alpha-ring formation and keeps the alpha-rings competent for the subsequent formation of half-proteasomes. Thus, our results identify a mechanism for the correct assembly of 20S proteasomes.","DOI":"10.1038/nature04106","ISSN":"1476-4687","note":"PMID: 16251969","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Hirano","given":"Yuko"},{"family":"Hendil","given":"Klavs B."},{"family":"Yashiroda","given":"Hideki"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Nagane","given":"Ryoichi"},{"family":"Hioki","given":"Yusaku"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2005",10,27]]}}},{"id":56,"uris":["http://zotero.org/users/4604651/items/CHJR4V3C"],"uri":["http://zotero.org/users/4604651/items/CHJR4V3C"],"itemData":{"id":56,"type":"article-journal","title":"Structure of a Proteasome Pba1-Pba2 Complex","container-title":"The Journal of Biological Chemistry","page":"37371-37382","volume":"287","issue":"44","source":"PubMed Central","abstract":"Background: Pba1-Pba2 facilitates proteasome α-ring assembly., Results: Pba1-Pba2 binds mature proteasomes using C-terminal motifs and sequesters α-subunit N termini. It does not activate and is not degraded by isolated 20S proteasomes., Conclusion: Pba1-Pba2 is important for proteasome-

dependent maintenance of mitochondrial function. The structure is consistent with multiple roles in proteasome assembly., Significance: Models of proteasome assembly and Pba1-Pba2 proteasome function are advanced., The 20S proteasome is an essential, 28-subunit protease that sequesters proteolytic sites within a central chamber, thereby repressing substrate degradation until proteasome activators open the entrance/exit gate. Two established activators, Blm10 and PAN/19S, induce gate opening by binding to the pockets between proteasome α-subunits using C-terminal HbYX (hydrophobic-tyrosine-any residue) motifs. Equivalent HbYX motifs have been identified in Pba1 and Pba2, which function in proteasome assembly. Here, we demonstrate that Pba1-Pba2 proteins form a stable heterodimer that utilizes its HbYX motifs to bind mature 20S proteasomes in vitro and that the Pba1-Pba2 HbYX motifs are important for a physiological function of proteasomes, the maintenance of mitochondrial function. Other factors that contribute to proteasome assembly or function also act in the maintenance of mitochondrial function and display complex genetic interactions with one another, possibly revealing an unexpected pathway of mitochondrial regulation involving the Pba1-Pba2 proteasome interaction. Our determination of a proteasome Pba1-Pba2 crystal structure reveals a Pba1 HbYX interaction that is superimposable with those of known activators, a Pba2 HbYX interaction that is different from those reported previously, and a gate structure that is disrupted but not sufficiently open to allow entry of even small peptides. These findings extend understanding of proteasome interactions with HbYX motifs and suggest multiple roles for Pba1-Pba2 interactions throughout proteasome assembly and function.","DOI":"10.1074/jbc.M112.367003","ISSN":"0021-9258","note":"PMID: 22930756\nPMCID: PMC3481334","journalAbbreviation":"J Biol Chem","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Kish-Trier","given":"Erik"},{"family":"Ferrell","given":"Katherine"},{"family":"Petersen","given":"Charisse N."},{"family":"Robinson","given":"Howard"},{"family":"Myszka","given":"David G."},{"family":"Eckert","given":"Debra M."},{"family":"Formosa","given":"Tim"},{"family":"Hill","given":"Christopher P."}],"issued":{"date-parts":[["2012",10,26]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. In yeast, the Pba3-Pba4 complex interacts with the α5 subunit of the intermediate to control the correct integration of α3 and α4 subunits. The deletion of Pba3 or Pba4 thereby causes the accumulation of proteasome intermediates and produces diverse aberrant proteasomes including proteasomes devoid of α4 and proteasomes harbouring a second copy of α4 instead of α3 (referred to as α4-α4 proteasome)[53]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ehn671s2","properties":{"formattedCitation":"{\\rtf \\super 53\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":61,"uris":["http://zotero.org/users/4604651/items/ANLBE8XP"],"uri":["http://zotero.org/users/4604651/items/ANLBE8XP"],"itemData":{"id":61,"type":"article-journal","title":"A multimeric assembly factor controls the formation of alternative 20S proteasomes","container-title":"Nature Structural & Molecular Biology","page":"237-244","volume":"15","issue":"3","source":"www.nature.com","abstract":"The proteasome is the central regulatory protease of eukaryotic cells. Heteroheptameric -subunit and -subunit rings stack to form the 20S proteasome, which associates with a 19S regulatory particle (RP). Here we show that two yeast proteins, Pba3 and Pba4, form a previously unidentified 20S proteasome–assembly chaperone. Pba3–Pba4 interacts genetically and physically with specific proteasomal subunits, and loss of Pba3–Pba4 causes both a reduction and a remodeling of cellular proteasomes. Notably, mutant cells accumulate proteasomes in which a second copy of the 4 subunit replaces 3. 20S proteasome–assembly defects also are associated with altered RP assembly; this unexpected result suggests that the 20S proteasome can function as an RP-assembly

factor in vivo. Our data demonstrate that Pba3–Pba4 orchestrates formation of a specific type of proteasome, the first example of a trans-acting factor that controls assembly of alternative proteasomal complexes.","DOI":"10.1038/nsmb.1389","ISSN":"1545-9993","journalAbbreviation":"Nat Struct Mol Biol","language":"en","author":[{"family":"Kusmierczyk","given":"Andrew R."},{"family":"Kunjappu","given":"Mary J."},{"family":"Funakoshi","given":"Minoru"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2008",3]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Such aberrant α4-α4 proteasomes have also been described in mammalian cells[54]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aq7gq3ic1t","properties":{"formattedCitation":"{\\rtf \\super 54\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":435,"uris":["http://zotero.org/users/4604651/items/XL9KCHR5"],"uri":["http://zotero.org/users/4604651/items/XL9KCHR5"],"itemData":{"id":435,"type":"article-journal","title":"Assembly of an Evolutionarily Conserved Alternative Proteasome Isoform in Human Cells","container-title":"Cell Reports","page":"2962-2974","volume":"14","issue":"12","source":"PubMed","abstract":"Targeted intracellular protein degradation in eukaryotes is largely mediated by the proteasome. Here, we report the formation of an alternative proteasome isoform in human cells, previously found only in budding yeast, that bears an altered subunit arrangement in the outer ring of the proteasome core particle. These proteasomes result from incorporation of an additional α4 (PSMA7) subunit in the position normally occupied by α3 (PSMA4). Assembly of \"α4-α4\" proteasomes depends on the relative cellular levels of α4 and α3 and on the proteasome assembly chaperone PAC3. The oncogenic tyrosine kinases ABL and ARG and the tumor suppressor BRCA1 regulate cellular α4 levels and formation of α4-α4 proteasomes. Cells primed to assemble α4-α4 proteasomes exhibit enhanced resistance to toxic metal ions. Taken together, our results establish the existence of an alternative mammalian proteasome isoform and suggest a potential role in enabling cells to adapt to environmental stresses.","DOI":"10.1016/j.celrep.2016.02.068","ISSN":"2211-1247","note":"PMID: 26997268\nPMCID: PMC4828729","journalAbbreviation":"Cell Rep","language":"eng","author":[{"family":"Padmanabhan","given":"Achuth"},{"family":"Vuong","given":"Simone Anh-Thu"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2016",3,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] β–ring formation

The α–ring serves as a platform for the assembly of the β–ring which begins with the sequential recruitment of β2, β3 and β4 subunits. Ump1 is incorporated along with the first β-subunits while the Pba3-Pba4 complex dissociates from the α–ring upon β3 integration[55,56]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a26r3n57p5i","properties":{"formattedCitation":"{\\rtf \\super 55,56\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":60,"uris":["http://zotero.org/users/4604651/items/ILR2KMRQ"],"uri":["http://zotero.org/users/4604651/items/ILR2KMRQ"],"itemData":{"id":60,"type":"article-journal","title":"Dissecting β-ring assembly pathway of the mammalian 20S proteasome","container-title":"The EMBO Journal","page":"2204-2213","volume":"27","issue":"16","source":"PubMed Central","abstract":"The 20S proteasome is the catalytic core of the 26S proteasome. It comprises four stacked rings of seven subunits each, α1–7β1–7β1–7α1–7. Recent studies indicated that proteasome-specific chaperones and β-subunit appendages assist in the formation of α-rings and dimerization of half-proteasomes, but the process involved in the assembly of β-rings is poorly understood. Here, we clarify the mechanism of β-ring formation on α-rings by characterizing assembly intermediates accumulated in cells depleted of each β-subunit. Starting from β2, incorporation of β-subunits occurs in an orderly manner dependent on the propeptides of β2 and β5, and the C-terminal tail of β2. Unexpectedly, hUmp1, a chaperone functioning at the final assembly step, is incorporated as early as β2 and is required for the structural integrity of early assembly intermediates. We propose a model in which β-ring formation is assisted by both intramolecular and extrinsic chaperones, whose roles are partially different between yeast and mammals.","DOI":"10.1038/emboj.2008.148","ISSN":"0261-4189","note":"PMID: 18650933\nPMCID: PMC2519102","journalAbbreviation":"EMBO J","author":[{"family":"Hirano","given":"Yuko"},{"family":"Kaneko","given":"Takeumi"},{"family":"Okamoto","given":"Kenta"},{"family":"Bai","given":"Minghui"},{"family":"Yashiroda","given":"Hideki"},{"family":"Furuyama","given":"Kaori"},{"family":"Kato","given":"Koichi"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2008",8,20]]}}},{"id":59,"uris":["http://zotero.org/users/4604651/items/KNKIYCWL"],"uri":["http://zotero.org/users/4604651/items/KNKIYCWL"],"itemData":{"id":59,"type":"article-journal","title":"β-Subunit appendages promote 20S proteasome assembly by overcoming an Ump1-dependent checkpoint","container-title":"The EMBO Journal","page":"2339-2349","volume":"26","issue":"9","source":"PubMed Central","abstract":"Proteasomes are responsible for most intracellular protein degradation in eukaryotes. The 20S proteasome comprises a dyad-symmetric stack of four heptameric rings made from 14 distinct subunits. How it assembles is not understood. Most subunits in the central pair of β-subunit rings are synthesized in precursor form. Normally, the β5 (Doa3) propeptide is essential for yeast proteasome biogenesis, but overproduction of β7 (Pre4) bypasses this requirement. Bypass depends on a unique β7 extension, which contacts the opposing β ring. The resulting proteasomes appear normal but assemble inefficiently, facilitating identification of assembly intermediates. Assembly occurs stepwise into precursor dimers, and intermediates contain the Ump1 assembly factor and a novel complex, Pba1–Pba2. β7 incorporation occurs late and is closely linked to the association of two half-proteasomes. We propose that dimerization is normally driven by the β5 propeptide, an intramolecular chaperone, but β7 addition overcomes an Ump1-dependent assembly checkpoint and stabilizes the precursor dimer.","DOI":"10.1038/sj.emboj.7601681","ISSN":"0261-4189","note":"PMID: 17431397\nPMCID: PMC1864979","journalAbbreviation":"EMBO J","author":[{"family":"Li","given":"Xia"},{"family":"Kusmierczyk","given":"Andrew

R"},{"family":"Wong","given":"Peter"},{"family":"Emili","given":"Andrew"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2007",5,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The resulting intermediate, known as 13S complex, then recruits β5, β6, β1 and β7 to form the 15S complex also called half-proteasome (FIG. 2). Half-proteasome dimerization is directly initiated after β7 incorporation[55–57]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a7lelgclv","properties":{"formattedCitation":"{\\rtf \\super 55\\uc0\\u8211{}57\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":60,"uris":["http://zotero.org/users/4604651/items/ILR2KMRQ"],"uri":["http://zotero.org/users/4604651/items/ILR2KMRQ"],"itemData":{"id":60,"type":"article-journal","title":"Dissecting β-ring assembly pathway of the mammalian 20S proteasome","container-title":"The EMBO Journal","page":"2204-2213","volume":"27","issue":"16","source":"PubMed Central","abstract":"The 20S proteasome is the catalytic core of the 26S proteasome. It comprises four stacked rings of seven subunits each, α1–7β1–7β1–7α1–7. Recent studies indicated that proteasome-specific chaperones and β-subunit appendages assist in the formation of α-rings and dimerization of half-proteasomes, but the process involved in the assembly of β-rings is poorly understood. Here, we clarify the mechanism of β-ring formation on α-rings by characterizing assembly intermediates accumulated in cells depleted of each β-subunit. Starting from β2, incorporation of β-subunits occurs in an orderly manner dependent on the propeptides of β2 and β5, and the C-terminal tail of β2. Unexpectedly, hUmp1, a chaperone functioning at the final assembly step, is incorporated as early as β2 and is required for the structural integrity of early assembly intermediates. We propose a model in which β-ring formation is assisted by both intramolecular and extrinsic chaperones, whose roles are partially different between yeast and mammals.","DOI":"10.1038/emboj.2008.148","ISSN":"0261-4189","note":"PMID: 18650933\nPMCID: PMC2519102","journalAbbreviation":"EMBO J","author":[{"family":"Hirano","given":"Yuko"},{"family":"Kaneko","given":"Takeumi"},{"family":"Okamoto","given":"Kenta"},{"family":"Bai","given":"Minghui"},{"family":"Yashiroda","given":"Hideki"},{"family":"Furuyama","given":"Kaori"},{"family":"Kato","given":"Koichi"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2008",8,20]]}}},{"id":59,"uris":["http://zotero.org/users/4604651/items/KNKIYCWL"],"uri":["http://zotero.org/users/4604651/items/KNKIYCWL"],"itemData":{"id":59,"type":"article-journal","title":"β-Subunit appendages promote 20S proteasome assembly by overcoming an Ump1-dependent checkpoint","container-title":"The EMBO Journal","page":"2339-2349","volume":"26","issue":"9","source":"PubMed Central","abstract":"Proteasomes are responsible for most intracellular protein degradation in eukaryotes. The 20S proteasome comprises a dyad-symmetric stack of four heptameric rings made from 14 distinct subunits. How it assembles is not understood. Most subunits in the central pair of β-subunit rings are synthesized in precursor form. Normally, the β5 (Doa3) propeptide is essential for yeast proteasome biogenesis, but overproduction of β7 (Pre4) bypasses this requirement. Bypass depends on a unique β7 extension, which contacts the opposing β ring. The resulting proteasomes appear normal but assemble inefficiently, facilitating identification of assembly intermediates. Assembly occurs stepwise into precursor dimers, and intermediates contain the Ump1 assembly factor and a novel complex, Pba1–Pba2. β7 incorporation occurs late and is closely linked to the association of two half-proteasomes. We propose that dimerization is normally driven by the β5 propeptide, an intramolecular chaperone, but β7 addition overcomes an Ump1-dependent assembly checkpoint and stabilizes the precursor dimer.","DOI":"10.1038/sj.emboj.7601681","ISSN":"0261-4189","note":"PMID:

17431397\nPMCID: PMC1864979","journalAbbreviation":"EMBO J","author":[{"family":"Li","given":"Xia"},{"family":"Kusmierczyk","given":"Andrew R"},{"family":"Wong","given":"Peter"},{"family":"Emili","given":"Andrew"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2007",5,2]]}},{"id":55,"uris":["http://zotero.org/users/4604651/items/BJ6ZRT9H"],"uri":["http://zotero.org/users/4604651/items/BJ6ZRT9H"],"itemData":{"id":55,"type":"article-journal","title":"Distinct Elements in the Proteasomal β5 Subunit Propeptide Required for Autocatalytic Processing and Proteasome Assembly","container-title":"The Journal of Biological Chemistry","page":"1991-2003","volume":"291","issue":"4","source":"PubMed Central","abstract":"Eukaryotic 20S proteasome assembly remains poorly understood. The subunits stack into four heteroheptameric rings; three inner-ring subunits (β1, β2, and β5) bear the protease catalytic residues and are synthesized with N-terminal propeptides. These propeptides are removed autocatalytically late in assembly. In Saccharomyces cerevisiae, β5 (Doa3/Pre2) has a 75-residue propeptide, β5pro, that is essential for proteasome assembly and can work in trans. We show that deletion of the poorly conserved N-terminal half of the β5 propeptide nonetheless causes substantial defects in proteasome maturation. Sequences closer to the cleavage site have critical but redundant roles in both assembly and self-cleavage. A conserved histidine two residues upstream of the autocleavage site strongly promotes processing. Surprisingly, although β5pro is functionally linked to the Ump1 assembly factor, trans-expressed β5pro associates only weakly with Ump1-containing precursors. Several genes were identified as dosage suppressors of trans-expressed β5pro mutants; the strongest encoded the β7 proteasome subunit. Previous data suggested that β7 and β5pro have overlapping roles in bringing together two half-proteasomes, but the timing of β7 addition relative to half-mer joining was unclear. Here we report conditions where dimerization lags behind β7 incorporation into the half-mer. Our results suggest that β7 insertion precedes half-mer dimerization, and the β7 tail and β5 propeptide have unequal roles in half-mer joining.","DOI":"10.1074/jbc.M115.677047","ISSN":"0021-9258","note":"PMID: 26627836\nPMCID: PMC4722473","journalAbbreviation":"J Biol Chem","author":[{"family":"Li","given":"Xia"},{"family":"Li","given":"Yanjie"},{"family":"Arendt","given":"Cassandra S."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2016",1,22]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] Half-proteasome dimerization and maturation

Ump1 prevents inappropriate dimerization of half-proteasomes by obstructing their dimerization until all β-subunits are properly incorporated[56,58]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"agi3uak74v","properties":{"formattedCitation":"{\\rtf \\super 56,58\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":59,"uris":["http://zotero.org/users/4604651/items/KNKIYCWL"],"uri":["http://zotero.org/users/4604651/items/KNKIYCWL"],"itemData":{"id":59,"type":"article-journal","title":"β-Subunit appendages promote 20S proteasome assembly by overcoming an Ump1-dependent checkpoint","container-title":"The EMBO Journal","page":"2339-2349","volume":"26","issue":"9","source":"PubMed Central","abstract":"Proteasomes are responsible for most intracellular protein degradation in eukaryotes. The 20S proteasome comprises a dyad-symmetric stack of four heptameric rings made from 14 distinct subunits. How it assembles is not understood. Most subunits in the central pair of β-subunit rings are synthesized in precursor form. Normally, the β5 (Doa3) propeptide is essential for yeast proteasome biogenesis, but overproduction of β7 (Pre4) bypasses this requirement. Bypass depends

on a unique β7 extension, which contacts the opposing β ring. The resulting proteasomes appear normal but assemble inefficiently, facilitating identification of assembly intermediates. Assembly occurs stepwise into precursor dimers, and intermediates contain the Ump1 assembly factor and a novel complex, Pba1–Pba2. β7 incorporation occurs late and is closely linked to the association of two half-proteasomes. We propose that dimerization is normally driven by the β5 propeptide, an intramolecular chaperone, but β7 addition overcomes an Ump1-dependent assembly checkpoint and stabilizes the precursor dimer.","DOI":"10.1038/sj.emboj.7601681","ISSN":"0261-4189","note":"PMID: 17431397\nPMCID: PMC1864979","journalAbbreviation":"EMBO J","author":[{"family":"Li","given":"Xia"},{"family":"Kusmierczyk","given":"Andrew R"},{"family":"Wong","given":"Peter"},{"family":"Emili","given":"Andrew"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2007",5,2]]}}},{"id":54,"uris":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"uri":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"itemData":{"id":54,"type":"article-journal","title":"Ump1p Is Required for Proper Maturation of the 20S Proteasome and Becomes Its Substrate upon Completion of the Assembly","container-title":"Cell","page":"489-499","volume":"92","issue":"4","source":"ScienceDirect","abstract":"We report the discovery of a short-lived chaperone that is required for the correct maturation of the eukaryotic 20S proteasome and is destroyed at a specific stage of the assembly process. The S. cerevisiae Ump1p protein is a component of proteasome precursor complexes containing unprocessed β subunits but is not detected in the mature 20S proteasome. Upon the association of two precursor complexes, Ump1p is encased and is rapidly degraded after the proteolytic sites in the interior of the nascent proteasome are activated. Cells lacking Ump1p exhibit a lack of coordination between the processing of β subunits and proteasome assembly, resulting in functionally impaired proteasomes. We also show that the propeptide of the Pre2p/Doa3p β subunit is required for Ump1p's function in proteasome maturation.","DOI":"10.1016/S0092-8674(00)80942-3","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Ramos","given":"Paula C"},{"family":"Höckendorff","given":"Jörg"},{"family":"Johnson","given":"Erica S"},{"family":"Varshavsky","given":"Alexander"},{"family":"Dohmen","given":"R. Jürgen"}],"issued":{"date-parts":[["1998",2,20]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. After half-proteasome dimerization, the resulting nascent CP is remodelled by the removal of amino-terminal propeptides from β1, β2, β5, β6 and β7 subunits. Ump1 is then degraded by the newly formed CP while the Pba1-Pba2 complex is recycled for a new round of CP assembly[48,58,59]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2estenh4fo","properties":{"formattedCitation":"{\\rtf \\super 48,58,59\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":54,"uris":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"uri":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"itemData":{"id":54,"type":"article-journal","title":"Ump1p Is Required for Proper Maturation of the 20S Proteasome and Becomes Its Substrate upon Completion of the Assembly","container-title":"Cell","page":"489-499","volume":"92","issue":"4","source":"ScienceDirect","abstract":"We report the discovery of a short-lived chaperone that is required for the correct maturation of the eukaryotic 20S proteasome and is destroyed at a specific stage of the assembly process. The S. cerevisiae Ump1p protein is a component of proteasome precursor complexes containing unprocessed β subunits but is not detected in the mature 20S proteasome. Upon the association of two precursor complexes, Ump1p is encased and is rapidly degraded after the proteolytic sites in the interior of the nascent proteasome are activated. Cells lacking Ump1p exhibit a lack of coordination between the processing of β subunits and proteasome

assembly, resulting in functionally impaired proteasomes. We also show that the propeptide of the Pre2p/Doa3p β subunit is required for Ump1p's function in proteasome maturation.","DOI":"10.1016/S0092-8674(00)80942-3","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Ramos","given":"Paula C"},{"family":"Höckendorff","given":"Jörg"},{"family":"Johnson","given":"Erica S"},{"family":"Varshavsky","given":"Alexander"},{"family":"Dohmen","given":"R. Jürgen"}],"issued":{"date-parts":[["1998",2,20]]}}},{"id":53,"uris":["http://zotero.org/users/4604651/items/SU62C5E2"],"uri":["http://zotero.org/users/4604651/items/SU62C5E2"],"itemData":{"id":53,"type":"article-journal","title":"Proteasome assembly from 15S precursors involves major conformational changes and recycling of the Pba1–Pba2 chaperone","container-title":"Nature Communications","page":"6123","volume":"6","source":"www.nature.com","abstract":"The barrel-shaped 20S proteasome core particle assembles via 15S intermediates through the action of Ump1 and Pba1–Pba2 chaperones. Using structural approaches, Kock et al. reveal conformational changes occurring upon formation of the nascent 20S particle leading to ejection of Pba1–Pba2.","DOI":"10.1038/ncomms7123","ISSN":"2041-1723","language":"en","author":[{"family":"Kock","given":"Malte"},{"family":"Nunes","given":"Maria M."},{"family":"Hemann","given":"Matthias"},{"family":"Kube","given":"Sebastian"},{"family":"Dohmen","given":"R. Jürgen"},{"family":"Herzog","given":"Franz"},{"family":"Ramos","given":"Paula C."},{"family":"Wendler","given":"Petra"}],"issued":{"date-parts":[["2015",1,22]]}}},{"id":63,"uris":["http://zotero.org/users/4604651/items/DD59CFJ9"],"uri":["http://zotero.org/users/4604651/items/DD59CFJ9"],"itemData":{"id":63,"type":"article-journal","title":"Cooperation of Multiple Chaperones Required for the Assembly of Mammalian 20S Proteasomes","container-title":"Molecular Cell","page":"977-984","volume":"24","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe 20S proteasome is a catalytic core of the 26S proteasome, a central enzyme in the degradation of ubiquitin-conjugated proteins. It is composed of 14 distinct gene products that form four stacked rings of seven subunits each, α1–7β1–7β1–7α1–7. It is reported that the biogenesis of mammalian 20S proteasomes is assisted by proteasome-specific chaperones, named PAC1, PAC2, and hUmp1, but the details are still unknown. Here, we report the identification of a chaperone, designated PAC3, as a component of α rings. Although it can intrinsically bind directly to both α and β subunits, PAC3 dissociates before the formation of half-proteasomes, a process coupled with the recruitment of β subunits and hUmp1. Knockdown of PAC3 impaired α ring formation. Further, PAC1/2/3 triple knockdown resulted in the accumulation of disorganized half-proteasomes that are incompetent for dimerization. Our results describe a cooperative system of multiple chaperones involved in the correct assembly of mammalian 20S proteasomes.","DOI":"10.1016/j.molcel.2006.11.015","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Hirano","given":"Yuko"},{"family":"Hayashi","given":"Hidemi"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Hendil","given":"Klavs B."},{"family":"Niwa","given":"Shin-ichiro"},{"family":"Kishimoto","given":"Toshihiko"},{"family":"Kasahara","given":"Masanori"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2006",12,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (FIG. 2). In contrast to the yeast Pba1-Pba2 complex, the human PAC1-PAC2 heterodimer has been shown

to be degraded upon completion of CP assembly[48]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"auanulqkvu","properties":{"formattedCitation":"{\\rtf \\super 48\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":63,"uris":["http://zotero.org/users/4604651/items/DD59CFJ9"],"uri":["http://zotero.org/users/4604651/items/DD59CFJ9"],"itemData":{"id":63,"type":"article-journal","title":"Cooperation of Multiple Chaperones Required for the Assembly of Mammalian 20S Proteasomes","container-title":"Molecular Cell","page":"977-984","volume":"24","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe 20S proteasome is a catalytic core of the 26S proteasome, a central enzyme in the degradation of ubiquitin-conjugated proteins. It is composed of 14 distinct gene products that form four stacked rings of seven subunits each, α1–7β1–7β1–7α1–7. It is reported that the biogenesis of mammalian 20S proteasomes is assisted by proteasome-specific chaperones, named PAC1, PAC2, and hUmp1, but the details are still unknown. Here, we report the identification of a chaperone, designated PAC3, as a component of α rings. Although it can intrinsically bind directly to both α and β subunits, PAC3 dissociates before the formation of half-proteasomes, a process coupled with the recruitment of β subunits and hUmp1. Knockdown of PAC3 impaired α ring formation. Further, PAC1/2/3 triple knockdown resulted in the accumulation of disorganized half-proteasomes that are incompetent for dimerization. Our results describe a cooperative system of multiple chaperones involved in the correct assembly of mammalian 20S proteasomes.","DOI":"10.1016/j.molcel.2006.11.015","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Hirano","given":"Yuko"},{"family":"Hayashi","given":"Hidemi"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Hendil","given":"Klavs B."},{"family":"Niwa","given":"Shin-ichiro"},{"family":"Kishimoto","given":"Toshihiko"},{"family":"Kasahara","given":"Masanori"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2006",12,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H1] Mechanisms of regulatory particle assembly

RP assembly is a multistep process and the two large subcomplexes, base and lid, can assemble independently (FIG. 3). In contrast to the lid, which either self-assembles[60]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a220hpufban","properties":{"formattedCitation":"{\\rtf \\super 60\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":51,"uris":["http://zotero.org/users/4604651/items/X3E5ZP8X"],"uri":["http://zotero.org/users/4604651/items/X3E5ZP8X"],"itemData":{"id":51,"type":"article-journal","title":"Incorporation of the Rpn12 Subunit Couples Completion of Proteasome Regulatory Particle Lid Assembly to Lid-Base Joining","container-title":"Molecular Cell","page":"907-917","volume":"44","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome, the central eukaryotic protease, comprises a core particle capped by a 19S regulatory particle (RP). The RP is divisible into base and lid subcomplexes. Lid biogenesis and incorporation into the RP remain poorly understood. We report several lid intermediates, including the free Rpn12 subunit and a lid particle (LP) containing the remaining eight subunits, LP2. Rpn12 binds LP2 in vitro, and each requires the other for assembly into 26S proteasomes. Stable Rpn12 incorporation depends on all other lid subunits, indicating that Rpn12 distinguishes LP2 from smaller lid subcomplexes. The highly conserved C terminus of Rpn12 bridges the lid and base, mediating both stable binding to LP2 and lid-base joining. Our data suggest a hierarchical assembly mechanism where Rpn12 binds LP2 only upon correct assembly of all other lid subunits, and the Rpn12 tail then helps

drive lid-base joining. Rpn12 incorporation thus links proper lid assembly to subsequent assembly steps.","DOI":"10.1016/j.molcel.2011.11.020","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Tomko Jr.","given":"Robert J."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2011",12,23]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } or for which assembly factors have not been found yet, the assembly of the base is known to be assisted by five RP assembly chaperones (RACs): Nas2 (p27 in human), Nas6 (p28 in human), Hsm3 (S5b in human), Rpn14 (Proteasomal ATPase Associated Factor 1 (PAAF1) in human) and Adc17 (ATPase dedicated chaperone of 17 kDa)[61–66]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1hr8jbht79","properties":{"formattedCitation":"{\\rtf \\super 61\\uc0\\u8211{}66\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":50,"uris":["http://zotero.org/users/4604651/items/PFLHQ275"],"uri":["http://zotero.org/users/4604651/items/PFLHQ275"],"itemData":{"id":50,"type":"article-journal","title":"Multiple Assembly Chaperones Govern Biogenesis of the Proteasome Regulatory Particle Base","container-title":"Cell","page":"887-899","volume":"137","issue":"5","source":"ScienceDirect","abstract":"Summary\nThe central protease of eukaryotes, the 26S proteasome, has a 20S proteolytic core particle (CP) and an attached 19S regulatory particle (RP). The RP is further subdivided into lid and base subcomplexes. Little is known about RP assembly. Here, we show that four conserved assembly factors govern biogenesis of the yeast RP base. Nas2 forms a complex with the Rpt4 and Rpt5 ATPases and enhances 26S proteasome formation in vivo and in vitro. Other RP subcomplexes contain Hsm3, which is related to mammalian proteasome subunit S5b. Hsm3 also contributes to base assembly. Larger Hsm3-containing complexes include two additional proteins, Nas6 and Rpn14, which function as assembly chaperones as well. Specific deletion combinations affecting these four factors cause severe perturbations to RP assembly. Our results demonstrate that proteasomal RP biogenesis requires multiple, functionally overlapping chaperones and suggest a model in which subunits form specific subcomplexes that then assemble into the base.","DOI":"10.1016/j.cell.2009.04.061","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Funakoshi","given":"Minoru"},{"family":"Tomko Jr.","given":"Robert J."},{"family":"Kobayashi","given":"Hideki"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2009",5,29]]}}},{"id":52,"uris":["http://zotero.org/users/4604651/items/TV7X6IC8"],"uri":["http://zotero.org/users/4604651/items/TV7X6IC8"],"itemData":{"id":52,"type":"article-journal","title":"Assembly Pathway of the Mammalian Proteasome Base Subcomplex Is Mediated by Multiple Specific Chaperones","container-title":"Cell","page":"914-925","volume":"137","issue":"5","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome is an enzymatic complex that degrades ubiquitinated proteins in eukaryotic cells. It is composed of the 20S core particle (CP) and the 19S regulatory particle (RP). The latter is further divided into the lid and base subcomplexes. While the mechanism involved in the assembly of the CP is well investigated, that of the RP is poorly understood. Here, we show that the formation of the mammalian base subcomplex involves three distinct modules, where specific pairs of ATPase subunits are associated with the distinct chaperones p28, S5b, or p27. The process of base formation starts from association of the p28-Rpt3-Rpt6-Rpn14 complex with the S5b-Rpt1-Rpt2-Rpn1 complex, followed by incorporation of the p27-Rpt5-Rpt4 complex and Rpn2, where p28, S5b, and p27 regulate the associations between the modules. These chaperones dissociate before completion of 26S proteasome formation. Our results demonstrate that base assembly is facilitated by multiple proteasome-dedicated chaperones, like

CP assembly.","DOI":"10.1016/j.cell.2009.05.008","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Kaneko","given":"Takeumi"},{"family":"Hamazaki","given":"Jun"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Furuyama","given":"Kaori"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2009",5,29]]}},{"id":49,"uris":["http://zotero.org/users/4604651/items/L96H6QF4"],"uri":["http://zotero.org/users/4604651/items/L96H6QF4"],"itemData":{"id":49,"type":"article-journal","title":"Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle","container-title":"Cell","page":"900-913","volume":"137","issue":"5","source":"PubMed","abstract":"The 26S proteasome is a highly conserved multisubunit protease that degrades ubiquitinated proteins in eukaryotic cells. The 26S proteasome consists of the proteolytic core particle (CP) and one or two 19S regulatory particles (RPs). Although the mechanisms of CP assembly are well described, the mechanism of RP assembly is largely unknown. Here, we show that four proteasome-interacting proteins (PIPs), Nas2/p27, Nas6/gankyrin, Rpn14/PAAF1, and Hsm3/S5b, bind specific Rpt subunits of the RP and interact each other genetically. Lack of these PIPs resulted in defective assembly of the 26S proteasome at an early stage, suggesting that these proteins are bona fide RP chaperones. Each of the RP chaperones formed distinct specific subassemblies of the base components and escorted them to mature RPs. Our results indicate that the RP assembly is a highly organized and elaborate process orchestrated by multiple proteasome-dedicated chaperones.","DOI":"10.1016/j.cell.2009.05.005","ISSN":"1097-4172","note":"PMID: 19446323","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Saeki","given":"Yasushi"},{"family":"Toh-E","given":"Akio"},{"family":"Kudo","given":"Tai"},{"family":"Kawamura","given":"Hitomi"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",5,29]]}},{"id":48,"uris":["http://zotero.org/users/4604651/items/UYC8PMCC"],"uri":["http://zotero.org/users/4604651/items/UYC8PMCC"],"itemData":{"id":48,"type":"article-journal","title":"Hsm3/S5b Participates in the Assembly Pathway of the 19S Regulatory Particle of the Proteasome","container-title":"Molecular Cell","page":"389-399","volume":"33","issue":"3","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome, the central enzyme of the ubiquitin-proteasome system, is comprised of the 20S catalytic core particle (CP) and the 19S regulatory particle (RP), itself composed of two subcomplexes, the base and the lid. 20S proteasome assembly is assisted by several chaperones. Integral subunits of the RP participate in its assembly, but no external factors have been identified so far. Here we characterize the yeast Hsm3 protein, which displays unique features regarding 19S assembly. Hsm3 associates with 19S subcomplexes via a carboxy-terminal domain of the Rpt1 base subunit but is missing in the final 26S proteasome. Moreover, Hsm3 is specifically required for the base subcomplex assembly. Finally, we identify the putative species-specific 19S subunit S5b as a functional homolog of the Hsm3 chaperone in mammals. These findings shed light on chaperone-assisted proteasome assembly in eukaryotes.","DOI":"10.1016/j.molcel.2009.01.010","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Le Tallec","given":"Benoît"},{"family":"Barrault","given":"Marie-Bénédicte"},{"family":"Guérois","given":"Raphaël"},{"family":"Carré","given":"Thibault"},{"family":"Peyroche","given":"Anne"}],"issued":{"date-parts":[["2009",2,13]]}}},{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/item

s/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}},{"id":46,"uris":["http://zotero.org/users/4604651/items/KV6SHJCF"],"uri":["http://zotero.org/users/4604651/items/KV6SHJCF"],"itemData":{"id":46,"type":"article-journal","title":"Chaperone-mediated pathway of proteasome regulatory particle assembly","container-title":"Nature","page":"861-865","volume":"459","issue":"7248","source":"www.nature.com","abstract":"The proteasome is a protease that controls diverse processes in eukaryotic cells. Its regulatory particle (RP) initiates the degradation of ubiquitin–protein conjugates by unfolding the substrate and translocating it into the proteasome core particle (CP) to be degraded. The RP has 19 subunits, and their pathway of assembly is not understood. Here we show that in the yeast Saccharomyces cerevisiae three proteins are found associated with RP but not with the RP–CP holoenzyme: Nas6, Rpn14 and Hsm3. Mutations in the corresponding genes confer proteasome loss-of-function phenotypes, despite their virtual absence from the holoenzyme. These effects result from deficient RP assembly. Thus, Nas6, Rpn14 and Hsm3 are RP chaperones. The RP contains six ATPases–the Rpt proteins–and each RP chaperone binds to the carboxy-terminal domain of a specific Rpt. We show in an accompanying study that RP assembly is templated through the Rpt C termini, apparently by their insertion into binding pockets in the CP. Thus, RP chaperones may regulate proteasome assembly by directly restricting the accessibility of Rpt C termini to the CP. In addition, competition between the RP chaperones and the CP for Rpt engagement may explain the release of RP chaperones as proteasomes mature.","DOI":"10.1038/nature08063","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Roelofs","given":"Jeroen"},{"family":"Park","given":"Soyeon"},{"family":"Haas","given":"Wilhelm"},{"family":"Tian","given":"Geng"},{"family":"McAllister","given":"Fiona E."},{"family":"Huo","given":"Ying"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Zhang","given":"Fan"},{"family":"Shi","given":"Yigong"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The loss of a single RAC is not lethal but the deletion of a combination of RACs is detrimental for cell survival, particularly under stress conditions[61,63,66]{

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ndk4pogd","properties":{"formattedCitation":"{\\rtf \\super 61,63,66\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":50,"uris":["http://zotero.org/users/4604651/items/PFLHQ275"],"uri":["http://zotero.org/users/4604651/items/PFLHQ275"],"itemData":{"id":50,"type":"article-journal","title":"Multiple Assembly Chaperones Govern Biogenesis of the Proteasome Regulatory Particle Base","container-title":"Cell","page":"887-899","volume":"137","issue":"5","source":"ScienceDirect","abstract":"Summary\nThe central protease of eukaryotes, the 26S proteasome, has a 20S proteolytic core particle (CP) and an attached 19S regulatory particle (RP). The RP is further subdivided into lid and base subcomplexes. Little is known about RP assembly. Here, we show that four conserved assembly factors govern biogenesis of the yeast RP base. Nas2 forms a complex with the Rpt4 and Rpt5 ATPases and enhances 26S proteasome formation in vivo and in vitro. Other RP subcomplexes contain Hsm3, which is related to mammalian proteasome subunit S5b. Hsm3 also contributes to base assembly. Larger Hsm3-containing complexes include two additional proteins, Nas6 and Rpn14, which function as assembly chaperones as well. Specific deletion combinations affecting these four factors cause severe perturbations to RP assembly. Our results demonstrate that proteasomal RP biogenesis requires multiple, functionally overlapping chaperones and suggest a model in which subunits form specific subcomplexes that then assemble into the base.","DOI":"10.1016/j.cell.2009.04.061","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Funakoshi","given":"Minoru"},{"family":"Tomko Jr.","given":"Robert J."},{"family":"Kobayashi","given":"Hideki"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2009",5,29]]}}},{"id":49,"uris":["http://zotero.org/users/4604651/items/L96H6QF4"],"uri":["http://zotero.org/users/4604651/items/L96H6QF4"],"itemData":{"id":49,"type":"article-journal","title":"Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle","container-title":"Cell","page":"900-913","volume":"137","issue":"5","source":"PubMed","abstract":"The 26S proteasome is a highly conserved multisubunit protease that degrades ubiquitinated proteins in eukaryotic cells. The 26S proteasome consists of the proteolytic core particle (CP) and one or two 19S regulatory particles (RPs). Although the mechanisms of CP assembly are well described, the mechanism of RP assembly is largely unknown. Here, we show that four proteasome-interacting proteins (PIPs), Nas2/p27, Nas6/gankyrin, Rpn14/PAAF1, and Hsm3/S5b, bind specific Rpt subunits of the RP and interact each other genetically. Lack of these PIPs resulted in defective assembly of the 26S proteasome at an early stage, suggesting that these proteins are bona fide RP chaperones. Each of the RP chaperones formed distinct specific subassemblies of the base components and escorted them to mature RPs. Our results indicate that the RP assembly is a highly organized and elaborate process orchestrated by multiple proteasome-dedicated chaperones.","DOI":"10.1016/j.cell.2009.05.005","ISSN":"1097-4172","note":"PMID: 19446323","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Saeki","given":"Yasushi"},{"family":"Toh-E","given":"Akio"},{"family":"Kudo","given":"Tai"},{"family":"Kawamura","given":"Hitomi"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",5,29]]}}},{"id":46,"uris":["http://zotero.org/users/4604651/items/KV6SHJCF"],"uri":["http://zotero.org/users/4604651/items/KV6SHJCF"],"itemData":{"id":46,"type":"article-journal","title":"Chaperone-mediated pathway of proteasome regulatory particle assembly","container-title":"Nature","page":"861-865","volume":"459","issue":"7248","source":"www.nature.com","abstract":"The proteasome is a protease that controls diverse processes in eukaryotic cells. Its regulatory particle (RP) initiates the degradation of ubiquitin–protein conjugates by unfolding the substrate and translocating it into the proteasome core particle (CP) to be degraded. The RP has 19

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925","volume":"137","issue":"5","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome is an enzymatic complex that degrades ubiquitinated proteins in eukaryotic cells. It is composed of the 20S core particle (CP) and the 19S regulatory particle (RP). The latter is further divided into the lid and base subcomplexes. While the mechanism involved in the assembly of the CP is well investigated, that of the RP is poorly understood. Here, we show that the formation of the mammalian base subcomplex involves three distinct modules, where specific pairs of ATPase subunits are associated with the distinct chaperones p28, S5b, or p27. The process of base formation starts from association of the p28-Rpt3-Rpt6-Rpn14 complex with the S5b-Rpt1-Rpt2-Rpn1 complex, followed by incorporation of the p27-Rpt5-Rpt4 complex and Rpn2, where p28, S5b, and p27 regulate the associations between the modules. These chaperones dissociate before completion of 26S proteasome formation. Our results demonstrate that base assembly is facilitated by multiple proteasome-dedicated chaperones, like CP assembly.","DOI":"10.1016/j.cell.2009.05.008","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Kaneko","given":"Takeumi"},{"family":"Hamazaki","given":"Jun"},{"family":"Iemura","given":"Shun-ichiro"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Furuyama","given":"Kaori"},{"family":"Natsume","given":"Tohru"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2009",5,29]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} whilst in the other model the CP is used as a platform for RP base assembly[66–68]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ao4cm2l1da","properties":{"formattedCitation":"{\\rtf \\super 66\\uc0\\u8211{}68\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":46,"uris":["http://zotero.org/users/4604651/items/KV6SHJCF"],"uri":["http://zotero.org/users/4604651/items/KV6SHJCF"],"itemData":{"id":46,"type":"article-journal","title":"Chaperone-mediated pathway of proteasome regulatory particle assembly","container-title":"Nature","page":"861-865","volume":"459","issue":"7248","source":"www.nature.com","abstract":"The proteasome is a protease that controls diverse processes in eukaryotic cells. Its regulatory particle (RP) initiates the degradation of ubiquitin–protein conjugates by unfolding the substrate and translocating it into the proteasome core particle (CP) to be degraded. The RP has 19 subunits, and their pathway of assembly is not understood. Here we show that in the yeast Saccharomyces cerevisiae three proteins are found associated with RP but not with the RP–CP holoenzyme: Nas6, Rpn14 and Hsm3. Mutations in the corresponding genes confer proteasome loss-of-function phenotypes, despite their virtual absence from the holoenzyme. These effects result from deficient RP assembly. Thus, Nas6, Rpn14 and Hsm3 are RP chaperones. The RP contains six ATPases–the Rpt proteins–and each RP chaperone binds to the carboxy-terminal domain of a specific Rpt. We show in an accompanying study that RP assembly is templated through the Rpt C termini, apparently by their insertion into binding pockets in the CP. Thus, RP chaperones may regulate proteasome assembly by directly restricting the accessibility of Rpt C termini to the CP. In addition, competition between the RP chaperones and the CP for Rpt engagement may explain the release of RP chaperones as proteasomes mature.","DOI":"10.1038/nature08063","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Roelofs","given":"Jeroen"},{"family":"Park","given":"Soyeon"},{"family":"Haas","given":"Wilhelm"},{"family":"Tian","given":"Geng"},{"family":"McAllister","given":"Fiona E."},{"family":"Huo","given":"Ying"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Zhang","given":"Fan"},{"family":"Shi","given":"Yigong"},{"family":"Gygi","given":"Steven

P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}},{"id":44,"uris":["http://zotero.org/users/4604651/items/IAY7N567"],"uri":["http://zotero.org/users/4604651/items/IAY7N567"],"itemData":{"id":44,"type":"article-journal","title":"Reconfiguration of the proteasome during chaperone-mediated assembly","container-title":"Nature","page":"512-516","volume":"497","issue":"7450","source":"www.nature.com","abstract":"The proteasomal ATPase ring, comprising Rpt1–Rpt6, associates with the heptameric α-ring of the proteasome core particle (CP) in the mature proteasome, with the Rpt carboxy-terminal tails inserting into pockets of the α-ring. Rpt ring assembly is mediated by four chaperones, each binding a distinct Rpt subunit. Here we report that the base subassembly of the Saccharomyces cerevisiae proteasome, which includes the Rpt ring, forms a high-affinity complex with the CP. This complex is subject to active dissociation by the chaperones Hsm3, Nas6 and Rpn14. Chaperone-mediated dissociation was abrogated by a non-hydrolysable ATP analogue, indicating that chaperone action is coupled to nucleotide hydrolysis by the Rpt ring. Unexpectedly, synthetic Rpt tail peptides bound α-pockets with poor specificity, except for Rpt6, which uniquely bound the α2/α3-pocket. Although the Rpt6 tail is not visualized within an α-pocket in mature proteasomes, it inserts into the α2/α3-pocket in the base–CP complex and is important for complex formation. Thus, the Rpt–CP interface is reconfigured when the lid complex joins the nascent proteasome to form the mature holoenzyme.","DOI":"10.1038/nature12123","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Park","given":"Soyeon"},{"family":"Li","given":"Xueming"},{"family":"Kim","given":"Ho Min"},{"family":"Singh","given":"Chingakham Ranjit"},{"family":"Tian","given":"Geng"},{"family":"Hoyt","given":"Martin A."},{"family":"Lovell","given":"Scott"},{"family":"Battaile","given":"Kevin P."},{"family":"Zolkiewski","given":"Michal"},{"family":"Coffino","given":"Philip"},{"family":"Roelofs","given":"Jeroen"},{"family":"Cheng","given":"Yifan"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2013",5,23]]}},{"id":45,"uris":["http://zotero.org/users/4604651/items/G28QIVC3"],"uri":["http://zotero.org/users/4604651/items/G28QIVC3"],"itemData":{"id":45,"type":"article-journal","title":"Hexameric assembly of the proteasomal ATPases is templated through their C termini","container-title":"Nature","page":"866-870","volume":"459","issue":"7248","source":"PubMed","abstract":"Substrates of the proteasome are recognized and unfolded by the regulatory particle, and then translocated into the core particle (CP) to be degraded. A hetero-hexameric ATPase ring, containing subunits Rpt1-6, is situated within the base subassembly of the regulatory particle. The ATPase ring sits atop the CP, with the Rpt carboxy termini inserted into pockets in the CP. Here we identify a previously unknown function of the Rpt proteins in proteasome biogenesis through deleting the C-terminal residue from each Rpt in the yeast Saccharomyces cerevisiae. Our results indicate that assembly of the hexameric ATPase ring is templated on the CP. We have also identified an apparent intermediate in base assembly, BP1, which contains Rpn1, three Rpts and Hsm3, a chaperone for base assembly. The Rpt proteins with the strongest assembly phenotypes, Rpt4 and Rpt6, were absent from BP1. We propose that Rpt4 and Rpt6 form a nucleating complex to initiate base assembly, and that this complex is subsequently joined by BP1 to complete the Rpt ring. Our studies show that assembly of the proteasome base is a rapid yet highly orchestrated process.","DOI":"10.1038/nature08065","ISSN":"1476-4687","note":"PMID: 19412160\nPMCID: PMC2722381","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Park","given":"Soyeon"},{"family":"Roelofs","given":"Jeroen"},{"family":"Kim","given":"Woong"},{"family":"Robert","given":"Jessica"},{"family":"Schmidt","given":"Marion"},{"family":"

Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] RP base assembly

The hexameric ATPase ring of the RP has a precisely ordered Rpt1-Rpt2-Rpt6-Rpt3-Rpt4-Rpt5 configuration and is built upon assembly of three modules composed of two AAA^{+}-ATPase pairs bound to selective RACs that prevent premature binding of RP intermediates to the CP[66,69,70]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a4q8v2uh4l","properties":{"formattedCitation":"{\\rtf \\super 66,69,70\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":46,"uris":["http://zotero.org/users/4604651/items/KV6SHJCF"],"uri":["http://zotero.org/users/4604651/items/KV6SHJCF"],"itemData":{"id":46,"type":"article-journal","title":"Chaperone-mediated pathway of proteasome regulatory particle assembly","container-title":"Nature","page":"861-865","volume":"459","issue":"7248","source":"www.nature.com","abstract":"The proteasome is a protease that controls diverse processes in eukaryotic cells. Its regulatory particle (RP) initiates the degradation of ubiquitin–protein conjugates by unfolding the substrate and translocating it into the proteasome core particle (CP) to be degraded. The RP has 19 subunits, and their pathway of assembly is not understood. Here we show that in the yeast Saccharomyces cerevisiae three proteins are found associated with RP but not with the RP–CP holoenzyme: Nas6, Rpn14 and Hsm3. Mutations in the corresponding genes confer proteasome loss-of-function phenotypes, despite their virtual absence from the holoenzyme. These effects result from deficient RP assembly. Thus, Nas6, Rpn14 and Hsm3 are RP chaperones. The RP contains six ATPases–the Rpt proteins–and each RP chaperone binds to the carboxy-terminal domain of a specific Rpt. We show in an accompanying study that RP assembly is templated through the Rpt C termini, apparently by their insertion into binding pockets in the CP. Thus, RP chaperones may regulate proteasome assembly by directly restricting the accessibility of Rpt C termini to the CP. In addition, competition between the RP chaperones and the CP for Rpt engagement may explain the release of RP chaperones as proteasomes mature.","DOI":"10.1038/nature08063","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Roelofs","given":"Jeroen"},{"family":"Park","given":"Soyeon"},{"family":"Haas","given":"Wilhelm"},{"family":"Tian","given":"Geng"},{"family":"McAllister","given":"Fiona E."},{"family":"Huo","given":"Ying"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Zhang","given":"Fan"},{"family":"Shi","given":"Yigong"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}},{"id":198,"uris":["http://zotero.org/users/4604651/items/8U3242RE"],"uri":["http://zotero.org/users/4604651/items/8U3242RE"],"itemData":{"id":198,"type":"article-journal","title":"Heterohexameric ring arrangement of the eukaryotic proteasomal ATPases: implications for proteasome structure and assembly","container-title":"Molecular Cell","page":"393-403","volume":"38","issue":"3","source":"PubMed","abstract":"The proteasome has a paramount role in eukaryotic cell regulation. It consists of a proteolytic core particle (CP) bound to one or two regulatory particles (RPs). Each RP is believed to include six different AAA+ ATPases in a heterohexameric ring that binds the CP while unfolding and translocating substrates into the core. No atomic-resolution RP structures are available. Guided by crystal structures of related homohexameric prokaryotic ATPases, we use disulfide engineering to show that the

eukaryotic ATPases form a ring with the arrangement Rpt1-Rpt2-Rpt6-Rpt3-Rpt4-Rpt5 in fully assembled proteasomes. The arrangement is consistent with known assembly intermediates. This quaternary organization clarifies the functional overlap of specific RP assembly chaperones and led us to identify a potential RP assembly intermediate that includes four ATPases (Rpt6-Rpt3-Rpt4-Rpt5) and their cognate chaperones (Rpn14, Nas6, and Nas2). Finally, the ATPase ring structure casts light on alternative RP structural models and the mechanism of RP action.","DOI":"10.1016/j.molcel.2010.02.035","ISSN":"1097-4164","note":"PMID: 20471945\nPMCID: PMC2879271","shortTitle":"Heterohexameric ring arrangement of the eukaryotic proteasomal ATPases","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Tomko","given":"Robert J."},{"family":"Funakoshi","given":"Minoru"},{"family":"Schneider","given":"Kyle"},{"family":"Wang","given":"Jimin"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2010",5,14]]}}},{"id":43,"uris":["http://zotero.org/users/4604651/items/TRQBACK9"],"uri":["http://zotero.org/users/4604651/items/TRQBACK9"],"itemData":{"id":43,"type":"article-journal","title":"An atomic model AAA-ATPase/20S core particle sub-complex of the 26S proteasome","container-title":"Biochemical and Biophysical Research Communications","page":"228-233","volume":"388","issue":"2","source":"PubMed","abstract":"The 26S proteasome is the most downstream element of the ubiquitin-proteasome pathway of protein degradation. It is composed of the 20S core particle (CP) and the 19S regulatory particle (RP). The RP consists of 6 AAA-ATPases and at least 13 non-ATPase subunits. Based on a cryo-EM map of the 26S proteasome, structures of homologs, and physical protein-protein interactions we derive an atomic model of the AAA-ATPase-CP sub-complex. The ATPase order in our model (Rpt1/Rpt2/Rpt6/Rpt3/Rpt4/Rpt5) is in excellent agreement with the recently identified base-precursor complexes formed during the assembly of the RP. Furthermore, the atomic CP-AAA-ATPase model suggests that the assembly chaperone Nas6 facilitates CP-RP association by enhancing the shape complementarity between Rpt3 and its binding CP alpha subunits partners.","DOI":"10.1016/j.bbrc.2009.07.145","ISSN":"1090-2104","note":"PMID: 19653995\nPMCID: PMC2771176","journalAbbreviation":"Biochem. Biophys. Res. Commun.","language":"eng","author":[{"family":"Förster","given":"Friedrich"},{"family":"Lasker","given":"Keren"},{"family":"Beck","given":"Florian"},{"family":"Nickell","given":"Stephan"},{"family":"Sali","given":"Andrej"},{"family":"Baumeister","given":"Wolfgang"}],"issued":{"date-parts":[["2009",10,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }

(FIG. 3). Rpn14, Nas6, Nas2 and Hsm3 bind the C-terminal tails of their cognate Rpt proteins forming three modules: Rpn14-Rpt6-Rpt3-Nas6, Rpt4-Rpt5-Nas2 and Hsm3-Rpt1-Rpt2-Rpn1[21,41]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"amvvde85k9","properties":{"formattedCitation":"{\\rtf \\super 21,41\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":76,"uris":["http://zotero.org/users/4604651/items/D2R2QDAY"],"uri":["http://zotero.org/users/4604651/items/D2R2QDAY"],"itemData":{"id":76,"type":"article-journal","title":"Molecular mechanisms of proteasome assembly","container-title":"Nature Reviews Molecular Cell Biology","page":"104-115","volume":"10","issue":"2","source":"www.nature.com","abstract":"The 26S proteasome is a highly conserved protein degradation machine that consists of the 20S proteasome and 19S regulatory particles, which include 14 and 19 different polypeptides, respectively. How the proteasome components are assembled is a fundamental question towards understanding the process of protein degradation and its functions in diverse biological processes. Several proteasome-dedicated chaperones are involved in the efficient and correct assembly of the

20S proteasome. These chaperones help the initiation and progression of the assembly process by transiently associating with proteasome precursors. By contrast, little is known about the assembly of the 19S regulatory particles, but several hints have emerged.","DOI":"10.1038/nrm2630","ISSN":"1471-0072","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Murata","given":"Shigeo"},{"family":"Yashiroda","given":"Hideki"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2009",2]]}},{"id":67,"uris":["http://zotero.org/users/4604651/items/8C2R5GW6"],"uri":["http://zotero.org/users/4604651/items/8C2R5GW6"],"itemData":{"id":67,"type":"article-journal","title":"Molecular architecture and assembly of the eukaryotic proteasome","container-title":"Annual review of biochemistry","page":"415-445","volume":"82","source":"NCBI PubMed","abstract":"The eukaryotic ubiquitin-proteasome system is responsible for most aspects of regulatory and quality-control protein degradation in cells. Its substrates, which are usually modified by polymers of ubiquitin, are ultimately degraded by the 26S proteasome. This 2.6-MDa protein complex is separated into a barrel-shaped proteolytic 20S core particle (CP) of 28 subunits capped on one or both ends by a 19S regulatory particle (RP) comprising at least 19 subunits. The RP coordinates substrate recognition, removal of substrate polyubiquitin chains, and substrate unfolding and translocation into the CP for degradation. Although many atomic structures of the CP have been determined, the RP has resisted high-resolution analysis. Recently, however, a combination of cryo-electron microscopy, biochemical analysis, and crystal structure determination of several RP subunits has yielded a near-atomic-resolution view of much of the complex. Major new insights into chaperone-assisted proteasome assembly have also recently emerged. Here we review these novel findings.","DOI":"10.1146/annurev-biochem-060410-150257","ISSN":"1545-4509","note":"PMID: 23495936 \nPMCID: PMC3827779","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Tomko","given":"Robert J"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2013"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The first two modules associate with each other prior to incorporation of Hsm3-Rpt1-Rpt2-Rpn1 complex, along with Rpn2 and Rpn13. Rpn10 is then recruited to complete the assembly of the RP base (FIG. 3). The incorporation of Hsm3-Rpt1-Rpt2-Rpn1 complex triggers the release of Nas2 from the base while Rpn14, Nas6 and Hsm3 are removed upon the association between the RP and the CP[68,71–73]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a62040arh5","properties":{"formattedCitation":"{\\rtf \\super 68,71\\uc0\\u8211{}73\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":45,"uris":["http://zotero.org/users/4604651/items/G28QIVC3"],"uri":["http://zotero.org/users/4604651/items/G28QIVC3"],"itemData":{"id":45,"type":"article-journal","title":"Hexameric assembly of the proteasomal ATPases is templated through their C termini","container-title":"Nature","page":"866-870","volume":"459","issue":"7248","source":"PubMed","abstract":"Substrates of the proteasome are recognized and unfolded by the regulatory particle, and then translocated into the core particle (CP) to be degraded. A hetero-hexameric ATPase ring, containing subunits Rpt1-6, is situated within the base subassembly of the regulatory particle. The ATPase ring sits atop the CP, with the Rpt carboxy termini inserted into pockets in the CP. Here we identify a previously unknown function of the Rpt proteins in proteasome biogenesis through deleting the C-terminal residue from each Rpt in the yeast Saccharomyces cerevisiae. Our results indicate that assembly of the hexameric ATPase ring is templated on the CP. We have also identified an apparent intermediate in base assembly, BP1, which contains Rpn1, three Rpts and Hsm3,

a chaperone for base assembly. The Rpt proteins with the strongest assembly phenotypes, Rpt4 and Rpt6, were absent from BP1. We propose that Rpt4 and Rpt6 form a nucleating complex to initiate base assembly, and that this complex is subsequently joined by BP1 to complete the Rpt ring. Our studies show that assembly of the proteasome base is a rapid yet highly orchestrated process.","DOI":"10.1038/nature08065","ISSN":"1476-4687","note":"PMID: 19412160\nPMCID: PMC2722381","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Park","given":"Soyeon"},{"family":"Roelofs","given":"Jeroen"},{"family":"Kim","given":"Woong"},{"family":"Robert","given":"Jessica"},{"family":"Schmidt","given":"Marion"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}},{"id":42,"uris":["http://zotero.org/users/4604651/items/6UQDINEA"],"uri":["http://zotero.org/users/4604651/items/6UQDINEA"],"itemData":{"id":42,"type":"article-journal","title":"Nucleotide-dependent switch in proteasome assembly mediated by the Nas6 chaperone","container-title":"Proceedings of the National Academy of Sciences","page":"1548-1553","volume":"114","issue":"7","source":"www.pnas.org","abstract":"The proteasome is assembled via the nine-subunit lid, nine-subunit base, and 28-subunit core particle (CP). Previous work has shown that the chaperones Rpn14, Nas6, Hsm3, and Nas2 each bind a specific ATPase subunit of the base and antagonize base–CP interaction. Here, we show that the Nas6 chaperone also obstructs base–lid association. Nas6 alternates between these two inhibitory modes according to the nucleotide state of the base. When ATP cannot be hydrolyzed, Nas6 interferes with base–lid, but not base–CP, association. In contrast, under conditions of ATP hydrolysis, Nas6 obstructs base–CP, but not base–lid, association. Modeling of Nas6 into cryoelectron microscopy structures of the proteasome suggests that Nas6 controls both base–lid affinity and base–CP affinity through steric hindrance; Nas6 clashes with the lid in the ATP-hydrolysis–blocked proteasome, but clashes instead with the CP in the ATP-hydrolysis–competent proteasome. Thus, Nas6 provides a dual mechanism to control assembly at both major interfaces of the proteasome.","DOI":"10.1073/pnas.1612922114","ISSN":"0027-8424, 1091-6490","note":"PMID: 28137839","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Li","given":"Frances"},{"family":"Tian","given":"Geng"},{"family":"Langager","given":"Deanna"},{"family":"Sokolova","given":"Vladyslava"},{"family":"Finley","given":"Daniel"},{"family":"Park","given":"Soyeon"}],"issued":{"date-parts":[["2017",2,14]]}},{"id":41,"uris":["http://zotero.org/users/4604651/items/AMB36MMV"],"uri":["http://zotero.org/users/4604651/items/AMB36MMV"],"itemData":{"id":41,"type":"article-journal","title":"Structural Basis for Proteasome Formation Controlled by an Assembly Chaperone Nas2","container-title":"Structure","page":"731-743","volume":"22","issue":"5","source":"ScienceDirect","abstract":"Summary\nProteasome formation does not occur due to spontaneous self-organization but results from a highly ordered process assisted by several assembly chaperones. The assembly of the proteasome ATPase subunits is assisted by four client-specific chaperones, of which three have been structurally resolved. Here, we provide the structural basis for the working mechanisms of the last, hereto structurally uncharacterized assembly chaperone, Nas2. We revealed that Nas2 binds to the Rpt5 subunit in a bivalent mode: the N-terminal helical domain of Nas2 masks the Rpt1-interacting surface of Rpt5, whereas its C-terminal PDZ domain caps the C-terminal proteasome-activating motif. Thus, Nas2 operates as a proteasome activation blocker, offering a checkpoint during the formation of the 19S ATPase prior to its docking onto the proteolytic 20S core particle.","DOI":"10.1016/j.str.2014.02.014","ISSN":"0969-2126","journalAbbreviation":"Structure","author":[{"family":"Satoh","given":"Tadashi"},{"family":"Saeki","given":"Yasushi"},{"family":"

Hiromoto","given":"Takeshi"},{"family":"Wang","given":"Ying-Hui"},{"family":"Uekusa","given":"Yoshinori"},{"family":"Yagi","given":"Hirokazu"},{"family":"Yoshihara","given":"Hidehito"},{"family":"Yagi-Utsumi","given":"Maho"},{"family":"Mizushima","given":"Tsunehiro"},{"family":"Tanaka","given":"Keiji"},{"family":"Kato","given":"Koichi"}],"issued":{"date-parts":[["2014",5,6]]}}},{"id":197,"uris":["http://zotero.org/users/4604651/items/NCSIHEKX"],"uri":["http://zotero.org/users/4604651/items/NCSIHEKX"],"itemData":{"id":197,"type":"article-journal","title":"Dual functions of the Hsm3 protein in chaperoning and scaffolding regulatory particle subunits during the proteasome assembly","container-title":"Proceedings of the National Academy of Sciences","page":"E1001-E1010","volume":"109","issue":"17","source":"www.pnas.org","abstract":"The 26S proteasome, a molecular machine responsible for regulated protein degradation, consists of a proteolytic core particle (20S CP) associated with 19S regulatory particles (19S RPs) subdivided into base and lid subcomplexes. The assembly of 19S RP base subcomplex is mediated by multiple dedicated chaperones. Among these, Hsm3 is important for normal growth and directly targets the carboxyl-terminal (C-terminal) domain of Rpt1 of the Rpt1–Rpt2–Rpn1 assembly intermediate. Here, we report crystal structures of the yeast Hsm3 chaperone free and bound to the C-terminal domain of Rpt1. Unexpectedly, the structure of the complex suggests that within the Hsm3–Rpt1–Rpt2 module, Hsm3 also contacts Rpt2. We show that in both yeast and mammals, Hsm3 actually directly binds the AAA domain of Rpt2. The Hsm3 C-terminal region involved in this interaction is required in vivo for base assembly, although it is dispensable for binding Rpt1. Although Rpt1 and Rpt2 exhibit weak affinity for each other, Hsm3 unexpectedly acts as an essential matchmaker for the Rpt1-Rpt2-Rpn1 assembly by bridging both Rpt1 and Rpt2. In addition, we provide structural and biochemical evidence on how Hsm3/S5b may regulate the 19S RP association to the 20S CP proteasome. Our data point out the diverse functions of assembly chaperones.","DOI":"10.1073/pnas.1116538109","ISSN":"0027-8424, 1091-6490","note":"PMID: 22460800","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Barrault","given":"Marie-Bénédicte"},{"family":"Richet","given":"Nicolas"},{"family":"Godard","given":"Chloe"},{"family":"Murciano","given":"Brice"},{"family":"Tallec","given":"Benoît Le"},{"family":"Rousseau","given":"Erwann"},{"family":"Legrand","given":"Pierre"},{"family":"Charbonnier","given":"Jean-Baptiste"},{"family":"Du","given":"Marie-Hélène Le"},{"family":"Guérois","given":"Raphaël"},{"family":"Ochsenbein","given":"Françoise"},{"family":"Peyroche","given":"Anne"}],"issued":{"date-parts":[["2012",4,24]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Yeast have an additional RAC called Adc17[65]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ado658pdgm","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen

aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Unlike the other RACs that bind to the carboxyl-terminal tails of Rpts, Adc17 assists RP assembly by binding to the amino-terminal region of Rpt6 to promote the pairing of Rpt6 with Rpt3 (FIG. 3). The Rpt6-Rpt3 intermediate is not found in cells whilst the other module Rpt4-Rpt5 is readily available[65]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aqt2if2c14","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . This suggests that the different modules may assemble independently, and the formation of the Rpt6-Rpt3 module may be a rate-limiting step in RP assembly[65]. In cell lysates, Adc17 is found in a complex with Rpt6 and not in higher assemblies, suggesting that

Adc17 is rapidly released after the Rpt6-Rpt3 pairing[65]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2bhedjo6je","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] RP lid assembly

Recombinant RP lid subunits can assemble in the absence of CP or RP base[22,74]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2i219m5hho","properties":{"formattedCitation":"{\\rtf \\super 22,74\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the

ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}},{"id":195,"uris":["http://zotero.org/users/4604651/items/7GLL5NFA"],"uri":["http://zotero.org/users/4604651/items/7GLL5NFA"],"itemData":{"id":195,"type":"article-journal","title":"The Intrinsically Disordered Sem1 Protein Functions as a Molecular Tether during Proteasome Lid Biogenesis","container-title":"Molecular Cell","page":"433-443","volume":"53","issue":"3","source":"ScienceDirect","abstract":"Summary\nThe intrinsically disordered yeast protein Sem1 (DSS1 in mammals) participates in multiple protein complexes, including the proteasome, but its role(s) within these complexes is uncertain. We report that Sem1 enforces the ordered incorporation of subunits Rpn3 and Rpn7 into the assembling proteasome lid. Sem1 uses conserved acidic segments separated by a flexible linker to grasp Rpn3 and Rpn7. The same segments are used for protein binding in other complexes, but in the proteasome lid they are uniquely deployed for recognizing separate polypeptides. We engineered TEV protease-cleavage sites into Sem1 to show that the tethering function of Sem1 is important for the biogenesis and integrity of the Rpn3-Sem1-Rpn7 ternary complex but becomes dispensable once the ternary complex incorporates into larger lid precursors. Thus, although Sem1 is a stoichiometric component of the mature proteasome, it has a distinct, chaperone-like function specific to early stages of proteasome assembly.","DOI":"10.1016/j.molcel.2013.12.009","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Tomko Jr.","given":"Robert J."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2014",2,6]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Lid formation is initiated by the formation of two intermediates: one composed of Rpn5-6, Rpn8-9 and Rpn11, and another one composed of Rpn3, Rpn7 and Sem1[74,75]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1gtuknfpjj","properties":{"formattedCitation":"{\\rtf \\super 74,75\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":195,"uris":["http://zotero.org/users/4604651/items/7GLL5NFA"],"uri":["http://zotero.org/users/4604651/items/7GLL5NFA"],"itemData":{"id":195,"type":"article-journal","title":"The Intrinsically Disordered Sem1 Protein Functions as a Molecular Tether during Proteasome Lid Biogenesis","container-title":"Molecular Cell","page":"433-443","volume":"53","issue":"3","source":"ScienceDirect","abstract":"Summary\nThe intrinsically disordered yeast protein Sem1 (DSS1 in mammals) participates in multiple protein complexes, including the proteasome, but its role(s) within these complexes is uncertain. We report that Sem1 enforces the ordered incorporation of subunits Rpn3 and Rpn7 into the assembling proteasome lid. Sem1 uses conserved acidic segments separated by a flexible linker to grasp Rpn3 and Rpn7. The same segments are used for protein binding in other complexes, but in the proteasome lid they are uniquely deployed for recognizing separate polypeptides. We engineered TEV protease-cleavage sites into Sem1 to show that the tethering function of Sem1 is important for the biogenesis and integrity of the Rpn3-Sem1-Rpn7 ternary complex but becomes dispensable once the ternary complex incorporates into larger lid precursors. Thus, although Sem1 is a stoichiometric component of the mature proteasome, it has a distinct, chaperone-like function specific to early stages of proteasome

assembly.","DOI":"10.1016/j.molcel.2013.12.009","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Tomko Jr.","given":"Robert J."},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2014",2,6]]}},{"id":189,"uris":["http://zotero.org/users/4604651/items/JPRJ7BUB"],"uri":["http://zotero.org/users/4604651/items/JPRJ7BUB"],"itemData":{"id":189,"type":"article-journal","title":"Dissection of the assembly pathway of the proteasome lid in Saccharomyces cerevisiae","container-title":"Biochemical and Biophysical Research Communications","page":"1048-1053","volume":"396","issue":"4","source":"ScienceDirect","abstract":"The 26S proteasome is a highly conserved multisubunit protease that degrades ubiquitinated proteins in eukaryotic cells. It comprises a 20S core particle and two 19S regulatory particles that are further divided into the lid and base complexes. The lid is a nine subunits complex that is structurally related to the COP9 signalosome and the eukaryotic initiation factor 3. Although the assembly pathway of the 20S and the base are well described, that of the lid is still unclear. In this study, we dissected the lid assembly using yeast lid mutant cells, rpn7-3, Δrpn9, and rpn12-1. Using mass spectrometry, we identified a number of lid subassemblies, such as Rpn3–Rpn7 pair and a lid-like complex lacking Rpn12, in the mutants. Our analysis suggests that the assembly of the lid is a highly ordered and multi-step process; first, Rpn5, 6, 8, 9, and 11 are assembled to form a core module, then a second module, consisting of Rpn3, 7, and Sem1, is attached, followed by the incorporation of Rpn12 to form the lid complex.","DOI":"10.1016/j.bbrc.2010.05.061","ISSN":"0006-291X","journalAbbreviation":"Biochemical and Biophysical Research Communications","author":[{"family":"Fukunaga","given":"Keisuke"},{"family":"Kudo","given":"Tai"},{"family":"Toh-e","given":"Akio"},{"family":"Tanaka","given":"Keiji"},{"family":"Saeki","given":"Yasushi"}],"issued":{"date-parts":[["2010",6,11]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}.

Intermediates self-assemble through a helical bundle formed by the C-terminal helices of lid subunits[76]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1stu1jn24u","properties":{"formattedCation":"{\\rtf \\super 76\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":188,"uris":["http://zotero.org/users/4604651/items/EF2ZREC2"],"uri":["http://zotero.org/users/4604651/items/EF2ZREC2"],"itemData":{"id":188,"type":"article-journal","title":"Formation of an Intricate Helical Bundle Dictates the Assembly of the 26S Proteasome Lid","container-title":"Structure","page":"1624-1635","volume":"21","issue":"9","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome is the major ATP-dependent protease in eukaryotes and thus involved in regulating a diverse array of vital cellular processes. Three subcomplexes form this massive degradation machine: the lid, the base, and the core. While assembly of base and core has been well-studied, the detailed molecular mechanisms involved in formation of the nine-subunit lid remain largely unknown. Here, we reveal that helices found at the C terminus of each lid subunit form a helical bundle that directs the ordered self-assembly of the lid subcomplex. Furthermore, we use an integrative modeling approach to gain critical insights into the bundle topology and provide an important structural framework for our biochemical data. We show that the helical bundle serves as a hub through which the last-added subunit Rpn12 monitors proper lid assembly before incorporation into the proteasome. Finally, we predict that the assembly of the COP9 signalosome depends on a similar helical bundle.","DOI":"10.1016/j.str.2013.06.023","ISSN":"0969-2126","journalAbbreviation":"Structure","author":[{"family":"Estrin","given":"Eric"},{"family":"Lopez-Blanco","given":"José Ramón"},{"family":"Chacón","given":"Pablo"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2013",9,3]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. After

association of these two intermediates, the last lid subunit, Rpn12, is incorporated (FIG. 3). Rpn12 incorporation triggers conformational changes of the lid which becomes competent for binding to the base[77]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a238u78ak52","properties":{"formattedCitation":"{\\rtf \\super 77\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":187,"uris":["http://zotero.org/users/4604651/items/DNLS2EDE"],"uri":["http://zotero.org/users/4604651/items/DNLS2EDE"],"itemData":{"id":187,"type":"article-journal","title":"A Single α Helix Drives Extensive Remodeling of the Proteasome Lid and Completion of Regulatory Particle Assembly","container-title":"Cell","page":"432-444","volume":"163","issue":"2","source":"PubMed","abstract":"Most short-lived eukaryotic proteins are degraded by the proteasome. A proteolytic core particle (CP) capped by regulatory particles (RPs) constitutes the 26S proteasome complex. RP biogenesis culminates with the joining of two large subcomplexes, the lid and base. In yeast and mammals, the lid appears to assemble completely before attaching to the base, but how this hierarchical assembly is enforced has remained unclear. Using biochemical reconstitutions, quantitative cross-linking/mass spectrometry, and electron microscopy, we resolve the mechanistic basis for the linkage between lid biogenesis and lid-base joining. Assimilation of the final lid subunit, Rpn12, triggers a large-scale conformational remodeling of the nascent lid that drives RP assembly, in part by relieving steric clash with the base. Surprisingly, this remodeling is triggered by a single Rpn12 α helix. Such assembly-coupled conformational switching is reminiscent of viral particle maturation and may represent a commonly used mechanism to enforce hierarchical assembly in multisubunit complexes.","DOI":"10.1016/j.cell.2015.09.022","ISSN":"1097-4172","note":"PMID: 26451487\nPMCID: PMC4601081","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Tomko","given":"Robert J."},{"family":"Taylor","given":"David W."},{"family":"Chen","given":"Zhuo A."},{"family":"Wang","given":"Hong-Wei"},{"family":"Rappsilber","given":"Juri"},{"family":"Hochstrasser","given":"Mark"}],"issued":{"date-parts":[["2015",10,8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H1] Association between the CP and the RP

The association of the RP at one or both ends of the CP is crucial for the function of the 26S proteasome because the RP controls essential steps in proteasomal degradation: substrate recognition, deubiquitination, unfolding, translocation and opening of the CP gate (Fig. 1). All these steps ensure a selective degradation of proteins. RP-CP association is mediated by the insertion of the C-terminal HbYX (Hb: hydrophobic; Y: tyrosine or phenylalanine; X: any amino acid) motifs of Rpt proteins into the α-pockets[67,78]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2aent356u0","properties":{"formattedCitation":"{\\rtf \\super 67,78\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":44,"uris":["http://zotero.org/users/4604651/items/IAY7N567"],"uri":["http://zotero.org/users/4604651/items/IAY7N567"],"itemData":{"id":44,"type":"article-journal","title":"Reconfiguration of the proteasome during chaperone-mediated assembly","container-title":"Nature","page":"512-516","volume":"497","issue":"7450","source":"www.nature.com","abstract":"The proteasomal ATPase ring, comprising Rpt1–Rpt6,

associates with the heptameric α-ring of the proteasome core particle (CP) in the mature proteasome, with the Rpt carboxy-terminal tails inserting into pockets of the α-ring. Rpt ring assembly is mediated by four chaperones, each binding a distinct Rpt subunit. Here we report that the base subassembly of the Saccharomyces cerevisiae proteasome, which includes the Rpt ring, forms a high-affinity complex with the CP. This complex is subject to active dissociation by the chaperones Hsm3, Nas6 and Rpn14. Chaperone-mediated dissociation was abrogated by a non-hydrolysable ATP analogue, indicating that chaperone action is coupled to nucleotide hydrolysis by the Rpt ring. Unexpectedly, synthetic Rpt tail peptides bound α-pockets with poor specificity, except for Rpt6, which uniquely bound the α2/α3-pocket. Although the Rpt6 tail is not visualized within an α-pocket in mature proteasomes, it inserts into the α2/α3-pocket in the base–CP complex and is important for complex formation. Thus, the Rpt–CP interface is reconfigured when the lid complex joins the nascent proteasome to form the mature holoenzyme.","DOI":"10.1038/nature12123","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Park","given":"Soyeon"},{"family":"Li","given":"Xueming"},{"family":"Kim","given":"Ho Min"},{"family":"Singh","given":"Chingakham Ranjit"},{"family":"Tian","given":"Geng"},{"family":"Hoyt","given":"Martin A."},{"family":"Lovell","given":"Scott"},{"family":"Battaile","given":"Kevin P."},{"family":"Zolkiewski","given":"Michal"},{"family":"Coffino","given":"Philip"},{"family":"Roelofs","given":"Jeroen"},{"family":"Cheng","given":"Yifan"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2013",5,23]]}}},{"id":186,"uris":["http://zotero.org/users/4604651/items/HK8IUK8E"],"uri":["http://zotero.org/users/4604651/items/HK8IUK8E"],"itemData":{"id":186,"type":"article-journal","title":"Assembly manual for the proteasome regulatory particle: the first draft","container-title":"Biochemical Society transactions","page":"6-13","volume":"38","issue":"Pt 1","source":"PubMed Central","abstract":"The proteasome is the most complex protease known, with a molecular mass of approximately 3 MDa and 33 distinct subunits. Recent studies reported the discovery of four chaperones that promote the assembly of a 19-subunit subcomplex of the proteasome known as the regulatory particle, or RP. These and other findings define a new and highly unusual macromolecular assembly pathway. The RP mediates substrate selection by the proteasome and injects substrates into the core particle (CP) to be degraded. A heterohexameric ring of ATPases, the Rpt proteins, is critical for RP function. These ATPases abut the CP and their C-terminal tails help to stabilize the RP-CP interface. ATPase heterodimers bound to the chaperone proteins are early intermediates in assembly of the ATPase ring. The four chaperones have the common feature of binding the C-domains of Rpt proteins, apparently a remarkable example of convergent evolution; each chaperone binds a specific Rpt subunit. The C-domains are distinct from the C-terminal tails but proximal to them. Some but probably not all of the RP chaperones appear to compete with CP for binding of the Rpt proteins, as a result of the proximity of the tails to the C-domain. This competition may underlie the release mechanism for these chaperones. Genetic studies in yeast point to the importance of the interaction between the CP and the Rpt tails in assembly, and a recent biochemical study in mammals suggests that RP assembly takes place on pre-assembled CP. These results do not exclude a parallel, CP-independent pathway of assembly. Ongoing work should soon clarify the roles of both the CP and the four chaperones in RP assembly.","DOI":"10.1042/BST0380006","ISSN":"0300-5127","note":"PMID: 20074027\nPMCID: PMC3431156","shortTitle":"Assembly manual for the proteasome regulatory particle","journalAbbreviation":"Biochem Soc Trans","author":[{"family":"Park","given":"Soyeon"},{"family":"Tian","given":"Geng"},{"family":"Roelofs","given":"Jeroen"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2010",2]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} }. This interaction induces conformational changes of the CP displacing the N-terminal tails of the α-subunits from the centre of the CP channel to open the CP gate when the substrate is engaged[7]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1r1d2jo1fb","properties":{"formattedCitation":"{\\rtf \\super 7\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Interestingly, Pba1 and Pba2 also contain HbYX motifs explaining how Pba1-Pba2 heterodimer prevents premature RP-CP association[52]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1a0j5ub246","properties":{"formattedCitation":"{\\rtf \\super 52\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":56,"uris":["http://zotero.org/users/4604651/items/CHJR4V3C"],"uri":["http://zotero.org/users/4604651/items/CHJR4V3C"],"itemData":{"id":56,"type":"article-journal","title":"Structure of a Proteasome Pba1-Pba2 Complex","container-title":"The Journal of Biological Chemistry","page":"37371-37382","volume":"287","issue":"44","source":"PubMed Central","abstract":"Background: Pba1-Pba2 facilitates proteasome α-ring assembly., Results: Pba1-Pba2 binds mature proteasomes using C-terminal motifs and sequesters α-subunit N termini. It does not activate and is not degraded by isolated 20S proteasomes., Conclusion: Pba1-Pba2 is important for proteasome-dependent maintenance of mitochondrial function. The structure is consistent with multiple roles in proteasome assembly., Significance: Models of proteasome assembly and Pba1-Pba2 proteasome function are advanced., The 20S proteasome is an essential, 28-subunit protease that sequesters proteolytic sites within a central chamber, thereby repressing substrate degradation until proteasome activators open the entrance/exit gate. Two established activators, Blm10 and PAN/19S, induce gate opening by binding to the pockets between proteasome α-subunits using C-terminal HbYX (hydrophobic-tyrosine-any residue) motifs. Equivalent HbYX motifs have

been identified in Pba1 and Pba2, which function in proteasome assembly. Here, we demonstrate that Pba1-Pba2 proteins form a stable heterodimer that utilizes its HbYX motifs to bind mature 20S proteasomes in vitro and that the Pba1-Pba2 HbYX motifs are important for a physiological function of proteasomes, the maintenance of mitochondrial function. Other factors that contribute to proteasome assembly or function also act in the maintenance of mitochondrial function and display complex genetic interactions with one another, possibly revealing an unexpected pathway of mitochondrial regulation involving the Pba1-Pba2 proteasome interaction. Our determination of a proteasome Pba1-Pba2 crystal structure reveals a Pba1 HbYX interaction that is superimposable with those of known activators, a Pba2 HbYX interaction that is different from those reported previously, and a gate structure that is disrupted but not sufficiently open to allow entry of even small peptides. These findings extend understanding of proteasome interactions with HbYX motifs and suggest multiple roles for Pba1-Pba2 interactions throughout proteasome assembly and function.","DOI":"10.1074/jbc.M112.367003","ISSN":"0021-9258","note":"PMID: 22930756\nPMCID: PMC3481334","journalAbbreviation":"J Biol Chem","author":[{"family":"Stadtmueller","given":"Beth M."},{"family":"Kish-Trier","given":"Erik"},{"family":"Ferrell","given":"Katherine"},{"family":"Petersen","given":"Charisse N."},{"family":"Robinson","given":"Howard"},{"family":"Myszka","given":"David G."},{"family":"Eckert","given":"Debra M."},{"family":"Formosa","given":"Tim"},{"family":"Hill","given":"Christopher P."}],"issued":{"date-parts":[["2012",10,26]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Similarly, Nas6, by interacting with Rpt3, sterically clashes with CP-binding, which prevents premature docking of the RP to the CP[66,79]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1vk36qt3oh","properties":{"formattedCitation":"{\\rtf \\super 66,79\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":46,"uris":["http://zotero.org/users/4604651/items/KV6SHJCF"],"uri":["http://zotero.org/users/4604651/items/KV6SHJCF"],"itemData":{"id":46,"type":"article-journal","title":"Chaperone-mediated pathway of proteasome regulatory particle assembly","container-title":"Nature","page":"861-865","volume":"459","issue":"7248","source":"www.nature.com","abstract":"The proteasome is a protease that controls diverse processes in eukaryotic cells. Its regulatory particle (RP) initiates the degradation of ubiquitin–protein conjugates by unfolding the substrate and translocating it into the proteasome core particle (CP) to be degraded. The RP has 19 subunits, and their pathway of assembly is not understood. Here we show that in the yeast Saccharomyces cerevisiae three proteins are found associated with RP but not with the RP–CP holoenzyme: Nas6, Rpn14 and Hsm3. Mutations in the corresponding genes confer proteasome loss-of-function phenotypes, despite their virtual absence from the holoenzyme. These effects result from deficient RP assembly. Thus, Nas6, Rpn14 and Hsm3 are RP chaperones. The RP contains six ATPases–the Rpt proteins–and each RP chaperone binds to the carboxy-terminal domain of a specific Rpt. We show in an accompanying study that RP assembly is templated through the Rpt C termini, apparently by their insertion into binding pockets in the CP. Thus, RP chaperones may regulate proteasome assembly by directly restricting the accessibility of Rpt C termini to the CP. In addition, competition between the RP chaperones and the CP for Rpt engagement may explain the release of RP chaperones as proteasomes mature.","DOI":"10.1038/nature08063","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Roelofs","given":"Jeroen"},{"family":"Park","given":"Soyeon"},{"family":"Haas","given":"Wilhelm"},{"family":"Tian","given":"Geng"},{"family":"McAllister","given":"Fiona E."},{"family":"Huo","given":"Ying"},{"family":"Lee","given":"Byung-

Hoon"},{"family":"Zhang","given":"Fan"},{"family":"Shi","given":"Yigong"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009",6,11]]}},{"id":194,"uris":["http://zotero.org/users/4604651/items/HXDLBSZP"],"uri":["http://zotero.org/users/4604651/items/HXDLBSZP"],"itemData":{"id":194,"type":"article-journal","title":"Proteasome Activation is Mediated via a Functional Switch of the Rpt6 C-terminal Tail Following Chaperone-dependent Assembly","container-title":"Scientific Reports","page":"srep14909","volume":"5","source":"www.nature.com","abstract":"Article","DOI":"10.1038/srep14909","ISSN":"2045-2322","language":"en","author":[{"family":"Sokolova","given":"Vladyslava"},{"family":"Li","given":"Frances"},{"family":"Polovin","given":"George"},{"family":"Park","given":"Soyeon"}],"issued":{"date-parts":[["2015",10,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Additionally, Nas6 also obstructs RP base-lid association and thus has two functions in proteasome assembly[71]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2c4og2ajqt","properties":{"formattedCitation":"{\\rtf \\super 71\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":42,"uris":["http://zotero.org/users/4604651/items/6UQDINEA"],"uri":["http://zotero.org/users/4604651/items/6UQDINEA"],"itemData":{"id":42,"type":"article-journal","title":"Nucleotide-dependent switch in proteasome assembly mediated by the Nas6 chaperone","container-title":"Proceedings of the National Academy of Sciences","page":"1548-1553","volume":"114","issue":"7","source":"www.pnas.org","abstract":"The proteasome is assembled via the nine-subunit lid, nine-subunit base, and 28-subunit core particle (CP). Previous work has shown that the chaperones Rpn14, Nas6, Hsm3, and Nas2 each bind a specific ATPase subunit of the base and antagonize base–CP interaction. Here, we show that the Nas6 chaperone also obstructs base–lid association. Nas6 alternates between these two inhibitory modes according to the nucleotide state of the base. When ATP cannot be hydrolyzed, Nas6 interferes with base–lid, but not base–CP, association. In contrast, under conditions of ATP hydrolysis, Nas6 obstructs base–CP, but not base–lid, association. Modeling of Nas6 into cryoelectron microscopy structures of the proteasome suggests that Nas6 controls both base–lid affinity and base–CP affinity through steric hindrance; Nas6 clashes with the lid in the ATP-hydrolysis–blocked proteasome, but clashes instead with the CP in the ATP-hydrolysis–competent proteasome. Thus, Nas6 provides a dual mechanism to control assembly at both major interfaces of the proteasome.","DOI":"10.1073/pnas.1612922114","ISSN":"0027-8424, 1091-6490","note":"PMID: 28137839","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Li","given":"Frances"},{"family":"Tian","given":"Geng"},{"family":"Langager","given":"Deanna"},{"f

amily":"Sokolova","given":"Vladyslava"},{"family":"Finley","given":"Daniel"},{"family":"Park","given":"Soyeon"}],"issued":{"date-parts":[["2017",2,14]]}},"locator":"6"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Structural insights into the RP have also shown that the lid subunits Rpn5 and Rpn6 form finger-like structures that contact the CP subunits α1 and α2, respectively[22]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2o3uht7gvg","properties":{"formattedCitation":"{\\rtf \\super 22\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. This unexpected interaction between the lid and the CP suggests that Rpn5 and Rpn6 may enhance and stabilize the association between the RP and the CP[22]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ajadt7b7gs","properties":{"formattedCitation":"{\\rtf \\super 22\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies

reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H1] Substrate recognition by the proteasome

An important aspect of the regulation of proteasomal degradation is achieved by controlling access of substrates inside the proteasome. Ubiquitinated proteins are directly recognized by the proteasome by three ubiquitin receptors which are the intrinsic and stoichiometric proteasome subunits Rpn1, Rpn10 and Rpn13[7,14,80]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a11f5vnu5t7","properties":{"formattedCitation":"{\\rtf \\super 7,14,80\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":12,"uris":["http://zotero.org/users/4604651/items/4V75P44H"],"uri":["http://zotero.org/users/4604651/items/4V75P44H"],"itemData":{"id":12,"type":"article-journal","title":"Recognition of Client Proteins by the Proteasome","container-title":"Annual Review of Biophysics","page":"149-173","volume":"46","source":"PubMed","abstract":"The ubiquitin proteasome system controls the concentrations of regulatory proteins and removes damaged and misfolded proteins from cells. Proteins are targeted to the protease at the center of this system, the proteasome, by ubiquitin tags, but ubiquitin is also used as a signal in other cellular processes. Specificity is conferred by the size and structure of the ubiquitin tags, which are recognized by receptors associated with the different cellular processes. However, the ubiquitin code remains ambiguous, and the same ubiquitin tag can target different proteins to different fates. After binding substrate protein at the ubiquitin tag, the proteasome initiates degradation at a disordered region in the substrate. The proteasome has pronounced preferences for the initiation site, and its recognition represents a second component of the degradation signal.","DOI":"10.1146/annurev-biophys-070816-033719","ISSN":"1936-1238","note":"PMID: 28301771","journalAbbreviation":"Annu Rev Biophys","language":"eng","author":[{"family":"Yu","given":"Houqing"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2017",5,22]]}}},{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber

within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}},{"id":205,"uris":["http://zotero.org/users/4604651/items/TII2I3V4"],"uri":["http://zotero.org/users/4604651/items/TII2I3V4"],"itemData":{"id":205,"type":"article-journal","title":"Rpn1 provides adjacent receptor sites for substrate binding and deubiquitination by the proteasome","container-title":"Science (New York, N.Y.)","volume":"351","issue":"6275","source":"PubMed","abstract":"Hundreds of pathways for degradation converge at ubiquitin recognition by a proteasome. Here, we found that the five known proteasomal ubiquitin receptors in yeast are collectively nonessential for ubiquitin recognition and identified a sixth receptor, Rpn1. A site (T1:) in the Rpn1 toroid recognized ubiquitin and ubiquitin-like (UBL:) domains of substrate shuttling factors. T1 structures with monoubiquitin or lysine 48 diubiquitin show three neighboring outer helices engaging two ubiquitins. T1 contributes a distinct substrate-binding pathway with preference for lysine 48-linked chains. Proximal to T1 within the Rpn1 toroid is a second UBL-binding site (T2:) that assists in ubiquitin chain disassembly, by binding the UBL of deubiquitinating enzyme Ubp6. Thus, a two-site recognition domain intrinsic to the proteasome uses distinct ubiquitin-fold ligands to assemble substrates, shuttling factors, and a deubiquitinating enzyme.","DOI":"10.1126/science.aad9421","ISSN":"1095-9203","note":"PMID: 26912900\nPMCID: PMC4980823","journalAbbreviation":"Science","language":"eng","author":[{"family":"Shi","given":"Yuan"},{"family":"Chen","given":"Xiang"},{"family":"Elsasser","given":"Suzanne"},{"family":"Stocks","given":"Bradley B."},{"family":"Tian","given":"Geng"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Shi","given":"Yanhong"},{"family":"Zhang","given":"Naixia"},{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tuebing","given":"Fabian"},{"family":"Sun","given":"Shuangwu"},{"family":"Vannoy","given":"Jacob"},{"family":"Tarasov","given":"Sergey G."},{"family":"Engen","given":"John R."},{"family":"Finley","given":"Daniel"},{"family":"Walters","given":"Kylie J."}],"issued":{"date-parts":[["2016",2,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Rpn10 and Rpn13 are not essential in yeast[81]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a8tngf6uss","properties":{"formattedCitation":"{\\rtf \\super 81\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":380,"uris":["http://zotero.org/users/4604651/items/P3ZP7BJM"],"uri":["http://zotero.org/users/4604651/items/P3ZP7BJM"],"itemData":{"id":380,"type":"article-journal","title":"The multiubiquitin-chain-binding protein Mcb1 is a component of the 26S proteasome in Saccharomyces cerevisiae and plays a nonessential, substrate-specific role in protein

turnover","container-title":"Molecular and Cellular Biology","page":"6020-6028","volume":"16","issue":"11","source":"PubMed","abstract":"The 26S proteasome is an essential proteolytic complex that is responsible for degrading proteins conjugated with ubiquitin. It has been proposed that the recognition of substrates by the 26S proteasome is mediated by a multiubiquitin-chain-binding protein that has previously been characterized in both plants and animals. In this study, we identified a Saccharomyces cerevisiae homolog of this protein, designated Mcb1. Mcb1 copurified with the 26S proteasome in both conventional and nickel chelate chromatography. In addition, a significant fraction of Mcb1 in cell extracts was present in a low-molecular-mass form free of the 26S complex. Recombinant Mcb1 protein bound multiubiquitin chains in vitro and, like its plant and animal counterparts, exhibited a binding preference for longer chains. Surprisingly, (delta)mcb1 deletion mutants were viable, grew at near-wild-type rates, degraded the bulk of short-lived proteins normally, and were not sensitive to UV radiation or heat stress. These data indicate that Mcb1 is not an essential component of the ubiquitin-proteasome pathway in S.cerevisiae. However, the (delta)mcb1 mutant exhibited a modest sensitivity to amino acid analogs and had increased steady-state levels of ubiquitin-protein conjugates. Whereas the N-end rule substrate, Arg-beta-galactosidase, was degraded at the wild-type rate in the (delta)mcb1 strain, the ubiquitin fusion degradation pathway substrate, ubiquitin-Pro-beta-galactosidase, was markedly stabilized. Collectively, these data suggest that Mcb1 is not the sole factor involved in ubiquitin recognition by the 26S proteasome and that Mcb1 may interact with only a subset of ubiquitinated substrates.","ISSN":"0270-7306","note":"PMID: 8887631\nPMCID: PMC231604","journalAbbreviation":"Mol. Cell. Biol.","language":"eng","author":[{"family":"Nocker","given":"S.","non-dropping-particle":"van"},{"family":"Sadis","given":"S."},{"family":"Rubin","given":"D. M."},{"family":"Glickman","given":"M."},{"family":"Fu","given":"H."},{"family":"Coux","given":"O."},{"family":"Wefes","given":"I."},{"family":"Finley","given":"D."},{"family":"Vierstra","given":"R. D."}],"issued":{"date-parts":[["1996",11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}, suggesting they have overlapping functions, unlike Rpn1, which is vital[80]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a28kj4r7e6f","properties":{"formattedCitation":"{\\rtf \\super 80\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":205,"uris":["http://zotero.org/users/4604651/items/TII2I3V4"],"uri":["http://zotero.org/users/4604651/items/TII2I3V4"],"itemData":{"id":205,"type":"article-journal","title":"Rpn1 provides adjacent receptor sites for substrate binding and deubiquitination by the proteasome","container-title":"Science (New York, N.Y.)","volume":"351","issue":"6275","source":"PubMed","abstract":"Hundreds of pathways for degradation converge at ubiquitin recognition by a proteasome. Here, we found that the five known proteasomal ubiquitin receptors in yeast are collectively nonessential for ubiquitin recognition and identified a sixth receptor, Rpn1. A site (T1:) in the Rpn1 toroid recognized ubiquitin and ubiquitin-like (UBL:) domains of substrate shuttling factors. T1 structures with monoubiquitin or lysine 48 diubiquitin show three neighboring outer helices engaging two ubiquitins. T1 contributes a distinct substrate-binding pathway with preference for lysine 48-linked chains. Proximal to T1 within the Rpn1 toroid is a second UBL-binding site (T2:) that assists in ubiquitin chain disassembly, by binding the UBL of deubiquitinating enzyme Ubp6. Thus, a two-site recognition domain intrinsic to the proteasome uses distinct ubiquitin-fold ligands to assemble substrates, shuttling factors, and a deubiquitinating enzyme.","DOI":"10.1126/science.aad9421","ISSN":"1095-9203","note":"PMID: 26912900\nPMCID: PMC4980823","journalAbbreviation":"Science","language":"eng","author":[{"family":"Shi","given":"Yuan"},{"family":"Chen","given":"X

iang"},{"family":"Elsasser","given":"Suzanne"},{"family":"Stocks","given":"Bradley B."},{"family":"Tian","given":"Geng"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Shi","given":"Yanhong"},{"family":"Zhang","given":"Naixia"},{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tuebing","given":"Fabian"},{"family":"Sun","given":"Shuangwu"},{"family":"Vannoy","given":"Jacob"},{"family":"Tarasov","given":"Sergey G."},{"family":"Engen","given":"John R."},{"family":"Finley","given":"Daniel"},{"family":"Walters","given":"Kylie J."}],"issued":{"date-parts":[["2016",2,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Liver-specific deletion of either Rpn10 or Rpn13 in adult mice is tolerated, whereas loss of both subunits causes severe liver damage with accumulation of polyubiquitinated conjugates[82]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a12amooq4eo","properties":{"formattedCitation":"{\\rtf \\super 82\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":382,"uris":["http://zotero.org/users/4604651/items/GJU32LRL"],"uri":["http://zotero.org/users/4604651/items/GJU32LRL"],"itemData":{"id":382,"type":"article-journal","title":"Redundant Roles of Rpn10 and Rpn13 in Recognition of Ubiquitinated Proteins and Cellular Homeostasis","container-title":"PLOS Genetics","page":"e1005401","volume":"11","issue":"7","source":"PLoS Journals","abstract":"Author Summary At least two major ubiquitin receptor subunits that directly capture ubiquitin chains have been identified in the proteasome: Rpn10 and Rpn13. Analyses in Saccharomyces cerevisiae have suggested only a modest role of Rpn10 and Rpn13 in the recruitment of ubiquitinated proteins, as double deletion of Rpn10 and Rpn13 causes very mild phenotypes. Considering that ubiquitin recognition is an essential process for protein degradation by the proteasome and that failure in degradation of ubiquitinated proteins leads to human diseases such as neurodegeneration, it is important to evaluate the role of Rpn10 and Rpn13 in mammals. Liver-specific deletion of either Rpn10 or Rpn13 showed modest impairment, but simultaneous loss of both Rpn10 and Rpn13 caused severe liver injury accompanied by massive accumulation of ubiquitin conjugates and failure in recruiting mHR23B and ubiquilin/Plic-1 and -4 proteins, which deliver ubiquitinated proteins to the proteasome. Our findings indicate that the largely redundant roles of Rpn10 and Rpn13 in ubiquitin recognition and recruitment of mHR23B and ubiquilin/Plic-1 and -4 are essential for cellular homeostasis in mammals and should provide information for understanding the mechanism of ubiquitin recognition by the 26S proteasome in mammals and for development of therapeutic agents targeting protein degradation.","DOI":"10.1371/journal.pgen.1005401","ISSN":"1553-7404","journalAbbreviation":"PLOS Genetics","language":"en","author":[{"family":"Hamazaki","given":"Jun"},{"family":"Hirayama","given":"Shoshiro"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2015",7,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . However, Rpn10 deletion in mice embryos causes embryonic lethality, indicating that specific Rpn10 functions are important for mammalian development[83]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1nj5543hh1","properties":{"formattedCitation":"{\\rtf \\super 83\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":124,"uris":["http://zotero.org/users/4604651/items/VTMZAJQ7"],"uri":["http://zotero.org/users/4604651/items/VTMZAJQ7"],"itemData":{"id":124,"type":"article-journal","title":"Rpn10-Mediated Degradation of Ubiquitinated Proteins Is Essential for Mouse Development","container-title":"Molecular and Cellular Biology","page":"6629-

6638","volume":"27","issue":"19","source":"mcb.asm.org","abstract":"Rpn10 is a subunit of the 26S proteasome that recognizes polyubiquitinated proteins. The importance of Rpn10 in ubiquitin-mediated proteolysis is debatable, since a deficiency of Rpn10 causes different phenotypes in different organisms. To date, the role of mammalian Rpn10 has not been examined genetically. Moreover, vertebrates have five splice variants of Rpn10 whose expressions are developmentally regulated, but their biological significance is not understood. To address these issues, we generated three kinds of Rpn10 mutant mice. Rpn10 knockout resulted in early-embryonic lethality, demonstrating the essential role of Rpn10 in mouse development. Rpn10a knock-in mice, which exclusively expressed the constitutive type of Rpn10 and did not express vertebrate-specific variants, grew normally, indicating that Rpn10 diversity is not essential for conventional development. Mice expressing the N-terminal portion of Rpn10, which contained a von Willebrand factor A (VWA) domain but lacked ubiquitin-interacting motifs (Rpn10ΔUIM), also exhibited embryonic lethality, suggesting the important contribution of UIM domains to viability, but survived longer than Rpn10-null mice, consistent with a “facilitator” function of the VWA domain. Biochemical analysis of the Rpn10ΔUIM liver showed specific impairment of degradation of ubiquitinated proteins. Our results demonstrate that Rpn10-mediated degradation of ubiquitinated proteins, catalyzed by UIMs, is indispensable for mammalian life.","DOI":"10.1128/MCB.00509-07","ISSN":"0270-7306, 1098-5549","note":"PMID: 17646385","journalAbbreviation":"Mol. Cell. Biol.","language":"en","author":[{"family":"Hamazaki","given":"Jun"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Kawahara","given":"Hiroyuki"},{"family":"Hisanaga","given":"Shin-ichi"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2007",10,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. In yeast, shuttling factors Rad23, Dsk2, and Ddi1 escort ubiquitinated substrates to the proteasome[7,14,80]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"auipb6n7fd","properties":{"formattedCitation":"{\\rtf \\super 7,14,80\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":12,"uris":["http://zotero.org/users/4604651/items/4V75P44H"],"uri":["http://zotero.org/users/4604651/items/4V75P44H"],"itemData":{"id":12,"type":"article-journal","title":"Recognition of Client Proteins by the Proteasome","container-title":"Annual Review of Biophysics","page":"149-173","volume":"46","source":"PubMed","abstract":"The ubiquitin proteasome system controls the concentrations of regulatory proteins and removes damaged and misfolded proteins from cells. Proteins are targeted to the protease at the center of this system, the proteasome, by ubiquitin tags, but ubiquitin is also used as a signal in other cellular processes. Specificity is conferred by the size and structure of the ubiquitin tags, which are recognized by receptors associated with the different cellular processes. However, the ubiquitin code remains ambiguous, and the same ubiquitin tag can target different proteins to different fates. After binding substrate protein at the ubiquitin tag, the proteasome initiates degradation at a disordered region in the substrate. The proteasome has pronounced preferences for the initiation site, and its recognition represents a second component of the degradation signal.","DOI":"10.1146/annurev-biophys-070816-033719","ISSN":"1936-1238","note":"PMID: 28301771","journalAbbreviation":"Annu Rev Biophys","language":"eng","author":[{"family":"Yu","given":"Houqing"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2017",5,22]]}}},{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The

proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}},{"id":205,"uris":["http://zotero.org/users/4604651/items/TII2I3V4"],"uri":["http://zotero.org/users/4604651/items/TII2I3V4"],"itemData":{"id":205,"type":"article-journal","title":"Rpn1 provides adjacent receptor sites for substrate binding and deubiquitination by the proteasome","container-title":"Science (New York, N.Y.)","volume":"351","issue":"6275","source":"PubMed","abstract":"Hundreds of pathways for degradation converge at ubiquitin recognition by a proteasome. Here, we found that the five known proteasomal ubiquitin receptors in yeast are collectively nonessential for ubiquitin recognition and identified a sixth receptor, Rpn1. A site (T1:) in the Rpn1 toroid recognized ubiquitin and ubiquitin-like (UBL:) domains of substrate shuttling factors. T1 structures with monoubiquitin or lysine 48 diubiquitin show three neighboring outer helices engaging two ubiquitins. T1 contributes a distinct substrate-binding pathway with preference for lysine 48-linked chains. Proximal to T1 within the Rpn1 toroid is a second UBL-binding site (T2:) that assists in ubiquitin chain disassembly, by binding the UBL of deubiquitinating enzyme Ubp6. Thus, a two-site recognition domain intrinsic to the proteasome uses distinct ubiquitin-fold ligands to assemble substrates, shuttling factors, and a deubiquitinating enzyme.","DOI":"10.1126/science.aad9421","ISSN":"1095-9203","note":"PMID: 26912900\nPMCID: PMC4980823","journalAbbreviation":"Science","language":"eng","author":[{"family":"Shi","given":"Yuan"},{"family":"Chen","given":"Xiang"},{"family":"Elsasser","given":"Suzanne"},{"family":"Stocks","given":"Bradley B."},{"family":"Tian","given":"Geng"},{"family":"Lee","given":"Byung-Hoon"},{"family":"Shi","given":"Yanhong"},{"family":"Zhang","given":"Naixia"},{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tuebing","given":"Fabian"},{"family":"Sun","given":"Shuangwu"},{"family":"Vannoy","given":"Jacob"},{"family":"Tarasov","given":"Sergey G."},{"family":"Engen","given":"John R."},{"family":"Finley","given":"Daniel"},{"family":"Walters","given":"Kylie J."}],"issued":{"date-parts":[["2016",2,19]]}},"locator":"1"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} .

The shuttling factors are UBL-UBA proteins: they bind to the proteasome through a ubiquitin-like (UBL) domain and to ubiquitin chains with a ubiquitin-associated domain (UBA). These

shuttling factors and the intrinsic substrate receptors coordinate substrate degradation and their requirement varies for different proteins.

Substrate degradation is coupled to deubiquitylation[7]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"af2otqrf0l","properties":{"formattedCitation":"{\\rtf \\super 7\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":98,"uris":["http://zotero.org/users/4604651/items/B2TRT8VS"],"uri":["http://zotero.org/users/4604651/items/B2TRT8VS"],"itemData":{"id":98,"type":"article-journal","title":"Recognition and processing of ubiquitin-protein conjugates by the proteasome","container-title":"Annual Review of Biochemistry","page":"477-513","volume":"78","source":"PubMed","abstract":"The proteasome is an intricate molecular machine, which serves to degrade proteins following their conjugation to ubiquitin. Substrates dock onto the proteasome at its 19-subunit regulatory particle via a diverse set of ubiquitin receptors and are then translocated into an internal chamber within the 28-subunit proteolytic core particle (CP), where they are hydrolyzed. Substrate is threaded into the CP through a narrow gated channel, and thus translocation requires unfolding of the substrate. Six distinct ATPases in the regulatory particle appear to form a ring complex and to drive unfolding as well as translocation. ATP-dependent, degradation-coupled deubiquitination of the substrate is required both for efficient substrate degradation and for preventing the degradation of the ubiquitin tag. However, the proteasome also contains deubiquitinating enzymes (DUBs) that can remove ubiquitin before substrate degradation initiates, thus allowing some substrates to dissociate from the proteasome and escape degradation. Here we examine the key elements of this molecular machine and how they cooperate in the processing of proteolytic substrates.","DOI":"10.1146/annurev.biochem.78.081507.101607","ISSN":"1545-4509","note":"PMID: 19489727\nPMCID: PMC3431160","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }, which is an important element of control for proteasomal degradation exerted by proteasome-associated DUBs[84]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"at7hpef62m","properties":{"formattedCitation":"{\\rtf \\super 84\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":389,"uris":["http://zotero.org/users/4604651/items/LXRXWHD7"],"uri":["http://zotero.org/users/4604651/items/LXRXWHD7"],"itemData":{"id":389,"type":"article-journal","title":"Meddling with Fate: The Proteasomal Deubiquitinating Enzymes","container-title":"Journal of Molecular Biology","page":"3525-3545","volume":"429","issue":"22","source":"PubMed","abstract":"Three deubiquitinating enzymes-Rpn11, Usp14, and Uch37-are associated with the proteasome regulatory particle. These enzymes allow proteasomes to remove ubiquitin from substrates before they are translocated into the core particle to be degraded. Although the translocation channel is too narrow for folded proteins, the force of translocation unfolds them mechanically. As translocation proceeds, ubiquitin chains bound to substrate are drawn to the channel's entry port, where they can impede further translocation. Rpn11, situated over the port, can remove these chains without compromising degradation because substrates must be irreversibly committed to degradation before Rpn11 acts. This coupling between deubiquitination and substrate degradation is ensured by the Ins-1 loop of Rpn11, which controls ubiquitin access to its catalytic site. In contrast to Rpn11, Usp14 and Uch37 can rescue substrates from degradation by promoting substrate dissociation from the proteasome prior to the commitment step. Uch37 is unique in being a component of both the proteasome and a second multisubunit assembly, the INO80 complex. However, only recruitment

into the proteasome activates Uch37. Recruitment to the proteasome likewise activates Usp14. However, the influence of Usp14 on the proteasome depends on the substrate, due to its marked preference for proteins that carry multiple ubiquitin chains. Usp14 exerts complex control over the proteasome, suppressing proteasome activity even when inactive in deubiquitination. A major challenge for the field will be to elucidate the specificities of Rpn11, Usp14, and Uch37 in greater depth, employing not only model in vitro substrates but also their endogenous targets.","DOI":"10.1016/j.jmb.2017.09.015","ISSN":"1089-8638","note":"PMID: 28988953\nPMCID: PMC5675770","shortTitle":"Meddling with Fate","journalAbbreviation":"J. Mol. Biol.","language":"eng","author":[{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tian","given":"Geng"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2017",11,10]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. In a manner conceptually similar to the ubiquitin receptors, one DUB is an intrinsic proteasome subunit and others are associated factors. Rpn11 is a proteasome DUB that cleaves the ubiquitin chains after the substrates have been irreversibly engaged into the narrow proteasome entry channel[84]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1f1r30atnp","properties":{"formattedCitation":"{\\rtf \\super 84\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":389,"uris":["http://zotero.org/users/4604651/items/LXRXWHD7"],"uri":["http://zotero.org/users/4604651/items/LXRXWHD7"],"itemData":{"id":389,"type":"article-journal","title":"Meddling with Fate: The Proteasomal Deubiquitinating Enzymes","container-title":"Journal of Molecular Biology","page":"3525-3545","volume":"429","issue":"22","source":"PubMed","abstract":"Three deubiquitinating enzymes-Rpn11, Usp14, and Uch37-are associated with the proteasome regulatory particle. These enzymes allow proteasomes to remove ubiquitin from substrates before they are translocated into the core particle to be degraded. Although the translocation channel is too narrow for folded proteins, the force of translocation unfolds them mechanically. As translocation proceeds, ubiquitin chains bound to substrate are drawn to the channel's entry port, where they can impede further translocation. Rpn11, situated over the port, can remove these chains without compromising degradation because substrates must be irreversibly committed to degradation before Rpn11 acts. This coupling between deubiquitination and substrate degradation is ensured by the Ins-1 loop of Rpn11, which controls ubiquitin access to its catalytic site. In contrast to Rpn11, Usp14 and Uch37 can rescue substrates from degradation by promoting substrate dissociation from the proteasome prior to the commitment step. Uch37 is unique in being a component of both the proteasome and a second multisubunit assembly, the INO80 complex. However, only recruitment into the proteasome activates Uch37. Recruitment to the proteasome likewise activates Usp14. However, the influence of Usp14 on the proteasome depends on the substrate, due to its marked preference for proteins that carry multiple ubiquitin chains. Usp14 exerts complex control over the proteasome, suppressing proteasome activity even when inactive in deubiquitination. A major challenge for the field will be to elucidate the specificities of Rpn11, Usp14, and Uch37 in greater depth, employing not only model in vitro substrates but also their endogenous targets.","DOI":"10.1016/j.jmb.2017.09.015","ISSN":"1089-8638","note":"PMID: 28988953\nPMCID: PMC5675770","shortTitle":"Meddling with Fate","journalAbbreviation":"J. Mol. Biol.","language":"eng","author":[{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tian","given":"Geng"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2017",11,10]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Usp14

(Ubp6 in yeast) and Uch37 are DUBs that can associate with the proteasome and by deubiquitylating substrates, modulate their fate[84]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"at02ufcakb","properties":{"formattedCitation":"{\\rtf \\super 84\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":389,"uris":["http://zotero.org/users/4604651/items/LXRXWHD7"],"uri":["http://zotero.org/users/4604651/items/LXRXWHD7"],"itemData":{"id":389,"type":"article-journal","title":"Meddling with Fate: The Proteasomal Deubiquitinating Enzymes","container-title":"Journal of Molecular Biology","page":"3525-3545","volume":"429","issue":"22","source":"PubMed","abstract":"Three deubiquitinating enzymes-Rpn11, Usp14, and Uch37-are associated with the proteasome regulatory particle. These enzymes allow proteasomes to remove ubiquitin from substrates before they are translocated into the core particle to be degraded. Although the translocation channel is too narrow for folded proteins, the force of translocation unfolds them mechanically. As translocation proceeds, ubiquitin chains bound to substrate are drawn to the channel's entry port, where they can impede further translocation. Rpn11, situated over the port, can remove these chains without compromising degradation because substrates must be irreversibly committed to degradation before Rpn11 acts. This coupling between deubiquitination and substrate degradation is ensured by the Ins-1 loop of Rpn11, which controls ubiquitin access to its catalytic site. In contrast to Rpn11, Usp14 and Uch37 can rescue substrates from degradation by promoting substrate dissociation from the proteasome prior to the commitment step. Uch37 is unique in being a component of both the proteasome and a second multisubunit assembly, the INO80 complex. However, only recruitment into the proteasome activates Uch37. Recruitment to the proteasome likewise activates Usp14. However, the influence of Usp14 on the proteasome depends on the substrate, due to its marked preference for proteins that carry multiple ubiquitin chains. Usp14 exerts complex control over the proteasome, suppressing proteasome activity even when inactive in deubiquitination. A major challenge for the field will be to elucidate the specificities of Rpn11, Usp14, and Uch37 in greater depth, employing not only model in vitro substrates but also their endogenous targets.","DOI":"10.1016/j.jmb.2017.09.015","ISSN":"1089-8638","note":"PMID: 28988953\nPMCID: PMC5675770","shortTitle":"Meddling with Fate","journalAbbreviation":"J. Mol. Biol.","language":"eng","author":[{"family":"Poot","given":"Stefanie A. H.","non-dropping-particle":"de"},{"family":"Tian","given":"Geng"},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2017",11,10]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Such enzymes are being examined as potential drug targets as they play a pivotal role in regulating degradation[85]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1321lft3ks","properties":{"formattedCitation":"{\\rtf \\super 85\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":391,"uris":["http://zotero.org/users/4604651/items/N54J53VP"],"uri":["http://zotero.org/users/4604651/items/N54J53VP"],"itemData":{"id":391,"type":"article-journal","title":"Enhancement of proteasome activity by a small-molecule inhibitor of USP14","container-title":"Nature","page":"179-184","volume":"467","issue":"7312","source":"PubMed","abstract":"Proteasomes, the primary mediators of ubiquitin-protein conjugate degradation, are regulated through complex and poorly understood mechanisms. Here we show that USP14, a proteasome-associated deubiquitinating enzyme, can inhibit the degradation of ubiquitin-protein conjugates both in vitro and in cells. A catalytically inactive variant of USP14 has reduced inhibitory activity, indicating that inhibition is mediated by trimming of the ubiquitin chain on the substrate. A high-

throughput screen identified a selective small-molecule inhibitor of the deubiquitinating activity of human USP14. Treatment of cultured cells with this compound enhanced degradation of several proteasome substrates that have been implicated in neurodegenerative disease. USP14 inhibition accelerated the degradation of oxidized proteins and enhanced resistance to oxidative stress. Enhancement of proteasome activity through inhibition of USP14 may offer a strategy to reduce the levels of aberrant proteins in cells under proteotoxic stress.","DOI":"10.1038/nature09299","ISSN":"1476-4687","note":"PMID: 20829789\nPMCID: PMC2939003","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Lee","given":"Byung-Hoon"},{"family":"Lee","given":"Min Jae"},{"family":"Park","given":"Soyeon"},{"family":"Oh","given":"Dong-Chan"},{"family":"Elsasser","given":"Suzanne"},{"family":"Chen","given":"Ping-Chung"},{"family":"Gartner","given":"Carlos"},{"family":"Dimova","given":"Nevena"},{"family":"Hanna","given":"John"},{"family":"Gygi","given":"Steven P."},{"family":"Wilson","given":"Scott M."},{"family":"King","given":"Randall W."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2010",9,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} .

Ubiquitin-independent degradation by the core 20S proteasome has also been reported[86,87]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a21lfjhjncs","properties":{"formattedCitation":"{\\rtf \\super 86,87\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":393,"uris":["http://zotero.org/users/4604651/items/K6JIG78Q"],"uri":["http://zotero.org/users/4604651/items/K6JIG78Q"],"itemData":{"id":393,"type":"article-journal","title":"Ubiquitin-free routes into the proteasome","container-title":"Cellular and molecular life sciences: CMLS","page":"1596-1600","volume":"61","issue":"13","source":"PubMed","abstract":"The majority of proteasome substrates identified to date are marked for degradation by polyubiquitinylation. Exceptions to this principle, however, are well documented and can help us understand the process proteasomes use to recognize their substrates. Examples include ornithine decarboxylase, p21/Cip1, TCRalpha, IkappaBalpha, c-Jun, calmodulin and thymidylate synthase. Degradation of these proteins can be completely ubiquitin-independent or coexist with ubiquitin-dependent pathways. Uncoupling degradation from ubiquitin modification may reflect the evolutionary conservation of mechanisms optimized for highly specialized regulatory functions.","DOI":"10.1007/s00018-004-4133-9","ISSN":"1420-682X","note":"PMID: 15224184","journalAbbreviation":"Cell. Mol. Life Sci.","language":"eng","author":[{"family":"Hoyt","given":"M. A."},{"family":"Coffino","given":"P."}],"issued":{"date-parts":[["2004",7]]}}},{"id":395,"uris":["http://zotero.org/users/4604651/items/3FT542GQ"],"uri":["http://zotero.org/users/4604651/items/3FT542GQ"],"itemData":{"id":395,"type":"article-journal","title":"Regulating the 20S proteasome ubiquitin-independent degradation pathway","container-title":"Biomolecules","page":"862-884","volume":"4","issue":"3","source":"PubMed","abstract":"For many years, the ubiquitin-26S proteasome degradation pathway was considered the primary route for proteasomal degradation. However, it is now becoming clear that proteins can also be targeted for degradation by the core 20S proteasome itself. Degradation by the 20S proteasome does not require ubiquitin tagging or the presence of the 19S regulatory particle; rather, it relies on the inherent structural disorder of the protein being degraded. Thus, proteins that contain unstructured regions due to oxidation, mutation, or aging, as well as naturally, intrinsically unfolded proteins, are susceptible to 20S degradation. Unlike the extensive knowledge acquired over the years concerning degradation by the 26S proteasome, relatively little is known about the means by which 20S-mediated proteolysis is controlled. Here, we describe our current understanding of

the regulatory mechanisms that coordinate 20S proteasome-mediated degradation, and highlight the gaps in knowledge that remain to be bridged.","DOI":"10.3390/biom4030862","ISSN":"2218-273X","note":"PMID: 25250704\nPMCID: PMC4192676","journalAbbreviation":"Biomolecules","language":"eng","author":[{"family":"Ben-Nissan","given":"Gili"},{"family":"Sharon","given":"Michal"}],"issued":{"date-parts":[["2014",9,23]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , although much less is known about the mechanisms by which proteins can be targeted and degraded by the 20S in absence of the 19S and ubiquitin. Regardless of the targeting mode, as the presence of an unstructured region is a prerequisite for the initiation of substrate degradation[14,16]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2pn4jfd5cc","properties":{"formattedCitation":"{\\rtf \\super 14,16\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":12,"uris":["http://zotero.org/users/4604651/items/4V75P44H"],"uri":["http://zotero.org/users/4604651/items/4V75P44H"],"itemData":{"id":12,"type":"article-journal","title":"Recognition of Client Proteins by the Proteasome","container-title":"Annual Review of Biophysics","page":"149-173","volume":"46","source":"PubMed","abstract":"The ubiquitin proteasome system controls the concentrations of regulatory proteins and removes damaged and misfolded proteins from cells. Proteins are targeted to the protease at the center of this system, the proteasome, by ubiquitin tags, but ubiquitin is also used as a signal in other cellular processes. Specificity is conferred by the size and structure of the ubiquitin tags, which are recognized by receptors associated with the different cellular processes. However, the ubiquitin code remains ambiguous, and the same ubiquitin tag can target different proteins to different fates. After binding substrate protein at the ubiquitin tag, the proteasome initiates degradation at a disordered region in the substrate. The proteasome has pronounced preferences for the initiation site, and its recognition represents a second component of the degradation signal.","DOI":"10.1146/annurev-biophys-070816-033719","ISSN":"1936-1238","note":"PMID: 28301771","journalAbbreviation":"Annu Rev Biophys","language":"eng","author":[{"family":"Yu","given":"Houqing"},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2017",5,22]]}}},{"id":78,"uris":["http://zotero.org/users/4604651/items/ERUTYSWW"],"uri":["http://zotero.org/users/4604651/items/ERUTYSWW"],"itemData":{"id":78,"type":"article-journal","title":"An unstructured initiation site is required for efficient proteasome-mediated degradation","container-title":"Nature Structural & Molecular Biology","page":"830-837","volume":"11","issue":"9","source":"PubMed","abstract":"The proteasome is the main ATP-dependent protease in eukaryotic cells and controls the concentration of many regulatory proteins in the cytosol and nucleus. Proteins are targeted to the proteasome by the covalent attachment of polyubiquitin chains. The ubiquitin modification serves as the proteasome recognition element but by itself is not sufficient for efficient degradation of folded proteins. We report that proteolysis of tightly folded proteins is accelerated greatly when an unstructured region is attached to the substrate. The unstructured region serves as the initiation site for degradation and is hydrolyzed first, after which the rest of the protein is digested sequentially. These results identify the initiation site as a novel component of the targeting signal, which is required to engage the proteasome unfolding machinery efficiently. The proteasome degrades a substrate by first binding to its ubiquitin modification and then initiating unfolding at an unstructured region.","DOI":"10.1038/nsmb814","ISSN":"1545-9993","note":"PMID: 15311270","journalAbbreviation":"Nat. Struct. Mol. Biol.","language":"eng","author":[{"family":"Prakash","given":"Sumit"},{"family":"Tian","given":"Lin"},{"family":"Ratliff","given":"Kevi

n S."},{"family":"Lehotzky","given":"Rebecca E."},{"family":"Matouschek","given":"Andreas"}],"issued":{"date-parts":[["2004",9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , protein unfolding could also be a direct mode of controlling degradation.

[H1] Regulation of proteasome subunit abundance

Because making the proteasome is energetically costly and because compromised proteasomal degradation leads to cells death[88]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2m0af6sg5e","properties":{"formattedCitation":"{\\rtf \\super 88\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":185,"uris":["http://zotero.org/users/4604651/items/LX7XTDNR"],"uri":["http://zotero.org/users/4604651/items/LX7XTDNR"],"itemData":{"id":185,"type":"article-journal","title":"The 26 S proteasome: from basic mechanisms to drug targeting","container-title":"The Journal of Biological Chemistry","page":"33713-33718","volume":"284","issue":"49","source":"PubMed","abstract":"The regulated degradation of proteins within eukaryotes and bacterial cells is catalyzed primarily by large multimeric proteases in ATP-dependent manner. In eukaryotes, the 26 S proteasome is essential for the rapid destruction of key regulatory proteins, such as cell cycle regulators and transcription factors, whose fast and tuned elimination is necessary for the proper control of the fundamental cell processes they regulate. In addition, the 26 S proteasome is responsible for cell quality control by eliminating defective proteins from the cytosol and endoplasmic reticulum. These defective proteins can be misfolded proteins, nascent prematurely terminated polypeptides, or proteins that fail to assemble into complexes. These diverse activities and its central role in apoptosis have made the proteasome an important target for drug development, in particular to combat malignancies.","DOI":"10.1074/jbc.R109.018481","ISSN":"1083-351X","note":"PMID: 19812037\nPMCID: PMC2797140","shortTitle":"The 26 S proteasome","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Navon","given":"Ami"},{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2009",12,4]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , cells have mechanisms to maintain adequate amounts of proteasome.

Expression of the many different proteasome subunits must be tightly coordinated to produce the correct amount of each subunit. This is achieved through the controlled expression of proteasome subunits by a common transcription factor, Rpn4 in yeast[89,90]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"agl17ml0p5","properties":{"formattedCitation":"{\\rtf \\super 89,90\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":193,"uris":["http://zotero.org/users/4604651/items/T87PBUQC"],"uri":["http://zotero.org/users/4604651/items/T87PBUQC"],"itemData":{"id":193,"type":"article-journal","title":"Rpn4p acts as a transcription factor by binding to PACE, a nonamer box found upstream of 26S proteasomal and other genes in yeast","container-title":"FEBS Letters","page":"27-34","volume":"450","issue":"1-2","source":"Wiley Online Library","abstract":"We identified a new, unique upstream activating sequence (5′-GGTGGCAAA-3′) in the promoters of 26 out of the 32 proteasomal yeast genes characterized to date, which we propose to call proteasome-associated control element. By using the one-hybrid method, we show that the factor binding to the proteasome-associated control element is Rpn4p, a protein containing a C2H2-type finger motif and two acidic domains. Electrophoretic mobility shift

assays using proteasome-associated control element sequences from two regulatory proteasomal genes confirmed specific binding of purified Rpn4p to these sequences. The role of Rpn4p to function as a transregulator in yeast is corroborated by its ability of stimulating proteasome-associated control element-driven lacZ expression and by experiments using the RPT4 and RPT6 gene promoters coupled to the bacterial cat gene as a reporter. Additionally, we found the proteasome-associated control element to occur in a number of promoters to genes which are related to the ubiquitin-proteasome pathway in yeast.","DOI":"10.1016/S0014-5793(99)00467-6","ISSN":"1873-3468","language":"en","author":[{"family":"Mannhaupt","given":"Gertrud"},{"family":"Schnall","given":"Ralf"},{"family":"Karpov","given":"Vadim"},{"family":"Vetter","given":"Irene"},{"family":"Feldmann","given":"Horst"}],"issued":{"date-parts":[["1999",4,30]]}},{"id":184,"uris":["http://zotero.org/users/4604651/items/A8GD826V"],"uri":["http://zotero.org/users/4604651/items/A8GD826V"],"itemData":{"id":184,"type":"article-journal","title":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome: A negative feedback circuit","container-title":"Proceedings of the National Academy of Sciences","page":"3056-3061","volume":"98","issue":"6","source":"www.pnas.org","abstract":"The RPN4 (SON1, UFD5) protein of the yeast Saccharomyces cerevisiae is required for normal levels of intracellular proteolysis. RPN4 is a transcriptional activator of genes encoding proteasomal subunits. Here we show that RPN4 is required for normal levels of these subunits. Further, we demonstrate that RPN4 is extremely short-lived (t1/2 ≈2 min), that it directly interacts with RPN2, a subunit of the 26S proteasome, and that rpn4Δ cells are perturbed in their cell cycle. The degradation signal of RPN4 was mapped to its N-terminal region, outside the transcription–activation domains of RPN4. The ability of RPN4 to augment the synthesis of proteasomal subunits while being metabolically unstable yields a negative feedback circuit in which the same protein up-regulates the proteasome production and is destroyed by the assembled active proteasome.","DOI":"10.1073/pnas.071022298","ISSN":"0027-8424, 1091-6490","note":"PMID: 11248031","shortTitle":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Xie","given":"Youming"},{"family":"Varshavsky","given":"Alexander"}],"issued":{"date-parts":[["2001",3,13]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Rpn4 binds to a nonamer box (5'-GGTGGCAAA-3'), known as proteasome-associated control element (PACE, which is present in the promoters of most proteasome subunits as well as some other stress genes[89]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a24nk01da8p","properties":{"formattedCitation":"{\\rtf \\super 89\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":193,"uris":["http://zotero.org/users/4604651/items/T87PBUQC"],"uri":["http://zotero.org/users/4604651/items/T87PBUQC"],"itemData":{"id":193,"type":"article-journal","title":"Rpn4p acts as a transcription factor by binding to PACE, a nonamer box found upstream of 26S proteasomal and other genes in yeast","container-title":"FEBS Letters","page":"27-34","volume":"450","issue":"1-2","source":"Wiley Online Library","abstract":"We identified a new, unique upstream activating sequence (5′-GGTGGCAAA-3′) in the promoters of 26 out of the 32 proteasomal yeast genes characterized to date, which we propose to call proteasome-associated control element. By using the one-hybrid method, we show that the factor binding to the proteasome-associated control element is Rpn4p, a protein containing a C2H2-type finger motif and two acidic domains. Electrophoretic mobility shift assays using proteasome-associated control element sequences from two regulatory proteasomal genes confirmed specific binding of purified Rpn4p to these sequences. The role of Rpn4p to function as a transregulator in yeast is corroborated by its ability of stimulating proteasome-associated control element-

driven lacZ expression and by experiments using the RPT4 and RPT6 gene promoters coupled to the bacterial cat gene as a reporter. Additionally, we found the proteasome-associated control element to occur in a number of promoters to genes which are related to the ubiquitin-proteasome pathway in yeast.","DOI":"10.1016/S0014-5793(99)00467-6","ISSN":"1873-3468","language":"en","author":[{"family":"Mannhaupt","given":"Gertrud"},{"family":"Schnall","given":"Ralf"},{"family":"Karpov","given":"Vadim"},{"family":"Vetter","given":"Irene"},{"family":"Feldmann","given":"Horst"}],"issued":{"date-parts":[["1999",4,30]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (FIG. 4a). Remarkably, Rpn4 has a very short half-life ($t_{1/2}$~2 min) owing to rapid proteasomal degradation. As a result, Rpn4 abundance increases when proteasomal function is compromised, leading to an increased expression of proteasome subunits[90]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a13fin46s7s","properties":{"formattedCitation":"{\\rtf \\super 90\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":184,"uris":["http://zotero.org/users/4604651/items/A8GD826V"],"uri":["http://zotero.org/users/4604651/items/A8GD826V"],"itemData":{"id":184,"type":"article-journal","title":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome: A negative feedback circuit","container-title":"Proceedings of the National Academy of Sciences","page":"3056-3061","volume":"98","issue":"6","source":"www.pnas.org","abstract":"The RPN4 (SON1, UFD5) protein of the yeast Saccharomyces cerevisiae is required for normal levels of intracellular proteolysis. RPN4 is a transcriptional activator of genes encoding proteasomal subunits. Here we show that RPN4 is required for normal levels of these subunits. Further, we demonstrate that RPN4 is extremely short-lived (t1/2 ≈2 min), that it directly interacts with RPN2, a subunit of the 26S proteasome, and that rpn4Δ cells are perturbed in their cell cycle. The degradation signal of RPN4 was mapped to its N-terminal region, outside the transcription–activation domains of RPN4. The ability of RPN4 to augment the synthesis of proteasomal subunits while being metabolically unstable yields a negative feedback circuit in which the same protein up-regulates the proteasome production and is destroyed by the assembled active proteasome.","DOI":"10.1073/pnas.071022298","ISSN":"0027-8424, 1091-6490","note":"PMID: 11248031","shortTitle":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Xie","given":"Youming"},{"family":"Varshavsky","given":"Alexander"}],"issued":{"date-parts":[["2001",3,13]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (FIG. 4). Consequently, deletion of *rpn4* compromises cell fitness[90]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"arprrrhs46","properties":{"formattedCitation":"{\\rtf \\super 90\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":184,"uris":["http://zotero.org/users/4604651/items/A8GD826V"],"uri":["http://zotero.org/users/4604651/items/A8GD826V"],"itemData":{"id":184,"type":"article-journal","title":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome: A negative feedback circuit","container-title":"Proceedings of the National Academy of Sciences","page":"3056-3061","volume":"98","issue":"6","source":"www.pnas.org","abstract":"The RPN4 (SON1, UFD5) protein of the yeast Saccharomyces cerevisiae is required for normal levels of intracellular proteolysis. RPN4 is a transcriptional activator of genes encoding proteasomal subunits. Here we show that RPN4 is required for normal levels of these subunits. Further, we demonstrate that RPN4 is extremely short-lived (t1/2 ≈2 min), that it directly interacts with RPN2, a subunit of the 26S proteasome, and that rpn4Δ cells are perturbed in their cell cycle. The degradation signal of RPN4 was mapped to its N-terminal region, outside the transcription–activation domains of RPN4. The ability

of RPN4 to augment the synthesis of proteasomal subunits while being metabolically unstable yields a negative feedback circuit in which the same protein up-regulates the proteasome production and is destroyed by the assembled active proteasome.","DOI":"10.1073/pnas.071022298","ISSN":"0027-8424, 1091-6490","note":"PMID: 11248031","shortTitle":"RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Xie","given":"Youming"},{"family":"Varshavsky","given":"Alexander"}],"issued":{"date-parts":[["2001",3,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Rpn4 abundance is not only regulated by its rapid proteasomal degradation but also transcriptionally, by various stress-inducible transcription factors such as Yap1, Pdr1, Pdr3 and Hsf1, indicating that increasing expression of proteasome subunits might be a common mechanism to adapt to diverse challenging conditions[91]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a9rv9mi5rb","properties":{"formattedCitation":"{\\rtf \\super 91\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":192,"uris":["http://zotero.org/users/4604651/items/TND5VCJ7"],"uri":["http://zotero.org/users/4604651/items/TND5VCJ7"],"itemData":{"id":192,"type":"article-journal","title":"Comparative transcriptome profiling analyses during the lag phase uncover YAP1, PDR1, PDR3, RPN4, and HSF1 as key regulatory genes in genomic adaptation to the lignocellulose derived inhibitor HMF for Saccharomyces cerevisiae","container-title":"BMC Genomics","page":"660","volume":"11","source":"BioMed Central","abstract":"The yeast Saccharomyces cerevisiae is able to adapt and in situ detoxify lignocellulose derived inhibitors such as furfural and HMF. The length of lag phase for cell growth in response to the inhibitor challenge has been used to measure tolerance of strain performance. Mechanisms of yeast tolerance at the genome level remain unknown. Using systems biology approach, this study investigated comparative transcriptome profiling, metabolic profiling, cell growth response, and gene regulatory interactions of yeast strains and selective gene deletion mutations in response to HMF challenges during the lag phase of growth.","DOI":"10.1186/1471-2164-11-660","ISSN":"1471-2164","journalAbbreviation":"BMC Genomics","author":[{"family":"Ma","given":"Menggen"},{"family":"Liu","given":"Z. Lewis"}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Mammals also induce a concerted increase in expression of proteasome subunits in response to proteasome inhibition[92]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"avimce4ea8","properties":{"formattedCitation":"{\\rtf \\super 92\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":191,"uris":["http://zotero.org/users/4604651/items/I9MEYLQT"],"uri":["http://zotero.org/users/4604651/items/I9MEYLQT"],"itemData":{"id":191,"type":"article-journal","title":"Inhibition of Proteasome Activity Induces Concerted Expression of Proteasome Genes and de Novo Formation of Mammalian Proteasomes","container-title":"Journal of Biological Chemistry","page":"21517-21525","volume":"278","issue":"24","source":"www.jbc.org","abstract":"The 26 S proteasome is a high molecular mass proteinase complex that is built by at least 32 different protein subunits. Such protease complexes in bacteria and yeast are systems that undergo a highly sophisticated network of gene expression regulation. However, regulation of mammalian proteasome gene expression has been neglected so far as a possible control mechanism for the amount of proteasomes in the cell. Here, we show that treatment

of cells with proteasome inhibitors and the concomitant impairment of proteasomal enzyme activity induce a transient and concerted up-regulation of all mammalian 26 S proteasome subunit mRNAs. Proteasome inhibition in combination with inhibition of transcription revealed that the observed up-regulation is mediated by coordinated transcriptional activation of the proteasome genes and not by post-transcriptional events. Our experiments also demonstrate that inhibitor-induced proteasome gene activation results in enhanced de novo protein synthesis of all subunits and in increased de novo formation of proteasomes. This phenomenon is accompanied by enhanced expression of the proteasome maturation factor POMP. Thus, our experiments present the first evidence that the amount of proteasomes in mammalia is regulated at the transcriptional level and that there exists an autoregulatory feedback mechanism that allows the compensation of reduced proteasome activity.","DOI":"10.1074/jbc.M301032200","ISSN":"0021-9258, 1083-351X","note":"PMID: 12676932","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Meiners","given":"Silke"},{"family":"Heyken","given":"Dirk"},{"family":"Weller","given":"Andrea"},{"family":"Ludwig","given":"Antje"},{"family":"Stangl","given":"Karl"},{"family":"Kloetzel","given":"Peter-M."},{"family":"Krüger","given":"Elke"}],"issued":{"date-parts":[["2003",6,13]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Two mammalian transcription factors have been proposed to fulfil the function of the yeast Rpn4: the nuclear factor erythroid derived 2-related factors 1 (Nrf1/SKN1) and Nrf2[93,94]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ddnpu5m46","properties":{"formattedCitation":"{\\rtf \\super 93,94\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":183,"uris":["http://zotero.org/users/4604651/items/V4JEW89M"],"uri":["http://zotero.org/users/4604651/items/V4JEW89M"],"itemData":{"id":183,"type":"article-journal","title":"Antioxidants Enhance Mammalian Proteasome Expression through the Keap1-Nrf2 Signaling Pathway","container-title":"Molecular and Cellular Biology","page":"8786-8794","volume":"23","issue":"23","source":"PubMed Central","abstract":"Proteasomes degrade damaged proteins formed during oxidative stress, thereby promoting cell survival. Neurodegenerative and other age-related disorders are associated with reduced proteasome activity. We show herein that expression of most subunits of 20S and 19S proteasomes, which collectively assemble the 26S proteasome, was enhanced up to threefold in livers of mice following treatment with dithiolethiones, which act as indirect antioxidants. Subunit protein levels and proteasome activity were coordinately increased. No induction was seen in mice where the transcription factor Nrf2 was disrupted. Promoter activity of the PSMB5 subunit of the 20S proteasome increased with either Nrf2 overexpression or treatment with antioxidants in mouse embryonic fibroblasts. Tandem antioxidant response elements in the proximal promoter of PSMB5 that controlled these responses were identified. We propose that induction of the 26S proteasome through the Nrf2 pathway represents an important indirect action of these antioxidants that can contribute to their protective effects against chronic diseases.","DOI":"10.1128/MCB.23.23.8786-8794.2003","ISSN":"0270-7306","note":"PMID: 14612418\nPMCID: PMC262680","journalAbbreviation":"Mol Cell Biol","author":[{"family":"Kwak","given":"Mi-Kyoung"},{"family":"Wakabayashi","given":"Nobunao"},{"family":"Greenlaw","given":"Jennifer L."},{"family":"Yamamoto","given":"Masayuki"},{"family":"Kensler","given":"Thomas W."}],"issued":{"date-parts":[["2003",12]]}}},{"id":190,"uris":["http://zotero.org/users/4604651/items/373X3MAR"],"uri":["http://zotero.org/users/4604651/items/373X3MAR"],"itemData":{"id":190,"type":"article-journal","title":"Transcription factor Nrf1 mediates the proteasome recovery pathway after proteasome inhibition in mammalian cells","container-title":"Molecular cell","page":"17-

28","volume":"38","issue":"1","source":"PubMed Central","abstract":"In Saccharomyces cerevisiae, chemical or genetic inhibition of proteasome activity induces new proteasome synthesis promoted by the transcription factor RPN4. This ensures that proteasome activity is matched to demand. This transcriptional feedback loop is conserved in mammals, but its molecular basis is not understood. Here we report that Nuclear factor erythroid derived 2-related factor 1 (Nrf1), a transcription factor of the cap 'n' collar basic leucine zipper family, but not the related Nrf2, is necessary for induced proteasome gene transcription in mouse embryonic fibroblasts (MEFs). Promoter-reporter assays revealed the importance of antioxidant response elements in Nrf1-mediated upregulation of proteasome subunit genes. Nrf1-/- MEFs were impaired in the recovery of proteasome activity after transient treatment with the covalent proteasome inhibitor YU101 and knockdown of Nrf1 in human cancer cells enhanced cell killing by YU101. Taken together, our results suggest that Nrf1-mediated proteasome homeostasis could be an attractive target for therapeutic intervention in cancer.","DOI":"10.1016/j.molcel.2010.02.029","ISSN":"1097-2765","note":"PMID: 20385086\nPMCID: PMC2874685","journalAbbreviation":"Mol Cell","author":[{"family":"Radhakrishnan","given":"Senthil K."},{"family":"Lee","given":"Candy S."},{"family":"Young","given":"Patrick"},{"family":"Beskow","given":"Anne"},{"family":"Chan","given":"Jefferson Y."},{"family":"Deshaies","given":"Raymond J."}],"issued":{"date-parts":[["2010",4,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Like Rpn4, Nrf2 is an unstable protein that is stabilized upon redox stress to increase proteasome gene expression[93,95]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a23j1jv35un","properties":{"formattedCitation":"{\\rtf \\super 93,95\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":183,"uris":["http://zotero.org/users/4604651/items/V4JEW89M"],"uri":["http://zotero.org/users/4604651/items/V4JEW89M"],"itemData":{"id":183,"type":"article-journal","title":"Antioxidants Enhance Mammalian Proteasome Expression through the Keap1-Nrf2 Signaling Pathway","container-title":"Molecular and Cellular Biology","page":"8786-8794","volume":"23","issue":"23","source":"PubMed Central","abstract":"Proteasomes degrade damaged proteins formed during oxidative stress, thereby promoting cell survival. Neurodegenerative and other age-related disorders are associated with reduced proteasome activity. We show herein that expression of most subunits of 20S and 19S proteasomes, which collectively assemble the 26S proteasome, was enhanced up to threefold in livers of mice following treatment with dithiolethiones, which act as indirect antioxidants. Subunit protein levels and proteasome activity were coordinately increased. No induction was seen in mice where the transcription factor Nrf2 was disrupted. Promoter activity of the PSMB5 subunit of the 20S proteasome increased with either Nrf2 overexpression or treatment with antioxidants in mouse embryonic fibroblasts. Tandem antioxidant response elements in the proximal promoter of PSMB5 that controlled these responses were identified. We propose that induction of the 26S proteasome through the Nrf2 pathway represents an important indirect action of these antioxidants that can contribute to their protective effects against chronic diseases.","DOI":"10.1128/MCB.23.23.8786-8794.2003","ISSN":"0270-7306","note":"PMID: 14612418\nPMCID: PMC262680","journalAbbreviation":"Mol Cell Biol","author":[{"family":"Kwak","given":"Mi-Kyoung"},{"family":"Wakabayashi","given":"Nobunao"},{"family":"Greenlaw","given":"Jennifer L."},{"family":"Yamamoto","given":"Masayuki"},{"family":"Kensler","given":"Thomas W."}],"issued":{"date-parts":[["2003",12]]}}},{"id":182,"uris":["http://zotero.org/users/4604651/items/DIKHIX7T"],"uri":["http://zotero.org/users/4604651/items/DIKHIX7T"],"itemData":{"id":182,"type":"article-journal","title":"Molecular mechanisms of the Keap1–Nrf2 pathway in stress response and

cancer evolution","container-title":"Genes to Cells: Devoted to Molecular & Cellular Mechanisms","page":"123-140","volume":"16","issue":"2","source":"PubMed","abstract":"The Keap1–Nrf2 regulatory pathway plays a central role in the protection of cells against oxidative and xenobiotic damage. Under unstressed conditions, Nrf2 is constantly ubiquitinated by the Cul3–Keap1 ubiquitin E3 ligase complex and rapidly degraded in proteasomes. Upon exposure to electrophilic and oxidative stresses, reactive cysteine residues of Keap1 become modified, leading to a decline in the E3 ligase activity, stabilization of Nrf2 and robust induction of a battery of cytoprotective genes. Biochemical and structural analyses have revealed that the intact Keap1 homodimer forms a cherry-bob structure in which one molecule of Nrf2 associates with two molecules of Keap1 by using two binding sites within the Neh2 domain of Nrf2. This two-site binding appears critical for Nrf2 ubiquitination. In many human cancers, missense mutations in KEAP1 and NRF2 genes have been identified. These mutations disrupt the Keap1–Nrf2 complex activity involved in ubiquitination and degradation of Nrf2 and result in constitutive activation of Nrf2. Elevated expression of Nrf2 target genes confers advantages in terms of stress resistance and cell proliferation in normal and cancer cells. Discovery and development of selective Nrf2 inhibitors should make a critical contribution to improved cancer therapy.","DOI":"10.1111/j.1365-2443.2010.01473.x","ISSN":"1365-2443","note":"PMID: 21251164","journalAbbreviation":"Genes Cells","language":"eng","author":[{"family":"Taguchi","given":"Keiko"},{"family":"Motohashi","given":"Hozumi"},{"family":"Yamamoto","given":"Masayuki"}],"issued":{"date-parts":[["2011",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Nrf2 was initially proposed to increase expression of proteasome subunits when the proteasome is inhibited[96]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aifruppv9m","properties":{"formattedCitation":"{\\rtf \\super 96\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":181,"uris":["http://zotero.org/users/4604651/items/3J6NCFJB"],"uri":["http://zotero.org/users/4604651/items/3J6NCFJB"],"itemData":{"id":181,"type":"article-journal","title":"Preincubation with the proteasome inhibitor MG-132 enhances proteasome activity via the Nrf2 transcription factor in aging human skin fibroblasts","container-title":"Annals of the New York Academy of Sciences","page":"420-424","volume":"1067","source":"PubMed","abstract":"Strategies that lead to the upregulation of the proteasome are known to elicit beneficial consequences to the organism by countering oxidative stress-associated disorders, such as protein conformational diseases, cancer, and aging. Mild treatment with proteasome inhibitors has been previously demonstrated to stimulate proteasome activity and cellular resistance against oxidative injury. However, the mechanism for this action has not been clearly defined. We examined the role of the nuclear factor-E2-related factor 2 (Nrf2) in fibroblasts, a key transactivator of the antioxidant response pathway, in the regulation of the proteasome by its inhibitor MG-132. Here, we demonstrate that the stimulation of the proteasome by low levels of MG-132 can be abrogated by small interfering RNAs (siRNAs) targeted against Nrf2. Consistently, cells that constitutively express Nrf2 exhibit elevated levels of proteasome activities. We further investigate how its beneficial effects, that is, proteasome stimulation, are manifested in young and replicative-senescent cells. Our data underscore that manipulation of Nrf2 by the administration of pharmacologically low levels of proteasome inhibitors may prove to be an alternatively potent strategy for inducing long-term protective effects against oxidative stress.","DOI":"10.1196/annals.1354.060","ISSN":"0077-8923","note":"PMID: 16804021","journalAbbreviation":"Ann. N. Y. Acad. Sci.","language":"eng","author":[{"family":"Kraft","given":"David Christian"},{"family":"Deocaris","given":"Custer C."},{"family":"Wadhwa","given":"Renu"},{"family":"Rattan","given":"Suresh I. S."}],"issued":{"date-parts":[["2006",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. However, a

later study attributed the induction of proteasome subunits following proteasome inhibition to Nrf1[94]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1r627oas4i","properties":{"formattedCitation":"{\\rtf \\super 94\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":190,"uris":["http://zotero.org/users/4604651/items/373X3MAR"],"uri":["http://zotero.org/users/4604651/items/373X3MAR"],"itemData":{"id":190,"type":"article-journal","title":"Transcription factor Nrf1 mediates the proteasome recovery pathway after proteasome inhibition in mammalian cells","container-title":"Molecular cell","page":"17-28","volume":"38","issue":"1","source":"PubMed Central","abstract":"In Saccharomyces cerevisiae, chemical or genetic inhibition of proteasome activity induces new proteasome synthesis promoted by the transcription factor RPN4. This ensures that proteasome activity is matched to demand. This transcriptional feedback loop is conserved in mammals, but its molecular basis is not understood. Here we report that Nuclear factor erythroid derived 2-related factor 1 (Nrf1), a transcription factor of the cap 'n' collar basic leucine zipper family, but not the related Nrf2, is necessary for induced proteasome gene transcription in mouse embryonic fibroblasts (MEFs). Promoter-reporter assays revealed the importance of antioxidant response elements in Nrf1-mediated upregulation of proteasome subunit genes. Nrf1-/- MEFs were impaired in the recovery of proteasome activity after transient treatment with the covalent proteasome inhibitor YU101 and knockdown of Nrf1 in human cancer cells enhanced cell killing by YU101. Taken together, our results suggest that Nrf1-mediated proteasome homeostasis could be an attractive target for therapeutic intervention in cancer.","DOI":"10.1016/j.molcel.2010.02.029","ISSN":"1097-2765","note":"PMID: 20385086\nPMCID: PMC2874685","journalAbbreviation":"Mol Cell","author":[{"family":"Radhakrishnan","given":"Senthil K."},{"family":"Lee","given":"Candy S."},{"family":"Young","given":"Patrick"},{"family":"Beskow","given":"Anne"},{"family":"Chan","given":"Jefferson Y."},{"family":"Deshaies","given":"Raymond J."}],"issued":{"date-parts":[["2010",4,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Nrf1 is an integral ER membrane protein which, under normal conditions, is constantly retrotranslocated from the ER to the cytosol, where it is rapidly ubiquitinated and degraded by the proteasome (Fig. 4b). When proteasomal function is compromised, Nrf1 escapes from proteasomal degradation and is cleaved by the aspartyl protease DDI2 to produce the active form of Nrf1[97,98]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2f799p4e85","properties":{"formattedCitation":"{\\rtf \\super 97,98\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":180,"uris":["http://zotero.org/users/4604651/items/GMWM3JU9"],"uri":["http://zotero.org/users/4604651/items/GMWM3JU9"],"itemData":{"id":180,"type":"article-journal","title":"The aspartyl protease DDI2 activates Nrf1 to compensate for proteasome dysfunction","container-title":"eLife","page":"e18357","volume":"5","source":"elifesciences.org","abstract":"Peptidase activity of DDI2 is required to activate Nrf1 in order to enable proteasome recovery in response to proteasome inhibition.","DOI":"10.7554/eLife.18357","ISSN":"2050-084X","note":"PMID: 27528193","language":"en","author":[{"family":"Koizumi","given":"Shun"},{"family":"Irie","given":"Taro"},{"family":"Hirayama","given":"Shoshiro"},{"family":"Sakurai","given":"Yasuyuki"},{"family":"Yashiroda","given":"Hideki"},{"family":"Naguro","given":"Isao"},{"fa

mily":"Ichijo","given":"Hidenori"},{"family":"Hamazaki","given":"Jun"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2016",8,16]]}},"locator":"2"},{"id":528,"uris":["http://zotero.org/users/4604651/items/BAG4H6PZ"],"uri":["http://zotero.org/users/4604651/items/BAG4H6PZ"],"itemData":{"id":528,"type":"article-journal","title":"Proteasome dysfunction triggers activation of SKN-1A/Nrf1 by the aspartic protease DDI-1","container-title":"eLife","page":"e17721","volume":"5","source":"elifesciences.org","abstract":"Post-translational processing of the SKN-1A/Nrf1 transcription factor regulates proteasome expression.","DOI":"10.7554/eLife.17721","ISSN":"2050-084X","journalAbbreviation":"eLife Sciences","language":"en","author":[{"family":"Lehrbach","given":"Nicolas J."},{"family":"Ruvkun","given":"Gary"}],"issued":{"date-parts":[["2016",8,16]]}},"locator":"-"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} .

Active Nrf1 then translocates from the cytosol to the nucleus to induce expression of proteasome subunits[94,97]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1kti4qjdrs","properties":{"formattedCitation":"{\\rtf \\super 94,97\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":190,"uris":["http://zotero.org/users/4604651/items/373X3MAR"],"uri":["http://zotero.org/users/4604651/items/373X3MAR"],"itemData":{"id":190,"type":"article-journal","title":"Transcription factor Nrf1 mediates the proteasome recovery pathway after proteasome inhibition in mammalian cells","container-title":"Molecular cell","page":"17-28","volume":"38","issue":"1","source":"PubMed Central","abstract":"In Saccharomyces cerevisiae, chemical or genetic inhibition of proteasome activity induces new proteasome synthesis promoted by the transcription factor RPN4. This ensures that proteasome activity is matched to demand. This transcriptional feedback loop is conserved in mammals, but its molecular basis is not understood. Here we report that Nuclear factor erythroid derived 2-related factor 1 (Nrf1), a transcription factor of the cap ‘n’ collar basic leucine zipper family, but not the related Nrf2, is necessary for induced proteasome gene transcription in mouse embryonic fibroblasts (MEFs). Promoter-reporter assays revealed the importance of antioxidant response elements in Nrf1-mediated upregulation of proteasome subunit genes. Nrf1-/- MEFs were impaired in the recovery of proteasome activity after transient treatment with the covalent proteasome inhibitor YU101 and knockdown of Nrf1 in human cancer cells enhanced cell killing by YU101. Taken together, our results suggest that Nrf1-mediated proteasome homeostasis could be an attractive target for therapeutic intervention in cancer.","DOI":"10.1016/j.molcel.2010.02.029","ISSN":"1097-2765","note":"PMID: 20385086\nPMCID: PMC2874685","journalAbbreviation":"Mol Cell","author":[{"family":"Radhakrishnan","given":"Senthil K."},{"family":"Lee","given":"Candy S."},{"family":"Young","given":"Patrick"},{"family":"Beskow","given":"Anne"},{"family":"Chan","given":"Jefferson Y."},{"family":"Deshaies","given":"Raymond J."}],"issued":{"date-parts":[["2010",4,9]]}}},{"id":180,"uris":["http://zotero.org/users/4604651/items/GMWM3JU9"],"uri":["http://zotero.org/users/4604651/items/GMWM3JU9"],"itemData":{"id":180,"type":"article-journal","title":"The aspartyl protease DDI2 activates Nrf1 to compensate for proteasome dysfunction","container-title":"eLife","page":"e18357","volume":"5","source":"elifesciences.org","abstract":"Peptidase activity of DDI2 is required to activate Nrf1 in order to enable proteasome recovery in response to proteasome inhibition.","DOI":"10.7554/eLife.18357","ISSN":"2050-084X","note":"PMID: 27528193","language":"en","author":[{"family":"Koizumi","given":"Shun"},{"family":"Irie","given":"Taro"},{"family":"Hirayama","given":"Shoshiro"},{"family":"Sakurai","given":"Yasuyuki"},{"family":"Yashiroda","given":"Hideki"},{"family":"Naguro","given":"Isao"},{"fa

mily":"Ichijo","given":"Hidenori"},{"family":"Hamazaki","given":"Jun"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2016",8,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}(Fig. 4b). Both Nrf1 and Nrf2 are members to the Cap'n'Collar transcription factor family harbouring a basic-leucine zipper (bZIP) domain, which binds antioxidant response elements (AREs) found in the promoter of antioxidant response genes[99]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ga5sgp3lb","properties":{"formattedCitation":"{\\rtf \\super 99\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":179,"uris":["http://zotero.org/users/4604651/items/XGWSHN8S"],"uri":["http://zotero.org/users/4604651/items/XGWSHN8S"],"itemData":{"id":179,"type":"article-journal","title":"Stress-activated cap'n'collar transcription factors in aging and human disease","container-title":"Science Signaling","page":"re3","volume":"3","issue":"112","source":"PubMed","abstract":"Cap'n'collar (Cnc) transcription factors are conserved in metazoans and have important developmental and homeostatic functions. The vertebrate Nrf1, Nrf2, and Nrf3; the Caenorhabditis elegans SKN-1; and the Drosophila CncC comprise a subgroup of Cnc factors that mediate adaptive responses to cellular stress. The most studied stress-activated Cnc factor is Nrf2, which orchestrates the transcriptional response of cells to oxidative stressors and electrophilic xenobiotics. In rodent models, signaling by Nrf2 defends against oxidative stress and aging-associated disorders, such as neurodegeneration, respiratory diseases, and cancer. In humans, polymorphisms that decrease Nrf2 abundance have been associated with various pathologies of the skin, respiratory system, and digestive tract. In addition to preventing disease in rodents and humans, Cnc factors have life-span-extending and anti-aging functions in invertebrates. However, despite the pro-longevity and antioxidant roles of stress-activated Cnc factors, their activity paradoxically declines in aging model organisms and in humans suffering from progressive respiratory disease or neurodegeneration. We review the roles and regulation of stress-activated Cnc factors across species, present all reported instances in which their activity is paradoxically decreased in aging and disease, and discuss the possibility that the pharmacological restoration of Nrf2 signaling may be useful in the prevention and treatment of age-related diseases.","DOI":"10.1126/scisignal.3112re3","ISSN":"1937-9145","note":"PMID: 20215646\nPMCID: PMC2991085","journalAbbreviation":"Sci Signal","language":"eng","author":[{"family":"Sykiotis","given":"Gerasimos P."},{"family":"Bohmann","given":"Dirk"}],"issued":{"date-parts":[["2010",3,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Interestingly, the promoters of several proteasomal subunit genes contain AREs, raising the possibility that Nrf proteins increase proteasome levels under stress conditions [93,100–102] by binding to these AREs { ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1rck0ahpi5","properties":{"formattedCitation":"{\\rtf \\super 93,100\\uc0\\u8211{}102\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":183,"uris":["http://zotero.org/users/4604651/items/V4JEW89M"],"uri":["http://zotero.org/users/4604651/items/V4JEW89M"],"itemData":{"id":183,"type":"article-journal","title":"Antioxidants Enhance Mammalian Proteasome Expression through the Keap1-Nrf2 Signaling Pathway","container-title":"Molecular and Cellular Biology","page":"8786-8794","volume":"23","issue":"23","source":"PubMed Central","abstract":"Proteasomes degrade damaged proteins formed during oxidative stress, thereby promoting cell survival. Neurodegenerative and other age-related disorders are associated with reduced proteasome activity. We show herein that expression of most subunits of 20S and 19S proteasomes, which collectively assemble the 26S proteasome, was enhanced up to threefold in livers of mice following treatment with dithiolethiones, which act as indirect antioxidants. Subunit

protein levels and proteasome activity were coordinately increased. No induction was seen in mice where the transcription factor Nrf2 was disrupted. Promoter activity of the PSMB5 subunit of the 20S proteasome increased with either Nrf2 overexpression or treatment with antioxidants in mouse embryonic fibroblasts. Tandem antioxidant response elements in the proximal promoter of PSMB5 that controlled these responses were identified. We propose that induction of the 26S proteasome through the Nrf2 pathway represents an important indirect action of these antioxidants that can contribute to their protective effects against chronic diseases.","DOI":"10.1128/MCB.23.23.8786-8794.2003","ISSN":"0270-7306","note":"PMID: 14612418\nPMCID: PMC262680","journalAbbreviation":"Mol Cell Biol","author":[{"family":"Kwak","given":"Mi-Kyoung"},{"family":"Wakabayashi","given":"Nobunao"},{"family":"Greenlaw","given":"Jennifer L."},{"family":"Yamamoto","given":"Masayuki"},{"family":"Kensler","given":"Thomas W."}],"issued":{"date-parts":[["2003",12]]}}},{"id":178,"uris":["http://zotero.org/users/4604651/items/W9GRI8CZ"],"uri":["http://zotero.org/users/4604651/items/W9GRI8CZ"],"itemData":{"id":178,"type":"article-journal","title":"Modulation of gene expression by cancer chemopreventive dithiolethiones through the Keap1-Nrf2 pathway. Identification of novel gene clusters for cell survival","container-title":"The Journal of Biological Chemistry","page":"8135-8145","volume":"278","issue":"10","source":"PubMed","abstract":"Enzyme inducers such as 3H-1,2-dithiole-3-thione (D3T) enhance the detoxication of environmental carcinogens and protect against neoplasia. The putative molecular sensor for inducers is Keap1, a sulfhydryl-rich protein that sequesters the transcription factor Nrf2 in the cytoplasm. Expression of these detoxication enzymes is blunted in nrf2-deficient mice; moreover, these mice are more sensitive to carcinogenesis, and the protective actions of dithiolethiones are lost with nrf2 disruption. Hepatic gene expression profiles were examined by oligonucleotide microarray analysis in vehicle- or D3T-treated wild-type mice as well as in nrf2 single and keap1-nrf2 double knockout mice to identify those genes regulated by the Keap1-Nrf2 pathway. Transcript levels of 292 genes were elevated in wild-type mice 24 h after treatment with D3T; 79% of these genes were induced in wild-type, but not nrf2-deficient mice. These nrf2-dependent, D3T-inducible genes included known detoxication and antioxidative enzymes. Unexpected clusters included genes for chaperones, protein trafficking, ubiquitin/26 S proteasome subunits, and signaling molecules. Gene expression patterns in keap1-nrf2 double knockout mice were similar to those in nrf2-single knockout mice. D3T also led to nrf2-dependent repression of 31 genes at 24 h; principally genes related to cholesterol/lipid biosynthesis. Collectively, D3T increases the expression of genes through the Keap1-Nrf2 signaling pathway that directly detoxify toxins and generate essential cofactors such as glutathione and reducing equivalents. Induction of nrf2-dependent genes involved in the recognition and repair/removal of damaged proteins expands the role of this pathway beyond primary control of electrophilic and oxidative stresses into secondary protective actions that enhance cell survival.","DOI":"10.1074/jbc.M211898200","ISSN":"0021-9258","note":"PMID: 12506115","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Kwak","given":"Mi-Kyoung"},{"family":"Wakabayashi","given":"Nobunao"},{"family":"Itoh","given":"Ken"},{"family":"Motohashi","given":"Hozumi"},{"family":"Yamamoto","given":"Masayuki"},{"family":"Kensler","given":"Thomas W."}],"issued":{"date-parts":[["2003",3,7]]}}},{"id":169,"uris":["http://zotero.org/users/4604651/items/T784MWZC"],"uri":["http://zotero.org/users/4604651/items/T784MWZC"],"itemData":{"id":169,"type":"article-journal","title":"Nuclear erythroid factor 2-mediated proteasome activation delays senescence in human fibroblasts","container-title":"The Journal of Biological Chemistry","page":"8171-8184","volume":"285","issue":"11","source":"PubMed","abstract":"Replicative senescence in human fibroblasts is accompanied with

alterations of various biological processes, including the impaired function of the proteasome. The proteasome is responsible for the removal of both normal and damaged proteins. Due to its latter function, proteasome is also considered a representative secondary antioxidant cellular mechanism. Nrf2 is a basic transcription factor responsible for the regulation of the cellular antioxidant response that has also been shown to regulate several proteasome subunits in mice. We have established in this study the proteasome-related function of Nrf2 in human fibroblasts undergoing replicative senescence. We demonstrate that Nrf2 has a declined function in senescence, whereas its silencing leads to premature senescence. However, upon its activation by a novel Nrf2 inducer, elevated levels of proteasome activity and content are recorded only in cell lines possessing a functional Nrf2. Moreover, treatment by the Nrf2 inducer results in the enhanced survival of cells following oxidative stress, whereas continuous treatment leads to lifespan extension of human fibroblasts. Importantly the Nrf2-proteasome axis is functional in terminally senescent cultures as these cells retain their responsiveness to the Nrf2 stimuli. In conclusion, these findings open up new directions for future manipulation of the senescence phenotype.","DOI":"10.1074/jbc.M109.031575","ISSN":"1083-351X","note":"PMID: 20068043\nPMCID: PMC2832969","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Kapeta","given":"Suzanne"},{"family":"Chondrogianni","given":"Niki"},{"family":"Gonos","given":"Efstathios S."}],"issued":{"date-parts":[["2010",3,12]]}},{"id":168,"uris":["http://zotero.org/users/4604651/items/P7FDX9HF"],"uri":["http://zotero.org/users/4604651/items/P7FDX9HF"],"itemData":{"id":168,"type":"article-journal","title":"Proteasome-Mediated Processing of Nrf1 Is Essential for Coordinate Induction of All Proteasome Subunits and p97","container-title":"Current Biology","page":"1573-1583","volume":"24","issue":"14","source":"ScienceDirect","abstract":"SummaryBackground\nProteasome inhibitors are widely used in the treatment of multiple myeloma and as research tools. Additionally, diminished proteasome function may contribute to neuronal dysfunction. In response to these inhibitors, cells enhance the expression of proteasome subunits by the transcription factor Nrf1. Here, we investigate the mechanisms by which decreased proteasome function triggers production of new proteasomes via Nrf1.\nResults\nExposure of myeloma or neuronal cells to proteasome inhibitors (bortezomib, epoxomicin, and MG132), but not to proteotoxic or ER stress, caused a 2- to 4-fold increase within 4 hr in mRNAs for all 26S subunits. In addition, p97 and its cofactors (Npl4, Ufd1, and p47), PA200, and USP14 were induced, but expression of immunoproteasome-specific subunits was suppressed. Nrf1 mediates this induction of proteasomes and p97, but only upon exposure to low concentrations of inhibitors that partially inhibit proteolysis. Surprisingly, high concentrations of these inhibitors prevent this compensatory response. Nrf1 is normally ER-bound, and its release requires its deglycosylation and ubiquitination. Normally ubiquitinated Nrf1 is rapidly degraded, but when partially inhibited, proteasomes carry out limited proteolysis and release the processed Nrf1 (lacking its N-terminal region) from the ER, which allows it to enter the nucleus and promote gene expression.\nConclusions\nWhen fully active, proteasomes degrade Nrf1, but when partially inhibited, they perform limited proteolysis that generates the active form of Nrf1. This elegant mechanism allows cells to compensate for reduced proteasome function by enhancing production of 26S subunits and p97.","DOI":"10.1016/j.cub.2014.06.004","ISSN":"0960-9822","journalAbbreviation":"Current Biology","author":[{"family":"Sha","given":"Zhe"},{"family":"Goldberg","given":"Alfred L."}],"issued":{"date-parts":[["2014",7,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} and that Nrf1 and Nrf2 are activated by different stresses.

In plants, two *Arabidopsis thaliana* NAM/ATAF1/CUC2 (NAC) transcription factors, NAC53 and NAC78, have been identified as key regulators of genes encoding proteasome subunit. NAC53 and NAC78 induce the expression of proteasome components under proteotoxic stress, which is essential for the plant to survive proteasome inhibition[103–105]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1s61ltjc10","properties":{"formattedCitation":"{\\rtf \\super 103\\uc0\\u8211{}105\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":167,"uris":["http://zotero.org/users/4604651/items/PULV2Q6H"],"uri":["http://zotero.org/users/4604651/items/PULV2Q6H"],"itemData":{"id":167,"type":"article-journal","title":"The Proteasome Stress Regulon Is Controlled by a Pair of NAC Transcription Factors in Arabidopsis","container-title":"The Plant Cell","page":"1279-1296","volume":"28","issue":"6","source":"www.plantcell.org","abstract":"Proteotoxic stress, which is generated by the accumulation of unfolded or aberrant proteins due to environmental or cellular perturbations, can be mitigated by several mechanisms, including activation of the unfolded protein response and coordinated increases in protein chaperones and activities that direct proteolysis, such as the 26S proteasome. Using RNA-seq analyses combined with chemical inhibitors or mutants that induce proteotoxic stress by impairing 26S proteasome capacity, we defined the transcriptional network that responds to this stress in Arabidopsis thaliana. This network includes genes encoding core and assembly factors needed to build the complete 26S particle, alternative proteasome capping factors, enzymes involved in protein ubiquitylation/deubiquitylation and cellular detoxification, protein chaperones, autophagy components, and various transcriptional regulators. Many loci in this proteasome-stress regulon contain a consensus cis-element upstream of the transcription start site, which was previously identified as a binding site for the NAM/ATAF1/CUC2 78 (NAC78) transcription factor. Double mutants disrupting NAC78 and its closest relative NAC53 are compromised in the activation of this regulon and notably are strongly hypersensitive to the proteasome inhibitors MG132 and bortezomib. Given that NAC53 and NAC78 homo- and heterodimerize, we propose that they work as a pair in activating the expression of numerous factors that help plants survive proteotoxic stress and thus play a central regulatory role in maintaining protein homeostasis.","DOI":"10.1105/tpc.15.01022","ISSN":", 1532-298X","note":"PMID: 27194708","journalAbbreviation":"Plant Cell","language":"en","author":[{"family":"Gladman","given":"Nicholas P."},{"family":"Marshall","given":"Richard S."},{"family":"Lee","given":"Kwang-Hee"},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2016",6,1]]}}},{"id":166,"uris":["http://zotero.org/users/4604651/items/SFVCCA96"],"uri":["http://zotero.org/users/4604651/items/SFVCCA96"],"itemData":{"id":166,"type":"article-journal","title":"Identification of recognition sequence of ANAC078 protein by the cyclic amplification and selection of targets technique","container-title":"Plant Signaling & Behavior","page":"695-697","volume":"5","issue":"6","source":"PubMed Central","abstract":"NAC (NAM, ATAF and CUC2) is one of the largest families of transcription factors in the plant genome, but the function and regulation of most NAC genes are still largely unknown. We recently isolated a gene encoding a NAC transcription factor designated ANAC078 from Arabidopsis plants and identified 166 genes upregulated in ANAC078-overexpressing plants compared with the wild-type plants under high-light stress. The cyclic amplification and selection of targets (CASTing) technique showed that the ANAC078 recognition sequence contains T[A/T/C] [A/T/G/C] C[T/G] TG[T/G]G as a DNA-binding site. The recognition sequence identified by this technique was detected in the promoter region of 52 upregulated genes, including the gene for a transcription factor, proteasome subunits, peroxidase and a protein kinase. The findings suggest these genes to be directly targeted by the ANAC078 protein.","ISSN":"1559-2316","note":"PMID: 20404498\nPMCID: PMC3001562","journalAbbreviation":"Plant Signal

Behav","author":[{"family":"Yabuta","given":"Yukinori"},{"family":"Morishita","given":"Teruyuki"},{"family":"Kojima","given":"Yusuke"},{"family":"Maruta","given":"Takanori"},{"family":"Nishizawa-Yokoi","given":"Ayako"},{"family":"Shigeoka","given":"Shigeru"}],"issued":{"date-parts":[["2010",6]]}},{"id":165,"uris":["http://zotero.org/users/4604651/items/68QRDD2C"],"uri":["http://zotero.org/users/4604651/items/68QRDD2C"],"itemData":{"id":165,"type":"article-journal","title":"An upstream regulator of the 26S proteasome modulates organ size in Arabidopsis thaliana","container-title":"The Plant Journal","page":"25-36","volume":"74","issue":"1","source":"Wiley Online Library","abstract":"In both animal and plant kingdoms, body size is a fundamental but still poorly understood attribute of biological systems. Here we report that the Arabidopsis NAC transcription factor 'Regulator of Proteasomal Gene Expression' (RPX) controls leaf size by positively modulating proteasome activity. We further show that the cis-element recognized by RPX is evolutionarily conserved between higher plant species. Upon over-expression of RPX, plants exhibit reduced growth, which may be reversed by a low concentration of the pharmacological proteasome inhibitor MG132. These data suggest that the rate of protein turnover during growth is a critical parameter for determining final organ size.","DOI":"10.1111/tpj.12097","ISSN":"1365-313X","journalAbbreviation":"Plant J","language":"en","author":[{"family":"Nguyen","given":"Hung M."},{"family":"Schippers","given":"Jos H. M."},{"family":"Gõni-Ramos","given":"Oscar"},{"family":"Christoph","given":"Mathias P."},{"family":"Dortay","given":"Hakan"},{"family":"Hoorn","given":"Renier A. L."},{"family":"Mueller-Roeber","given":"Bernd"}],"issued":{"date-parts":[["2013",4,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . As these transcription factors have probably evolved to ensure that proteasome homeostasis is adapted to the plant needs, it will be interesting to uncover the physiological pathways that are particularly sensitive to perturbations of this proteasome stress response.

[H1] Regulation of proteasome subunits assembly

Following the coordinated induction of proteasome subunits by designated transcription factors, the subunits need to be faithfully assembled to generate functional proteasomes. Proteasome assembly was initially thought to be a housekeeping process but recent studies have revealed that this process is complex and it is tightly regulated.

[H2] Regulation of RP assembly

The first indication that assembly of RP subunits might be regulated came with the identification of the yeast RAC, Adc17[65]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a26059ftmdj","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-

577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. In a genetic screen for pathways that can compensate for proteasome dysfunction, Adc17 was identified as a potent suppressor of the proteasome defects caused by a thermosensitive mutation in Rpt6^{65}{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2mmmd19ktm","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}.

Adc17 is induced by stress conditions such as heat shock and ER stress independently of Rpn4[65]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ldqmef4kg","properties":{"formattedCitation":"{\\rtf \\super 65\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":47,"uris":["http://zotero.org/users/4604651/items/DSB4G6H8"],"uri":["http://zotero.org/users/4604651/items/DSB4G6H8"],"itemData":{"id":47,"type":"article-journal","title":"An inducible chaperone adapts proteasome assembly to stress","container-title":"Molecular Cell","page":"566-577","volume":"55","issue":"4","source":"PubMed","abstract":"The proteasome is essential for the selective degradation of most cellular proteins. To survive overwhelming demands on the proteasome arising during environmental stresses, cells increase proteasome abundance. Proteasome assembly is known to be complex. How stressed cells overcome this vital challenge is unknown. In an unbiased suppressor screen aimed at rescuing the defects of a yeast Rpt6 thermosensitive proteasome mutant, we identified a protein, hereafter named Adc17, as it functions as an ATPase dedicated chaperone. Adc17 interacts with the amino terminus of Rpt6 to assist formation of the Rpt6-Rpt3 ATPase pair, an early step in proteasome assembly. Adc17 is important for cell fitness, and its absence aggravates proteasome defects. The abundance of Adc17 increases upon proteasome stresses, and its function is crucial to maintain homeostatic proteasome levels. Thus, cells have mechanisms to adjust proteasome assembly when demands increase, and Adc17 is a critical effector of this process.","DOI":"10.1016/j.molcel.2014.06.017","ISSN":"1097-4164","note":"PMID: 25042801\nPMCID: PMC4148588","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Hanssum","given":"Ariane"},{"family":"Zhong","given":"Zhen"},{"family":"Rousseau","given":"Adrien"},{"family":"Krzyzosiak","given":"Agnieszka"},{"family":"Sigurdardottir","given":"Anna"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2014",8,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The pathway controlling stress-induced expression of Adc17 was recently found to involve signalling through the central stress and growth controller TOR (Fig. 5, Box 2). Inhibition of TOR complex 1 (TORC1), either pharmacologically or genetically, is sufficient to increase Adc17 levels and this induction was shown to be dependent on the MAP kinase Mpk1[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a177qvo9v3k","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells.

Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Remarkably, Mpk1 activation following TORC1 inhibition also induces all other known yeast RACs (Nas2, Nas6, Hsm3 and Rpn14). This coordinated increase of RACs is essential to augment proteasome assembly and is essential for cell survival under challenging conditions that require increased proteolytic capacity[106] (Fig. 5){ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2aeiokd3pb","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Several lines of evidence indicate that Mpk1 acts post-transcriptionally by coordinating the expression of RACs and proteasome subunits at the translational level to increase proteasome abundance and enhance proteolysis[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a188uskpj9q","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily

conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Highlighting its importance, this adaptive proteasome assembly pathway is evolutionarily conserved, as mTOR and Erk5 (the homolog of Mpk1) regulate RACs and 26S proteasome assembly in mammalian cells[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2969g652li","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

In agreement with the increased translation of proteasome components following TORC1 inhibition[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a156nt2i8lp","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http:

//zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}, quantitative profiling of initiating ribosomes revealed that translation of proteasome components and proteasome activity are robustly enhanced upon starvation[107]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ap5hej6a9n","properties":{"formattedCitation":"{\\rtf \\super 107\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":164,"uris":["http://zotero.org/users/4604651/items/4KF3EV8I"],"uri":["http://zotero.org/users/4604651/items/4KF3EV8I"],"itemData":{"id":164,"type":"article-journal","title":"Quantitative profiling of initiating ribosomes in vivo","container-title":"Nature Methods","page":"147-153","volume":"12","issue":"2","source":"www.nature.com","abstract":"Cells have evolved exquisite mechanisms to fine-tune the rate of protein synthesis in response to stress. Systemic mapping of start-codon positions and precise measurement of the corresponding initiation rate would transform our understanding of translational control. Here we present quantitative translation initiation sequencing (QTI-seq), with which the initiating ribosomes can be profiled in real time at single-nucleotide resolution. Resultant initiation maps not only delineated variations of start-codon selection but also highlighted a dynamic range of initiation rates in response to nutrient starvation. The integrated data set provided unique insights into principles of alternative translation and mechanisms controlling different aspects of translation initiation. With RiboTag mice, QTI-seq permitted tissue-specific profiling of initiating ribosomes in vivo. Liver cell–specific ribosome profiling uncovered a robust translational reprogramming of the proteasome system in fasted mice. Our findings illuminated the prevalence and dynamic nature of translational regulation pivotal to physiological adaptation in vivo.","DOI":"10.1038/nmeth.3208","ISSN":"1548-7091","journalAbbreviation":"Nat Meth","language":"en","author":[{"family":"Gao","given":"Xiangwei"},{"family":"Wan","given":"Ji"},{"family":"Liu","given":"Botao"},{"family":"Ma","given":"Ming"},{"family":"Shen","given":"Ben"},{"family":"Qian","given":"Shu-Bing"}],"issued":{"date-parts":[["2015",2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Thus, there is

converging evidence indicating that the cellular levels of functional proteasome are regulated and that this regulation is important for cell survival and physiology.

[H2] Regulation of CP assembly

Ectopic overexpression of Rpn4, which promotes the transcription of proteasome subunits encoding-genes, further increases the levels functional proteasomes in wild-type cells that already contain high basal levels of proteasomes[108]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2g26qnvj7a","properties":{"formattedCitation":"{\\rtf \\super 108\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":176,"uris":["http://zotero.org/users/4604651/items/74TRNL56"],"uri":["http://zotero.org/users/4604651/items/74TRNL56"],"itemData":{"id":176,"type":"article-journal","title":"Identification of minimum Rpn4-responsive elements in genes related to proteasome functions","container-title":"FEBS Letters","page":"933-940","volume":"589","issue":"8","source":"Wiley Online Library","abstract":"The proteasome is an essential, 66-subunit protease that mediates ubiquitin-dependent proteolysis. The transcription factor Rpn4 regulates concerted expression of proteasome subunits to increase the proteasome by recognizing nonamer proteasome-associated control element (PACE) elements on the promoter regions. However, the genes for proteasome assembly chaperones and some of the subunits have no PACEs. Here we identified a minimal hexamer “PACE-core” sequence that responds to Rpn4. PACE-cores are found in many genes related to proteasome function including the assembly chaperones, but cannot substitute for PACE of the subunits. Our results add a new layer of complexity in transcriptional regulation of genes involved in protein degradation.","DOI":"10.1016/j.febslet.2015.02.025","ISSN":"1873-3468","language":"en","author":[{"family":"Shirozu","given":"Ryohei"},{"family":"Yashiroda","given":"Hideki"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2015",4,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1k3jai912","properties":{"formattedCitation":"{\\rtf \\super 108\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":176,"uris":["http://zotero.org/users/4604651/items/74TRNL56"],"uri":["http://zotero.org/users/4604651/items/74TRNL56"],"itemData":{"id":176,"type":"article-journal","title":"Identification of minimum Rpn4-responsive elements in genes related to proteasome functions","container-title":"FEBS Letters","page":"933-940","volume":"589","issue":"8","source":"Wiley Online Library","abstract":"The proteasome is an essential, 66-subunit protease that mediates ubiquitin-dependent proteolysis. The transcription factor Rpn4 regulates concerted expression of proteasome subunits to increase the proteasome by recognizing nonamer proteasome-associated control element (PACE) elements on the promoter regions. However, the genes for proteasome assembly chaperones and some of the subunits have no PACEs. Here we identified a minimal hexamer “PACE-core” sequence that responds to Rpn4. PACE-cores are found in many genes related to proteasome function including the assembly chaperones, but cannot substitute for PACE of the subunits. Our results add a new layer of complexity in transcriptional regulation of genes involved in protein degradation.","DOI":"10.1016/j.febslet.2015.02.025","ISSN":"1873-3468","language":"en","author":[{"family":"Shirozu","given":"Ryohei"},{"family":"Yashiroda","given":"Hideki"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2015",4,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Surprisingly, Rpn4 overexpression has been suggested to also increase the transcription of genes encoding proteasome assembly chaperones, to various degrees, although

no PACE element could be found in their promoter regions, with the exception of Nas6[108]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"af7dihn9oh","properties":{"formattedCitation":"{\\rtf \\super 108\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":176,"uris":["http://zotero.org/users/4604651/items/74TRNL56"],"uri":["http://zotero.org/users/4604651/items/74TRNL56"],"itemData":{"id":176,"type":"article-journal","title":"Identification of minimum Rpn4-responsive elements in genes related to proteasome functions","container-title":"FEBS Letters","page":"933-940","volume":"589","issue":"8","source":"Wiley Online Library","abstract":"The proteasome is an essential, 66-subunit protease that mediates ubiquitin-dependent proteolysis. The transcription factor Rpn4 regulates concerted expression of proteasome subunits to increase the proteasome by recognizing nonamer proteasome-associated control element (PACE) elements on the promoter regions. However, the genes for proteasome assembly chaperones and some of the subunits have no PACEs. Here we identified a minimal hexamer “PACE-core” sequence that responds to Rpn4. PACE-cores are found in many genes related to proteasome function including the assembly chaperones, but cannot substitute for PACE of the subunits. Our results add a new layer of complexity in transcriptional regulation of genes involved in protein degradation.","DOI":"10.1016/j.febslet.2015.02.025","ISSN":"1873-3468","language":"en","author":[{"family":"Shirozu","given":"Ryohei"},{"family":"Yashiroda","given":"Hideki"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2015",4,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. This increase is particularly pronounced for the CP chaperones, which contain a minimum sequence, referred to as “PACE-core”, that could functions as an Rpn4-responsive element[108]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mv895qd4f","properties":{"formattedCitation":"{\\rtf \\super 108\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":176,"uris":["http://zotero.org/users/4604651/items/74TRNL56"],"uri":["http://zotero.org/users/4604651/items/74TRNL56"],"itemData":{"id":176,"type":"article-journal","title":"Identification of minimum Rpn4-responsive elements in genes related to proteasome functions","container-title":"FEBS Letters","page":"933-940","volume":"589","issue":"8","source":"Wiley Online Library","abstract":"The proteasome is an essential, 66-subunit protease that mediates ubiquitin-dependent proteolysis. The transcription factor Rpn4 regulates concerted expression of proteasome subunits to increase the proteasome by recognizing nonamer proteasome-associated control element (PACE) elements on the promoter regions. However, the genes for proteasome assembly chaperones and some of the subunits have no PACEs. Here we identified a minimal hexamer “PACE-core” sequence that responds to Rpn4. PACE-cores are found in many genes related to proteasome function including the assembly chaperones, but cannot substitute for PACE of the subunits. Our results add a new layer of complexity in transcriptional regulation of genes involved in protein degradation.","DOI":"10.1016/j.febslet.2015.02.025","ISSN":"1873-3468","language":"en","author":[{"family":"Shirozu","given":"Ryohei"},{"family":"Yashiroda","given":"Hideki"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2015",4,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. It will be interesting to elucidate whether this Rpn4-mediated increase is direct or indirect, as this could reveal new nodes of regulation.

Recently, several studies highlighted that CP assembly is also regulated[106,109], however the underlying molecular mechanisms remain to be fully characterized. An indication of CP assembly being regulated came from the observation that the abundance of the yeast

proteasome assembly chaperones Pba1 and Pba2 is increased by tunicamycin **[G]**, which causes accumulation of misfolded proteins in the endoplasmic reticulum (ER), whilst the levels of Pba3–Pba4 dimers remain unchanged. This increase of Pba1 and Pba2 was associated with enhanced CP assembly[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1hfqcabdvk","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. It will be interesting to identify the pathway controlling the stress inducibility of Pba1 and Pba2 expression. Pba3 and Pba4 levels were reported to increase following mitochondrial protein import perturbation, as a consequence of the accumulation of mitochondrial precursors in the cytosol[110]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ah84ia3vn4","properties":{"formattedCitation":"{\\rtf \\super 109\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":174,"uris":["http://zotero.org/users/4604651/items/4JKM6V2C"],"uri":["http://zotero.org/users/4604651/items/4JKM6V2C"],"itemData":{"id":174,"type":"article-journal","title":"Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol","container-title":"Nature","page":"485-488","volume":"524","issue":"7566","source":"www.nature.com","abstract":"Most of the mitochondrial proteome originates from nuclear genes and is transported into the mitochondria after synthesis in the cytosol. Complex machineries which maintain the specificity of protein import and sorting include the TIM23 translocase responsible for the transfer of precursor proteins into the matrix, and the mitochondrial intermembrane space import and assembly (MIA) machinery required for the biogenesis of intermembrane space proteins. Dysfunction of mitochondrial protein sorting pathways results in diminishing specific substrate proteins, followed by systemic pathology of the organelle and organismal death. The cellular responses caused by accumulation of mitochondrial precursor proteins in the cytosol are mainly unknown. Here

we present a comprehensive picture of the changes in the cellular transcriptome and proteome in response to a mitochondrial import defect and precursor over-accumulation stress. Pathways were identified that protect the cell against mitochondrial biogenesis defects by inhibiting protein synthesis and by activation of the proteasome, a major machine for cellular protein clearance. Proteasomal activity is modulated in proportion to the quantity of mislocalized mitochondrial precursor proteins in the cytosol. We propose that this type of unfolded protein response activated by mistargeting of proteins (UPRam) is beneficial for the cells. UPRam provides a means for buffering the consequences of physiological slowdown in mitochondrial protein import and for counteracting pathologies that are caused or contributed by mitochondrial dysfunction.","DOI":"10.1038/nature14951","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Wrobel","given":"Lidia"},{"family":"Topf","given":"Ulrike"},{"family":"Bragoszewski","given":"Piotr"},{"family":"Wiese","given":"Sebastian"},{"family":"Sztolsztener","given":"Malgorzata E."},{"family":"Oeljeklaus","given":"Silke"},{"family":"Varabyova","given":"Aksana"},{"family":"Lirski","given":"Maciej"},{"family":"Chroscicki","given":"Piotr"},{"family":"Mroczek","given":"Seweryn"},{"family":"Januszewicz","given":"Elzbieta"},{"family":"Dziembowski","given":"Andrzej"},{"family":"Koblowska","given":"Marta"},{"family":"Warscheid","given":"Bettina"},{"family":"Chacinska","given":"Agnieszka"}],"issued":{"date-parts":[["2015",8,27]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Moreover, the stability and dimerization of the CP assembly chaperones PAC1 and PAC2 (the human homologs of Pba1 and Pba2, respectively), as well as proteasome activity, were found to increase upon ER-stress, and this increase was proposed to be mediated by Inactive rhomboid protein 1 (iRhom1)[111]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a9s98rega2","properties":{"formattedCitation":"{\\rtf \\super 110\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":175,"uris":["http://zotero.org/users/4604651/items/GDY4QCQM"],"uri":["http://zotero.org/users/4604651/items/GDY4QCQM"],"itemData":{"id":175,"type":"article-journal","title":"iRhom1 regulates proteasome activity via PAC1/2 under ER stress","container-title":"Scientific Reports","page":"11559","volume":"5","source":"PubMed","abstract":"Proteasome is a protein degradation complex that plays a major role in maintaining cellular homeostasis. Despite extensive efforts to identify protein substrates that are degraded through ubiquitination, the regulation of proteasome activity itself under diverse signals is poorly understood. In this study, we have isolated iRhom1 as a stimulator of proteasome activity from genome-wide functional screening using cDNA expression and an unstable GFP-degron. Downregulation of iRhom1 reduced enzymatic activity of proteasome complexes and overexpression of iRhom1 enhanced it. Native-gel and fractionation analyses revealed that knockdown of iRhom1 expression impaired the assembly of the proteasome complexes. The expression of iRhom1 was increased by endoplasmic reticulum (ER) stressors, such as thapsigargin and tunicamycin, leading to the enhancement of proteasome activity, especially in ER-containing microsomes. iRhom1 interacted with the 20S proteasome assembly chaperones PAC1 and PAC2, affecting their protein stability. Moreover, knockdown of iRhom1 expression impaired the dimerization of PAC1 and PAC2 under ER stress. In addition, iRhom1 deficiency in D. melanogaster accelerated the rough-eye phenotype of mutant Huntingtin, while transgenic flies expressing either human iRhom1 or Drosophila iRhom showed rescue of the rough-eye phenotype. Together, these results identify a novel regulator of proteasome activity, iRhom1, which functions via PAC1/2 under ER stress.","DOI":"10.1038/srep11559","ISSN":"2045-2322","note":"PMID: 26109405\nPMCID: PMC4479803","journalAbbreviation":"Sci

Rep","language":"eng","author":[{"family":"Lee","given":"WonJae"},{"family":"Kim","given":"YoungDoo"},{"family":"Park","given":"Jisu"},{"family":"Shim","given":"SangMi"},{"family":"Lee","given":"Jieun"},{"family":"Hong","given":"Se-hoon"},{"family":"Ahn","given":"Hye-Hyun"},{"family":"Lee","given":"Huikyong"},{"family":"Jung","given":"Yong-Keun"}],"issued":{"date-parts":[["2015",6,25]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. iRhom1 is a member of the rhomboid-like family of proteases **[G]** that lacks protease activity[112]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a18d144us9b","properties":{"formattedCitation":"{\\rtf \\super 111\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":511,"uris":["http://zotero.org/users/4604651/items/YZL7IUYW"],"uri":["http://zotero.org/users/4604651/items/YZL7IUYW"],"itemData":{"id":511,"type":"article-journal","title":"The Rhomboid-Like Superfamily: Molecular Mechanisms and Biological Roles","container-title":"Annual Review of Cell and Developmental Biology","page":"235-254","volume":"30","issue":"1","source":"Annual Reviews","abstract":"The rhomboid proteases were first discovered as regulators of Drosophila EGF receptor signaling; soon after, it was recognized that they represented the founder members of a widespread family of intramembrane serine proteases conserved in all kingdoms. More recently still, the family was promoted to a superfamily, encompassing a wide variety of distantly related proteins. One of the surprises has been that many members of the rhomboid-like superfamily are not active proteases. Given the size of this clan, and its relatively recent discovery, there is still much to learn. Nevertheless, we already understand much about how rhomboid proteases perform their surprising function of cleaving transmembrane domains. We also already know that members of the rhomboid-like superfamily participate in biological functions as diverse as growth factor signaling, mitochondrial dynamics, inflammation, parasite invasion, and the machinery of protein quality control. Their potential medical significance is now becoming apparent in several areas.","DOI":"10.1146/annurev-cellbio-100913-012944","note":"PMID: 25062361","shortTitle":"The Rhomboid-Like Superfamily","author":[{"family":"Freeman","given":"Matthew"}],"issued":{"date-parts":[["2014"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. iRhom1 is located at the ER and has been involved in membrane protein trafficking and in Endoplasmic-reticulum-associated protein degradation (ERAD)[112–114]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1qtoopptv5","properties":{"formattedCitation":"{\\rtf \\super 111\\uc0\\u8211{}113\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":452,"uris":["http://zotero.org/users/4604651/items/K3DSLGD9"],"uri":["http://zotero.org/users/4604651/items/K3DSLGD9"],"itemData":{"id":452,"type":"article-journal","title":"Rhomboid

Family Pseudoproteases Use the ER Quality Control Machinery to Regulate Intercellular Signaling","container-title":"Cell","page":"79-91","volume":"145","issue":"1","source":"www.cell.com","DOI":"10.1016/j.cell.2011.02.047","ISSN":"0092-8674, 1097-4172","note":"PMID: 21439629","journalAbbreviation":"Cell","language":"English","author":[{"family":"Zettl","given":"Markus"},{"family":"Adrain","given":"Colin"},{"family":"Strisovsky","given":"Kvido"},{"family":"Lastun","given":"Viorica"},{"family":"Freeman","given":"Matthew"}],"issued":{"date-parts":[["2011",4,1]]}},{"id":531,"uris":["http://zotero.org/users/4604651/items/2MF9SQ5W"],"uri":["http://zotero.org/users/4604651/items/2MF9SQ5W"],"itemData":{"id":531,"type":"article-journal","title":"Emerging role of rhomboid family proteins in mammalian biology and disease","container-title":"Biochimica Et Biophysica Acta","page":"2840-2848","volume":"1828","issue":"12","source":"PubMed","abstract":"From proteases that cleave peptide bonds in the plane of the membrane, rhomboids have evolved into a heterogeneous superfamily with a wide range of different mechanistic properties. In mammals 14 family members have been annotated based on a shared conserved membrane-integral rhomboid core domain, including intramembrane serine proteases and diverse proteolytically inactive homologues. While the function of rhomboid proteases is the proteolytic release of membrane-tethered factors, rhomboid pseudoproteases including iRhoms and derlins interact with their clients without cleaving them. It has become evident that specific recognition of membrane protein substrates and clients by the rhomboid fold reflects a spectrum of cellular functions ranging from growth factor activation, trafficking control to membrane protein degradation. This review summarizes recent progress on rhomboid family proteins in the mammalian secretory pathway and raises the question whether they can be seen as new drug targets for inflammatory diseases and cancer. This article is part of a special issue entitled: Intramembrane Proteases.","DOI":"10.1016/j.bbamem.2013.03.025","ISSN":"0006-3002","note":"PMID: 23562403","journalAbbreviation":"Biochim. Biophys. Acta","language":"eng","author":[{"family":"Bergbold","given":"Nina"},{"family":"Lemberg","given":"Marius K."}],"issued":{"date-parts":[["2013",12]]}},{"id":511,"uris":["http://zotero.org/users/4604651/items/YZL7IUYW"],"uri":["http://zotero.org/users/4604651/items/YZL7IUYW"],"itemData":{"id":511,"type":"article-journal","title":"The Rhomboid-Like Superfamily: Molecular Mechanisms and Biological Roles","container-title":"Annual Review of Cell and Developmental Biology","page":"235-254","volume":"30","issue":"1","source":"Annual

Reviews","abstract":"The rhomboid proteases were first discovered as regulators of Drosophila EGF receptor signaling; soon after, it was recognized that they represented the founder members of a widespread family of intramembrane serine proteases conserved in all kingdoms. More recently still, the family was promoted to a superfamily, encompassing a wide variety of distantly related proteins. One of the surprises has been that many members of the rhomboid-like superfamily are not active proteases. Given the size of this clan, and its relatively recent discovery, there is still much to learn. Nevertheless, we already understand much about how rhomboid proteases perform their surprising function of cleaving transmembrane domains. We also already know that members of the rhomboid-like superfamily participate in biological functions as diverse as growth factor signaling, mitochondrial dynamics, inflammation, parasite invasion, and the machinery of protein quality control. Their potential medical significance is now becoming apparent in several areas.","DOI":"10.1146/annurev-cellbio-100913-012944","note":"PMID: 25062361","shortTitle":"The Rhomboid-Like Superfamily","author":[{"family":"Freeman","given":"Matthew"}],"issued":{"date-parts":[["2014"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. How iRhom1 regulates the stability of PAC1-PAC2 dimers and promotes proteasome activity remains unknown.

The transmembrane domain recognition complex (TRC) pathway, which controls membrane insertion of tail-anchored proteins, has also been proposed to regulate CP assembly (FIG. 5), as loss of either TRC40 or Bag6 chaperones, two mammalian TRC components, lead to CP assembly defects[115]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1esk7f4rro","properties":{"formattedCitation":"{\\rtf \\super 114\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":173,"uris":["http://zotero.org/users/4604651/items/8CR8MIZQ"],"uri":["http://zotero.org/users/4604651/items/8CR8MIZQ"],"itemData":{"id":173,"type":"article-journal","title":"Involvement of Bag6 and the TRC pathway in proteasome assembly","container-title":"Nature Communications","page":"ncomms3234","volume":"4","source":"www.nature.com","abstract":" \nThe 26S proteasome comprises over 33 different subunits that must be correctly assembled by dedicated chaperones for efficient protein degradation. Here the authors find that general chaperone proteins are also vital for proper proteasome assembly. ","DOI":"10.1038/ncomms3234","ISSN":"2041-1723","language":"en","author":[{"family":"Akahane","given":"Takashi"},{"family":"Sahara","given":"Kazutaka"},{"family":"Yashiroda","given":"Hideki"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2013",7,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Although the precise mechanisms by which the TRC pathway regulates CP assembly remain to be established, it has been proposed that TRC40 and Bag6 may facilitate the incorporation of β-subunits on the α-ring or stabilize CP assembly intermediates[115].

miR-101, which is a potent tumor-suppressor, was also shown to regulate proteasome assembly[109], highlighting a possible link between proteasome assembly and cancer. miR-101 targets the mRNA encoding the CP assembly chaperone POMP to rapidly decrease POMP protein levels and thus inhibit proteasome assembly[109]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2mkctru5m1","properties":{"formattedCitation":"{\\rtf \\super 115\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":172,"uris":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"uri":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"itemData":{"id":172,"type":"article-journal","title":"MicroRNA-101 Suppresses Tumor Cell Proliferation by Acting as an Endogenous Proteasome Inhibitor via Targeting the Proteasome Assembly Factor POMP","container-title":"Molecular Cell","page":"243-257","volume":"59","issue":"2","source":"PubMed","abstract":"Proteasome inhibition represents a promising strategy of cancer pharmacotherapy, but resistant tumor cells often emerge. Here we show that the microRNA-101 (miR-101) targets the proteasome maturation protein POMP, leading to impaired proteasome assembly and activity, and resulting in accumulation of p53 and cyclin-dependent kinase inhibitors, cell cycle arrest, and apoptosis. miR-101-resistant POMP restores proper turnover of proteasome substrates and re-enables tumor cell growth. In ERα-positive breast cancers, miR-101 and POMP levels are inversely correlated, and high miR-101 expression or low POMP expression associates with prolonged survival. Mechanistically, miR-101 expression or POMP knockdown attenuated estrogen-driven transcription. Finally, suppressing POMP is sufficient to overcome tumor cell resistance to the proteasome inhibitor bortezomib. Taken together, proteasome activity can not only be manipulated through drugs, but is also subject to endogenous regulation through miR-101, which targets proteasome biogenesis to control overall protein turnover and tumor cell proliferation.","DOI":"10.1016/j.molcel.2015.05.036","ISSN":"1097-4164","note":"PMID: 26145175","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Zhang","given":"Xin"},{"family":"Schulz","given":"Ramona"},{"family":"Edmunds","given":"Shelley"},{"family":"Krüger","given":"Elke"},{"family":"Markert","given":"Elke"},{"family":"Gaedcke","given":"Jochen"},{"family":"Cormet-Boyaka","given":"Estelle"},{"family":"Ghadimi","given":"Michael"},{"family":"Beissbarth","given":"Tim"},{"family":"Levine","given":"Arnold J."},{"family":"Moll","given":"Ute M."},{"family":"Dobbelstein","given":"Matthias"}],"issued":{"date-parts":[["2015",7,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } (FIG. 5).

In recent years, it has become apparent that the accumulation of misfolded proteins leads to an increase in proteasome assembly. Regulated proteasome assembly and the resulting capacity to increase proteasomal degradation are important to enable the clearance of misfolded proteins that could be deleterious to cells. Although it had been known for a long time that ubiquitination of proteasome substrates dictates their degradation rates, the finding that proteasome abundance and assembly can be finely tuned to the cellular requirements indicates that the mechanisms that regulate proteasomal degradation to meet the cellular needs and maintain cell viability, are more complex than previously appreciated.

[H2] Regulation of RP-CP association

RP-CP association is crucial for proteasome activation because the amino-terminal tails of α-subunits form a gate to prevent access in the centre of the α-ring [32,116,117]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aqv334pqet","properties":{"formattedCitation":"{\\rtf \\super 32,116,117\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":71,"uris":["http://zotero.org/users/4604651/items/P7WQ3M7N"],"uri":["http://zotero.org/users/4604651/items/P7WQ3M7N"],"itemData":{"id":71,"type":"article-journal","title":"Structure of 20S proteasome from yeast at 2.4 A resolution","container-title":"Nature","page":"463-471","volume":"386","issue":"6624","source":"PubMed","abstract":"The crystal structure of the 20S proteasome from the yeast Saccharomyces cerevisiae shows that its 28 protein subunits are arranged as an (alpha1...alpha7, beta1...beta7)2 complex in four stacked rings and occupy unique locations. The interior of the particle, which harbours the active sites, is only accessible by some very narrow side entrances. The beta-type subunits are synthesized as proproteins before being proteolytically processed for assembly into the particle. The proforms of three of the seven different beta-type subunits, beta1/PRE3, beta2/PUP1 and beta5/PRE2, are cleaved between the threonine at position 1 and the last glycine of the pro-sequence, with release of the active-site residue Thr 1. These three beta-type subunits have inhibitor-binding sites, indicating that PRE2 has a chymotrypsin-like and a trypsin-like activity and that PRE3 has peptidylglutamyl peptide hydrolytic specificity. Other beta-type subunits are processed to an intermediate form, indicating that an additional nonspecific endopeptidase activity may exist which is important for peptide hydrolysis and for the generation of ligands for class I molecules of the major histocompatibility complex.","DOI":"10.1038/386463a0","ISSN":"0028-0836","note":"PMID: 9087403","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Groll","given":"M."},{"family":"Ditzel","given":"L."},{"family":"Löwe","given":"J."},{"family":"Stock","given":"D."},{"family":"Bochtler","given":"M."},{"family":"Bartunik","given":"H. D."},{"family":"Huber","given":"R."}],"issued":{"date-parts":[["1997",4,3]]}}},{"id":171,"uris":["http://zotero.org/users/4604651/items/VJ4N9WNY"],"uri":["http://zotero.org/users/4604651/items/VJ4N9WNY"],"itemData":{"id":171,"type":"article-journal","title":"Docking of the proteasomal ATPases' carboxyl termini in the 20S proteasome's alpha ring opens the gate for substrate entry","container-title":"Molecular Cell","page":"731-744","volume":"27","issue":"5","source":"PubMed","abstract":"The 20S proteasome functions in protein degradation in eukaryotes together with the 19S ATPases or in archaea with the homologous PAN ATPase complex. These ATPases contain a conserved C-terminal hydrophobic-tyrosine-X motif (HbYX). We show that these residues are essential for PAN to associate with the 20S and open its gated channel for substrate entry. Upon ATP binding, these C-terminal residues bind to pockets between the 20S's alpha subunits. Seven-residue or longer peptides from PAN's C terminus containing the HbYX motif also bind to these sites and induce gate opening in the 20S. Gate opening could be induced by C-terminal peptides from the 19S ATPase subunits, Rpt2, and Rpt5, but not by ones from PA28/26, which lack the HbYX motif and cause gate opening by distinct mechanisms. C-terminal residues in the 19S ATPases were also shown to be critical for gating and stability of 26S proteasomes. Thus, the C termini of the proteasomal ATPases function like a \"key in a lock\" to induce gate opening and allow substrate entry.","DOI":"10.1016/j.molcel.2007.06.033","ISSN":"1097-2765","note":"PMID: 17803938\nPMCID: PMC2083707","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Smith","given":"David M."},{"family":"Chang","given":"Shih-Chung"},{"family":"Park","given":"Soyeon"},{"family":"Finley","given":"Daniel"},{"family":"Cheng","given":"Yifan"},{"family":"Goldb

erg","given":"Alfred L."}],"issued":{"date-parts":[["2007",9,7]]}}},{"id":170,"uris":["http://zotero.org/users/4604651/items/XJQF3WFS"],"uri":["http://zotero.org/users/4604651/items/XJQF3WFS"],"itemData":{"id":170,"type":"article-journal","title":"Structure of the 26S proteasome with ATP-γS bound provides insights into the mechanism of nucleotide-dependent substrate translocation","container-title":"Proceedings of the National Academy of Sciences of the United States of America","page":"7264-7269","volume":"110","issue":"18","source":"PubMed","abstract":"The 26S proteasome is a 2.5-MDa, ATP-dependent multisubunit proteolytic complex that processively destroys proteins carrying a degradation signal. The proteasomal ATPase heterohexamer is a key module of the 19S regulatory particle; it unfolds substrates and translocates them into the 20S core particle where degradation takes place. We used cryoelectron microscopy single-particle analysis to obtain insights into the structural changes of 26S proteasome upon the binding and hydrolysis of ATP. The ATPase ring adopts at least two distinct helical staircase conformations dependent on the nucleotide state. The transition from the conformation observed in the presence of ATP to the predominant conformation in the presence of ATP-γS induces a sliding motion of the ATPase ring over the 20S core particle ring leading to an alignment of the translocation channels of the ATPase and the core particle gate, a conformational state likely to facilitate substrate translocation. Two types of intersubunit modules formed by the large ATPase domain of one ATPase subunit and the small ATPase domain of its neighbor exist. They resemble the contacts observed in the crystal structures of ClpX and proteasome-activating nucleotidase, respectively. The ClpX-like contacts are positioned consecutively and give rise to helical shape in the hexamer, whereas the proteasome-activating nucleotidase-like contact is required to close the ring. Conformational switching between these forms allows adopting different helical conformations in different nucleotide states. We postulate that ATP hydrolysis by the regulatory particle ATPase (Rpt) 5 subunit initiates a cascade of conformational changes, leading to pulling of the substrate, which is primarily executed by Rpt1, Rpt2, and Rpt6.","DOI":"10.1073/pnas.1305782110","ISSN":"1091-6490","note":"PMID: 23589842\nPMCID: PMC3645540","journalAbbreviation":"Proc. Natl. Acad. Sci. U.S.A.","language":"eng","author":[{"family":"Śledź","given":"Paweł"},{"family":"Unverdorben","given":"Pia"},{"family":"Beck","given":"Florian"},{"family":"Pfeifer","given":"Günter"},{"family":"Schweitzer","given":"Andreas"},{"family":"Förster","given":"Friedrich"},{"family":"Baumeister","given":"Wolfgang"}],"issued":{"date-parts":[["2013",4,30]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. RP-CP association is reversible, as the 26S proteasome can disassemble into stable RP and CP[118–120] { ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a135hi4koat","properties":{"formattedCitation":"{\\rtf \\super 118\\uc0\\u8211{}120\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":161,"uris":["http://zotero.org/users/4604651/items/PNZDHRFY"],"uri":["http://zotero.org/users/4604651/items/PNZDHRFY"],"itemData":{"id":161,"type":"article-journal","title":"Proteasome disassembly and downregulation is correlated with viability during stationary phase","container-title":"Current biology: CB","page":"1140-1144","volume":"13","issue":"13","source":"PubMed","abstract":"During prolonged starvation, yeast cells enter a stationary phase (SP) during which the synthesis of many proteins is dramatically decreased. We show that a parallel decrease in proteasome-dependent proteolysis also occurs. The reduction in proteolysis is correlated with disassembly of 26S proteasome holoenzymes into their 20S core particle (CP) and 19S regulatory particle (RP) components. Proteasomes are reassembled, and proteolysis resumes prior to cell cycle reentry. Free 20S CPs are found in an autoinhibited state in which the N-terminal tails from neighboring alpha subunits are anchored by an intricate lattice of interactions blocking the channel that leads into the 20S CPs. By deleting channel gating residues of CP alpha subunits, we generated an \"open channel\"

proteasome that exhibits faster rates of protein degradation both in vivo and in vitro, indicating that gating contributes to regulation of proteasome activity. This open channel mutant is delayed in outgrowth from SP and cannot survive following prolonged starvation. In summary, we have found that the ubiquitin-proteasome pathway can be subjected to global downregulation, that the proteasome is a target of this regulation, and that proteasome downregulation is linked to survival of SP cells. Maintaining high viability during SP is essential for evolutionary fitness, which may explain the extreme conservation of channel gating residues in eukaryotic proteasomes.","ISSN":"0960-9822","note":"PMID: 12842014","journalAbbreviation":"Curr. Biol.","language":"eng","author":[{"family":"Bajorek","given":"Monika"},{"family":"Finley","given":"Daniel"},{"family":"Glickman","given":"Michael H."}],"issued":{"date-parts":[["2003",7,1]]}},{"id":160,"uris":["http://zotero.org/users/4604651/items/L7K74X29"],"uri":["http://zotero.org/users/4604651/items/L7K74X29"],"itemData":{"id":160,"type":"article-journal","title":"Stability of the proteasome can be regulated allosterically through engagement of its proteolytic active sites","container-title":"Nature Structural & Molecular Biology","page":"1180-1188","volume":"14","issue":"12","source":"www.nature.com","abstract":"The 26S proteasome holoenzyme is formed by the association of a 20S core particle (CP) with a 19S regulatory particle (RP). The CP-RP interaction is labile and subject to regulation in vivo, but the factors controlling this association are poorly understood. Here we describe an in vitro proteasome reconstitution assay and a high-resolution, two-dimensional gel electrophoresis system. Using these techniques, we find that a yeast CP–RP complex can contain a substoichiometric amount of tightly bound, essentially non-exchangeable ATP. However, this nucleotide is dispensable for gating of the CP channel, provided that the CP–RP complex is preserved by the Ecm29 protein. Unexpectedly, proteasome inhibitors are potent in stabilizing proteasomes against the dissociation of CP–RP. These data indicate that active sites of the CP communicate with bound RP, despite their spatial separation. We propose that ongoing protein degradation may suppress proteasome disassembly, thereby enhancing the processivity of proteolysis.","DOI":"10.1038/nsmb1335","ISSN":"1545-9993","journalAbbreviation":"Nat Struct Mol Biol","language":"en","author":[{"family":"Kleijnen","given":"Maurits F."},{"family":"Roelofs","given":"Jeroen"},{"family":"Park","given":"Soyeon"},{"family":"Hathaway","given":"Nathaniel A."},{"family":"Glickman","given":"Michael"},{"family":"King","given":"Randall W."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2007",12]]}}},{"id":159,"uris":["http://zotero.org/users/4604651/items/KLANFWSB"],"uri":["http://zotero.org/users/4604651/items/KLANFWSB"],"itemData":{"id":159,"type":"article-journal","title":"Regulation of the 26S Proteasome Complex During Oxidative Stress","container-title":"Sci. Signal.","page":"ra88-ra88","volume":"3","issue":"151","source":"stke.sciencemag.org","abstract":"Separation of Powers\nThe proteasome is a large, multicatalytic complex that degrades proteins in an ATP- and ubiquitin-dependent manner. The 26S proteasome is composed of the 20S catalytic core and the 19S regulatory particle. The 19S particle consists of two subcomplexes that constitute the base and lid structures around the catalytic core. When separated from the 26S proteasome, the 20S core degrades oxidized (nonubiquitinated) proteins. Oxidative stress results in the accumulation of damaged proteins in the cell, which are removed by proteasomes. Wang et al. used mass spectrometry to examine the effects of hydrogen peroxide (H2O2)–induced stress on the 26S proteasome in yeast. H2O2 triggered recruitment to the 19S particle of the proteasome-binding protein Ecm29 and disassembly of the 26S proteasome into its 20S and 19S constituents. Yeast strains deficient in Ecm29 did not exhibit 26S disassembly and were more sensitive to H2O2 than were wild-type

cells. Indeed, an efficient response to H2O2 required disassembly of the 26S proteasome to generate sufficient amounts of free 20S core to degrade oxidized proteins. Similar results were obtained in experiments with a human cell line, which suggests that dissociation of the 26S proteasome in response to oxidative stress may be a conserved cellular response in eukaryotes.\nThe proteasome plays a pivotal role in the cellular response to oxidative stress. Here, we used biochemical and mass spectrometric methods to investigate structural changes in the 26S proteasomes from yeast and mammalian cells exposed to hydrogen peroxide (H2O2). Oxidative stress induced the dissociation of the 20S core particle from the 19S regulatory particle of the 26S proteasome, which resulted in loss of the activities of the 26S proteasome and accumulation of ubiquitinated proteins. H2O2 triggered the increased association of the proteasome-interacting protein Ecm29 with the purified 19S particle. Deletion of ECM29 in yeast cells prevented the disassembly of the 26S proteasome in response to oxidative stress, and ecm29 mutants were more sensitive to H2O2 than were wild-type cells, suggesting that separation of the 19S and 20S particles is important for cellular recovery from oxidative stress. The increased amount of free 20S core particles was required to degrade oxidized proteins. The Ecm29-dependent dissociation of the proteasome was independent of Yap1, a transcription factor that is critical for the oxidative stress response in yeast, and thus functions as a parallel defense pathway against H2O2-induced stress.\nOxidative stress triggers release of the core catalytic subunit of the yeast 26S proteasome, enabling degradation of toxic oxidized proteins.\nOxidative stress triggers release of the core catalytic subunit of the yeast 26S proteasome, enabling degradation of toxic oxidized proteins.","DOI":"10.1126/scisignal.2001232","ISSN":"1945-0877, 1937-9145","note":"PMID: 21139140","journalAbbreviation":"Sci. Signal.","language":"en","author":[{"family":"Wang","given":"Xiaorong"},{"family":"Yen","given":"James"},{"family":"Kaiser","given":"Peter"},{"family":"Huang","given":"Lan"}],"issued":{"date-parts":[["2010",12,7]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }(Fig. 5).

As purified RP and CP can associate *in vitro* without additional factors, it is believed that RP-CP association occurs spontaneously[121,122]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"av3i4pl6tv","properties":{"formattedCitation":"{\\rtf \\super 121,122\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":163,"uris":["http://zotero.org/users/4604651/items/VF86CLVC"],"uri":["http://zotero.org/users/4604651/items/VF86CLVC"],"itemData":{"id":163,"type":"article-journal","title":"ATP Binding and ATP Hydrolysis Play Distinct Roles in the Function of 26S Proteasome","container-title":"Molecular Cell","page":"39-50","volume":"24","issue":"1","source":"ScienceDirect","abstract":"Summary\nThe 26S proteasome degrades polyubiquitinated proteins by an energy-dependent mechanism. Here we define multiple roles for ATP in 26S proteasome function. ATP binding is necessary and sufficient for assembly of 26S proteasome from 20S proteasome and PA700/19S subcomplexes and for proteasome activation. Proteasome assembly and activation may require distinct ATP binding events. The 26S proteasome degrades nonubiquitylated, unstructured proteins without ATP hydrolysis, indicating that substrate translocation per se does not require the energy of hydrolysis. Nonubiquitylated folded proteins and certain polyubiquitylated folded proteins were refractory to proteolysis. The latter were deubiquitylated by an ATP-independent mechanism. Other folded as well as unstructured polyubiquitylated proteins required ATP hydrolysis for proteolysis and deubiquitylation. Thus, ATP hydrolysis is not used solely for substrate unfolding. These results indicate that 26S proteasome-catalyzed degradation of polyubiquitylated proteins involves mechanistic coupling of several processes and that such coupling imposes an energy requirement not apparent for any isolated process.","DOI":"10.1016/j.molcel.2006.08.025","ISSN":"1097-2765","journalAbbreviation":"Molecular

Cell","author":[{"family":"Liu","given":"Chang-Wei"},{"family":"Li","given":"Xiaohua"},{"family":"Thompson","given":"David"},{"family":"Wooding","given":"Kerry"},{"family":"Chang","given":"Tsui-ling"},{"family":"Tang","given":"Zhanyun"},{"family":"Yu","given":"Hongtao"},{"family":"Thomas","given":"Philip J."},{"family":"DeMartino","given":"George N."}],"issued":{"date-parts":[["2006",10,6]]}}},{"id":158,"uris":["http://zotero.org/users/4604651/items/45HCCJ8U"],"uri":["http://zotero.org/users/4604651/items/45HCCJ8U"],"itemData":{"id":158,"type":"article-journal","title":"Reversible 26S Proteasome Disassembly upon Mitochondrial Stress","container-title":"Cell Reports","page":"1371-1380","volume":"7","issue":"5","source":"ScienceDirect","abstract":"Summary\nIn eukaryotic cells, proteasomes exist primarily as 26S holoenzymes, the most efficient configuration for ubiquitinated protein degradation. Here, we show that acute oxidative stress caused by environmental insults or mitochondrial defects results in rapid disassembly of 26S proteasomes into intact 20S core and 19S regulatory particles. Consequently, polyubiquitinated substrates accumulate, mitochondrial networks fragment, and cellular reactive oxygen species (ROS) levels increase. Oxidation of cysteine residues is sufficient to induce proteasome disassembly, and spontaneous reassembly from existing components is observed both in vivo and in vitro upon reduction. Ubiquitin-dependent substrate turnover also resumes after treatment with antioxidants. Reversible attenuation of 26S proteasome activity induced by acute mitochondrial or oxidative stress may be a short-term response distinct from adaptation to long-term ROS exposure or changes during aging.","DOI":"10.1016/j.celrep.2014.04.030","ISSN":"2211-1247","journalAbbreviation":"Cell Reports","author":[{"family":"Livnat-Levanon","given":"Nurit"},{"family":"Kevei","given":"Éva"},{"family":"Kleifeld","given":"Oded"},{"family":"Krutauz","given":"Daria"},{"family":"Segref","given":"Alexandra"},{"family":"Rinaldi","given":"Teresa"},{"family":"Erpapazoglou","given":"Zoi"},{"family":"Cohen","given":"Mickael"},{"family":"Reis","given":"Noa"},{"family":"Hoppe","given":"Thorsten"},{"family":"Glickman","given":"Michael H."}],"issued":{"date-parts":[["2014",6,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

. It could be different in cells, given that several factors regulating RP-CP association have been identified. One such factor is the chaperone and heat-shock protein 90 (Hsp90), which has been implicated in various ways in maintaining the integrity of the 26S proteasome[123–126] { ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ern4kn9k0","properties":{"formattedCitation":"{\\rtf \\super 123\\uc0\\u8211{}126\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":157,"uris":["http://zotero.org/users/4604651/items/6EMP8Z4J"],"uri":["http://zotero.org/users/4604651/items/6EMP8Z4J"],"itemData":{"id":157,"type":"article-journal","title":"The molecular chaperone Hsp90 plays a role in the assembly and maintenance of the 26S proteasome","container-title":"The EMBO Journal","page":"3557-3567","volume":"22","issue":"14","source":"Wiley Online Library","abstract":"Hsp90 has a diverse array of cellular roles including protein folding, stress response and signal transduction. Herein we report a novel function for Hsp90 in the ATP-dependent assembly of the 26S proteasome. Functional loss of Hsp90 using a temperature-sensitive mutant in yeast caused dissociation of the 26S proteasome. Conversely, these dissociated constituents reassembled in

Hsp90-dependent fashion both in vivo and in vitro; the process required ATP-hydrolysis and was suppressed by the Hsp90 inhibitor geldanamycin. We also found genetic interactions between Hsp90 and several proteasomal Rpn (Regulatory particle non-ATPase subunit) genes, emphasizing the importance of Hsp90 to the integrity of the 26S proteasome. Our results indicate that Hsp90 interacts with the 26S proteasome and plays a principal role in the assembly and maintenance of the 26S proteasome.","DOI":"10.1093/emboj/cdg349","ISSN":"1460-2075","language":"en","author":[{"family":"Imai","given":"Jun"},{"family":"Maruya","given":"Mikako"},{"family":"Yashiroda","given":"Hideki"},{"family":"Yahara","given":"Ichiro"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2003",7,15]]}},{"id":162,"uris":["http://zotero.org/users/4604651/items/H3W6UZFA"],"uri":["http://zotero.org/users/4604651/items/H3W6UZFA"],"itemData":{"id":162,"type":"article-journal","title":"Hsp90-mediated Assembly of the 26 S Proteasome Is Involved in Major Histocompatibility Complex Class I Antigen Processing","container-title":"Journal of Biological Chemistry","page":"28060-28065","volume":"283","issue":"42","source":"www.jbc.org","abstract":"Heat shock protein 90 (hsp90) and the proteasome activator PA28 stimulate major histocompatibility complex (MHC) class I antigen processing. It is unknown whether hsp90 influences the proteasome activity to produce T cell epitopes, although association of PA28 with the 20 S proteasome stimulates the enzyme activity. Here, we show that hsp90 is essential in assembly of the 26 S proteasome and as a result, is involved in epitope production. Addition of recombinant hsp90α to cell lysate enhanced chymotrypsin-like activity of the 26 S proteasome in an ATP-dependent manner as determined by an in-gel hydrolysis assay. We successfully pulled down histidine-tagged hsp90α- and PA28α-induced, newly assembled 26 S proteasomes from the cell extracts for in vitro epitope production assay, and we found these structures to be sensitive to geldanamycin, an hsp90 inhibitor. We found a cleaved epitope unique to the proteasome pulled down by both hsp90α and PA28α, whereas two different epitopes were identified in the hsp90α- and PA28α-pulldowns, respectively. Processing of these respective peptides in vivo was enhanced faithfully by the protein combinations used for the proteasome pulldowns. Inhibition of hsp90 in vivo by geldanamycin partly disrupted the 26 S proteasome structure, consistent with down-regulated MHC class I expression. Our results indicate that hsp90 facilitates MHC class I antigen processing through epitope production in a complex of the 26 S proteasome.","DOI":"10.1074/jbc.M803077200","ISSN":"0021-9258, 1083-351X","note":"PMID: 18703510","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Yamano","given":"Taketoshi"},{"family":"Mi

zukami","given":"Shusaku"},{"family":"Murata","given":"Shigeo"},{"family":"Chiba","given":"Tomoki"},{"family":"Tanaka","given":"Keiji"},{"family":"Udono","given":"Heiichiro"}],"issued":{"date-parts":[["2008",10,17]]}}},{"id":156,"uris":["http://zotero.org/users/4604651/items/AK2WD6MW"],"uri":["http://zotero.org/users/4604651/items/AK2WD6MW"],"itemData":{"id":156,"type":"article-journal","title":"Hsp90 and ECM29 Are Important to Maintain the Integrity of Mammalian 26S Proteasome","container-title":"Advances in Biological Chemistry","page":"255","volume":"05","issue":"07","source":"file.scirp.org","abstract":"The proteasome is a protease complex composed of a core particle (CP) and regulatory particles (RPs) that bind to both ends of the CP. ECM29 is a protein that associates with the proteasome and is involved in the maintenance and regulation of the proteasome assembly. However, ECM29 deficient mice can form functional proteasome. In this paper we sought to identify the mechanisms and/or proteins that help and allow the maintenance of the proteasome activity in the absence of ECM29. We analyzed the proteasome components of ECM29-deficient mice and identified Hsp90 as a protein associated with the proteasome. Furthermore, the inhibition of Hsp90 led to a partial disassembly of the proteasome only in ECM29-deficient cells. Those findings attest to the importance of Hsp90 for the maintenance of the proteasome integrity in the absence of ECM29.","DOI":"10.4236/abc.2015.57022","language":"en","author":[{"family":"Acquah","given":"Jean-Rene Q."},{"family":"Haratake","given":"Kousuke"},{"family":"Rakwal","given":"Randeep"},{"family":"Udono","given":"Heiichiro"},{"family":"Chiba","given":"Tomoki"}],"issued":{"date-parts":[["2015"]]}}},{"id":29,"uris":["http://zotero.org/users/4604651/items/LNIH6E8Z"],"uri":["http://zotero.org/users/4604651/items/LNIH6E8Z"],"itemData":{"id":29,"type":"article-journal","title":"The HSP90 chaperone machinery","container-title":"Nature Reviews. Molecular Cell Biology","page":"345-360","volume":"18","issue":"6","source":"PubMed","abstract":"The heat shock protein 90 (HSP90) chaperone machinery is a key regulator of proteostasis under both physiological and stress conditions in eukaryotic cells. As HSP90 has several hundred protein substrates (or 'clients'), it is involved in many cellular processes beyond protein folding, which include DNA repair, development, the immune response and neurodegenerative disease. A large number of co-chaperones interact with HSP90 and regulate the ATPase-associated conformational changes of the HSP90 dimer that occur during the processing of clients. Recent progress has

allowed the interactions of clients with HSP90 and its co-chaperones to be defined. Owing to the importance of HSP90 in the regulation of many cellular proteins, it has become a promising drug target for the treatment of several diseases, which include cancer and diseases associated with protein misfolding.","DOI":"10.1038/nrm.2017.20","ISSN":"1471-0080","note":"PMID: 28429788","journalAbbreviation":"Nat. Rev. Mol. Cell Biol.","language":"eng","author":[{"family":"Schopf","given":"Florian H."},{"family":"Biebl","given":"Maximilian M."},{"family":"Buchner","given":"Johannes"}],"issued":{"date-parts":[["2017",6]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"amlgg1qfg7","properties":{"formattedCitation":"{\\rtf \\super 123\\uc0\\u8211{}125\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":157,"uris":["http://zotero.org/users/4604651/items/6EMP8Z4J"],"uri":["http://zotero.org/users/4604651/items/6EMP8Z4J"],"itemData":{"id":157,"type":"article-journal","title":"The molecular chaperone Hsp90 plays a role in the assembly and maintenance of the 26S proteasome","container-title":"The EMBO Journal","page":"3557-3567","volume":"22","issue":"14","source":"Wiley Online Library","abstract":"Hsp90 has a diverse array of cellular roles including protein folding, stress response and signal transduction. Herein we report a novel function for Hsp90 in the ATP-dependent assembly of the 26S proteasome. Functional loss of Hsp90 using a temperature-sensitive mutant in yeast caused dissociation of the 26S proteasome. Conversely, these dissociated constituents reassembled in Hsp90-dependent fashion both in vivo and in vitro; the process required ATP-hydrolysis and was suppressed by the Hsp90 inhibitor geldanamycin. We also found genetic interactions between Hsp90 and several proteasomal Rpn (Regulatory particle non-ATPase subunit) genes, emphasizing the importance of Hsp90 to the integrity of the 26S proteasome. Our results indicate that Hsp90 interacts with the 26S proteasome and plays a principal role in the assembly and maintenance of the 26S proteasome.","DOI":"10.1093/emboj/cdg349","ISSN":"1460-2075","language":"en","author":[{"family":"Imai","given":"Jun"},{"family":"Maruya","given":"Mikako"},{"family":"Yashiroda","given":"Hideki"},{"family":"Yahara","given":"Ichiro"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2003",7,15]]}}},{"id":162,"uris":["http://zotero.org/users/4604651/items/H3W6UZFA"],"uri":["http://zotero.org/users/4604651/items/H3W6UZFA"],"itemData":{"id":162,"type":"article-journal","title":"Hsp90-mediated Assembly of the 26 S Proteasome Is Involved in

Major Histocompatibility Complex Class I Antigen Processing","container-title":"Journal of Biological Chemistry","page":"28060-28065","volume":"283","issue":"42","source":"www.jbc.org","abstract":"Heat shock protein 90 (hsp90) and the proteasome activator PA28 stimulate major histocompatibility complex (MHC) class I antigen processing. It is unknown whether hsp90 influences the proteasome activity to produce T cell epitopes, although association of PA28 with the 20 S proteasome stimulates the enzyme activity. Here, we show that hsp90 is essential in assembly of the 26 S proteasome and as a result, is involved in epitope production. Addition of recombinant hsp90α to cell lysate enhanced chymotrypsin-like activity of the 26 S proteasome in an ATP-dependent manner as determined by an in-gel hydrolysis assay. We successfully pulled down histidine-tagged hsp90α- and PA28α-induced, newly assembled 26 S proteasomes from the cell extracts for in vitro epitope production assay, and we found these structures to be sensitive to geldanamycin, an hsp90 inhibitor. We found a cleaved epitope unique to the proteasome pulled down by both hsp90α and PA28α, whereas two different epitopes were identified in the hsp90α- and PA28α-pulldowns, respectively. Processing of these respective peptides in vivo was enhanced faithfully by the protein combinations used for the proteasome pulldowns. Inhibition of hsp90 in vivo by geldanamycin partly disrupted the 26 S proteasome structure, consistent with down-regulated MHC class I expression. Our results indicate that hsp90 facilitates MHC class I antigen processing through epitope production in a complex of the 26 S proteasome.","DOI":"10.1074/jbc.M803077200","ISSN":"0021-9258, 1083-351X","note":"PMID: 18703510","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Yamano","given":"Taketoshi"},{"family":"Mizukami","given":"Shusaku"},{"family":"Murata","given":"Shigeo"},{"family":"Chiba","given":"Tomoki"},{"family":"Tanaka","given":"Keiji"},{"family":"Udono","given":"Heiichiro"}],"issued":{"date-parts":[["2008",10,17]]}}},{"id":156,"uris":["http://zotero.org/users/4604651/items/AK2WD6MW"],"uri":["http://zotero.org/users/4604651/items/AK2WD6MW"],"itemData":{"id":156,"type":"article-journal","title":"Hsp90 and ECM29 Are Important to Maintain the Integrity of Mammalian 26S Proteasome","container-title":"Advances in Biological Chemistry","page":"255","volume":"05","issue":"07","source":"file.scirp.org","abstract":"The proteasome is a protease complex composed of a core particle (CP) and regulatory particles (RPs) that bind to both ends of the CP. ECM29 is a protein that associates with the proteasome and is involved in the maintenance and regulation of the proteasome assembly. However, ECM29 deficient mice can form functional proteasome. In this paper we sought to identify the

mechanisms and/or proteins that help and allow the maintenance of the proteasome activity in the absence of ECM29. We analyzed the proteasome components of ECM29-deficient mice and identified Hsp90 as a protein associated with the proteasome. Furthermore, the inhibition of Hsp90 led to a partial disassembly of the proteasome only in ECM29-deficient cells. Those findings attest to the importance of Hsp90 for the maintenance of the proteasome integrity in the absence of ECM29.","DOI":"10.4236/abc.2015.57022","language":"en","author":[{"family":"Acquah","given":"Jean-Rene Q."},{"family":"Haratake","given":"Kousuke"},{"family":"Rakwal","given":"Randeep"},{"family":"Udono","given":"Heiichiro"},{"family":"Chiba","given":"Tomoki"}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }(FIG. 5). The RP base subunit Rpn6 may also regulate RP-CP association because it binds directly to the α2 subunit of the CP[22]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2pt00miubl","properties":{"formattedCitation":"{\\rtf \\super 22\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } (FIG. 5). Ectopic expression of RPN-6.1 in *C. elegans* was found to increase proteasome activity and to improve the resistance to proteotoxic stresses[127]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a14lqfo43j4","properties":{"formattedCitation":"{\\rtf \\super

127\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":152,"uris":["http://zotero.org/users/4604651/items/Y35KLUE8"],"uri":["http://zotero.org/users/4604651/items/Y35KLUE8"],"itemData":{"id":152,"type":"article-journal","title":"RPN-6 determines C. elegans longevity under proteotoxic stress conditions","container-title":"Nature","page":"263-268","volume":"489","issue":"7415","source":"www.nature.com","abstract":"Organisms that protect their germ-cell lineages from damage often do so at considerable cost: limited metabolic resources become partitioned away from maintenance of the soma, leaving the ageing somatic tissues to navigate survival amid an environment containing damaged and poorly functioning proteins. Historically, experimental paradigms that limit reproductive investment result in lifespan extension. We proposed that germline-deficient animals might exhibit heightened protection from proteotoxic stressors in somatic tissues. We find that the forced re-investment of resources from the germ line to the soma in Caenorhabditis elegans results in elevated somatic proteasome activity, clearance of damaged proteins and increased longevity. This activity is associated with increased expression of rpn-6, a subunit of the 19S proteasome, by the FOXO transcription factor DAF-16. Ectopic expression of rpn-6 is sufficient to confer proteotoxic stress resistance and extend lifespan, indicating that rpn-6 is a candidate to correct deficiencies in age-related protein homeostasis disorders.","DOI":"10.1038/nature11315","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Vilchez","given":"David"},{"family":"Morantte","given":"Ianessa"},{"family":"Liu","given":"Zheng"},{"family":"Douglas","given":"Peter M."},{"family":"Merkwirth","given":"Carsten"},{"family":"Rodrigues","given":"Ana P. C."},{"family":"Manning","given":"Gerard"},{"family":"Dillin","given":"Andrew"}],"issued":{"date-parts":[["2012",9,13]]}},"locator":"1"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Rpn6 is also important to maintain high levels of proteasome in human embryonic stem cells (ESCs)[128]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2a12rqq2fg","properties":{"formattedCitation":"{\\rtf \\super 128\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":151,"uris":["http://zotero.org/users/4604651/items/FW4TRPXI"],"uri":["http://zotero.org/users/4604651/items/FW4TRPXI"],"itemData":{"id":151,"type":"article-journal","title":"Increased proteasome activity in human embryonic stem cells is regulated by PSMD11","container-title":"Nature","page":"304-308","volume":"489","issue":"7415","source":"www.nature.com","abstract":"Embryonic stem cells can replicate continuously in the absence of senescence and, therefore, are immortal in culture. Although genome stability is essential for the survival of stem cells, proteome stability may have an equally important role in stem-cell identity and function. Furthermore, with the asymmetric divisions invoked by stem cells, the passage of damaged proteins to daughter cells could potentially destroy the resulting lineage of cells. Therefore, a firm understanding of how stem cells maintain their proteome is of central importance. Here we show that human embryonic stem cells (hESCs) exhibit high proteasome activity that is correlated with increased levels of the 19S proteasome subunit PSMD11 (known as RPN-6 in Caenorhabditis elegans) and a corresponding increased assembly of the 26S/30S proteasome. Ectopic expression of PSMD11 is sufficient to increase proteasome assembly and activity. FOXO4, an insulin/insulin-like growth factor-I (IGF-I) responsive transcription factor associated with long lifespan in invertebrates, regulates proteasome activity by modulating the expression of PSMD11 in hESCs. Proteasome inhibition in hESCs affects the expression of pluripotency markers and the levels of specific markers of the distinct germ layers. Our results suggest a new regulation of proteostasis in hESCs that links longevity and stress resistance in invertebrates to hESC function and identity.","DOI":"10.1038/nature11468","ISSN":"0028-

0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Vilchez","given":"David"},{"family":"Boyer","given":"Leah"},{"family":"Morantte","given":"Ianessa"},{"family":"Lutz","given":"Margaret"},{"family":"Merkwirth","given":"Carsten"},{"family":"Joyce","given":"Derek"},{"family":"Spencer","given":"Brian"},{"family":"Page","given":"Lesley"},{"family":"Masliah","given":"Eliezer"},{"family":"Berggren","given":"W. Travis"},{"family":"Gage","given":"Fred H."},{"family":"Dillin","given":"Andrew"}],"issued":{"date-parts":[["2012",9,13]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

The HEAT-like repeat protein Ecm29 associates with the proteasome in yeast and recognizes aberrant RP-CP assemblies that accumulate in strains compromised for proteasome assembly or maturation, such as in *ump1Δ* cells[58,129] { ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"a2giq8mcpn0","properties":{"formattedCitation":"{\\rtf \\super 58,129\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":54,"uris":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"uri":["http://zotero.org/users/4604651/items/E7L5ZK3G"],"itemData":{"id":54,"type":"article-journal","title":"Ump1p Is Required for Proper Maturation of the 20S Proteasome and Becomes Its Substrate upon Completion of the Assembly","container-title":"Cell","page":"489-499","volume":"92","issue":"4","source":"ScienceDirect","abstract":"We report the discovery of a short-lived chaperone that is required for the correct maturation of the eukaryotic 20S proteasome and is destroyed at a specific stage of the assembly process. The S. cerevisiae Ump1p protein is a component of proteasome precursor complexes containing unprocessed β subunits but is not detected in the mature 20S proteasome. Upon the association of two precursor complexes, Ump1p is encased and is rapidly degraded after the proteolytic sites in the interior of the nascent proteasome are activated. Cells lacking Ump1p exhibit a lack of coordination between the processing of β subunits and proteasome assembly, resulting in functionally impaired proteasomes. We also show that the propeptide of the Pre2p/Doa3p β subunit is required for Ump1p's function in proteasome maturation.","DOI":"10.1016/S0092-8674(00)80942-3","ISSN":"0092-8674","journalAbbreviation":"Cell","author":[{"family":"Ramos","given":"Paula C"},{"family":"Höckendorff","given":"Jörg"},{"family":"Johnson","given":"Erica S"},{"family":"Varshavsky","given":"Alexander"},{"family":"Dohmen","given":"R. Jürgen"}],"issued":{"date-parts":[["1998",2,20]]}}},{"id":153,"uris":["http://zotero.org/users/4604651/items/2LGUUWAE"],"uri":["http://zotero.org/users/4604651/items/2LGUUWAE"],"itemData":{"id":153,"type":"article-journal","title":"Ecm29 Fulfils Quality Control Functions in Proteasome Assembly","container-title":"Molecular Cell","page":"879-888","volume":"38","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe proteasome, the central protease of eukaryotic cells, is composed of one core particle (CP) and one or two adjacent regulatory particles (RP), which contain multiple subunits. Several proteasome-dedicated chaperones govern the assembly of CP and RP, respectively. We sought for proteins that regulate final steps of RP-CP assembly in yeast and found Ecm29, a conserved HEAT-like repeat protein. Here, we show that Ecm29 controls the integrity of RP-CP assemblies. Ecm29 recognizes RP-CP species in which CP maturation is stalled due to the lack of distinct β subunits. Reconstitution assays revealed that Ecm29 functions as scaffold protein during the remodeling of incompletely matured RP-CP assemblies into regular enzymes. Upon the completion of CP maturation, Ecm29 is degraded and RP-CP is dissociated.","DOI":"10.1016/j.molcel.2010.06.016","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Lehmann","given":"Andrea"},{"family":"Niewienda","given":"Agathe"},{"family":"Jechow","given":"Katharina

"},{"family":"Janek","given":"Katharina"},{"family":"Enenkel","given":"Cordula"}],"issued":{"date-parts":[["2010",6,25]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} or in α-pocket lysine mutants, in which immature β-subunits are incorporated[130]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"agrm11ll8f","properties":{"formattedCitation":"{\\rtf \\super 130\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":149,"uris":["http://zotero.org/users/4604651/items/GBJBLYTD"],"uri":["http://zotero.org/users/4604651/items/GBJBLYTD"],"itemData":{"id":149,"type":"article-journal","title":"Structural Defects in the Regulatory Particle-Core Particle Interface of the Proteasome Induce a Novel Proteasome Stress Response","container-title":"Journal of Biological Chemistry","page":"36652-36666","volume":"286","issue":"42","source":"www.jbc.org","abstract":"Proteasomes consist of a 19-subunit regulatory particle (RP) and 28-subunit core particle (CP), an α7β7β7α7 structure. The RP recognizes substrates and translocates them into the CP for degradation. At the RP-CP interface, a heterohexameric Rpt ring joins to a heteroheptameric CP α ring. Rpt C termini insert individually into the α ring pockets to form a salt bridge with a pocket lysine residue. We report that substitutions of α pocket lysine residues produce an unexpected block to CP assembly, arising from a late stage defect in β ring assembly. Substitutions α5K66A and α6K62A resulted in abundant incorporation of immature CP β subunits, associated with a complete β ring, into proteasome holoenzymes. Incorporation of immature CP into the proteasome depended on a proteasome-associated protein, Ecm29. Using ump1 mutants, we identified Ecm29 as a potent negative regulator of RP assembly and confirmed our previous findings that proper RP assembly requires the CP. Ecm29 was enriched on proteasomes of pocket lysine mutants, as well as those of rpt4-Δ1 and rpt6-Δ1 mutants, in which the C-terminal residue, thought to contact the pocket lysine, is deleted. In both rpt6-Δ1 and α6K62A proteasomes, Ecm29 suppressed opening of the CP substrate translocation channel, which is gated through interactions between Rpt C termini and the α pockets. The ubiquitin ligase Hul5 was recruited to these proteasomes together with Ecm29. Proteasome remodeling through the addition of Ecm29 and Hul5 suggests a new layer of the proteasome stress response and may be a common response to structurally aberrant proteasomes or deficient proteasome function.","DOI":"10.1074/jbc.M111.285924","ISSN":"0021-9258, 1083-351X","note":"PMID: 21878652","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Park","given":"Soyeon"},{"family":"Kim","given":"Woong"},{"family":"Tian","given":"Geng"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2011",10,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. When bound to faulty proteasomes, Ecm29 represses proteasomal degradation by inhibiting both proteasomal ATPase activity and CP gate opening[129–132]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a156a0dvoii","properties":{"formattedCitation":"{\\rtf \\super 129\\uc0\\u8211{}132\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":153,"uris":["http://zotero.org/users/4604651/items/2LGUUWAE"],"uri":["http://zotero.org/users/4604651/items/2LGUUWAE"],"itemData":{"id":153,"type":"article-journal","title":"Ecm29 Fulfils Quality Control Functions in Proteasome Assembly","container-title":"Molecular Cell","page":"879-888","volume":"38","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe proteasome, the central protease of eukaryotic cells, is composed of one core particle (CP) and one or two adjacent regulatory particles (RP), which contain multiple subunits. Several proteasome-dedicated chaperones govern the assembly of CP and RP, respectively. We sought for proteins that regulate final steps of RP-CP assembly in yeast and found Ecm29, a conserved HEAT-like repeat protein. Here, we show that Ecm29 controls the integrity of RP-CP assemblies. Ecm29

recognizes RP-CP species in which CP maturation is stalled due to the lack of distinct β subunits. Reconstitution assays revealed that Ecm29 functions as scaffold protein during the remodeling of incompletely matured RP-CP assemblies into regular enzymes. Upon the completion of CP maturation, Ecm29 is degraded and RP-CP is dissociated.","DOI":"10.1016/j.molcel.2010.06.016","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Lehmann","given":"Andrea"},{"family":"Niewienda","given":"Agathe"},{"family":"Jechow","given":"Katharina"},{"family":"Janek","given":"Katharina"},{"family":"Enenkel","given":"Cordula"}],"issued":{"date-parts":[["2010",6,25]]}},{"id":149,"uris":["http://zotero.org/users/4604651/items/GBJBLYTD"],"uri":["http://zotero.org/users/4604651/items/GBJBLYTD"],"itemData":{"id":149,"type":"article-journal","title":"Structural Defects in the Regulatory Particle-Core Particle Interface of the Proteasome Induce a Novel Proteasome Stress Response","container-title":"Journal of Biological Chemistry","page":"36652-36666","volume":"286","issue":"42","source":"www.jbc.org","abstract":"Proteasomes consist of a 19-subunit regulatory particle (RP) and 28-subunit core particle (CP), an α7β7β7α7 structure. The RP recognizes substrates and translocates them into the CP for degradation. At the RP-CP interface, a heterohexameric Rpt ring joins to a heteroheptameric CP α ring. Rpt C termini insert individually into the α ring pockets to form a salt bridge with a pocket lysine residue. We report that substitutions of α pocket lysine residues produce an unexpected block to CP assembly, arising from a late stage defect in β ring assembly. Substitutions α5K66A and α6K62A resulted in abundant incorporation of immature CP β subunits, associated with a complete β ring, into proteasome holoenzymes. Incorporation of immature CP into the proteasome depended on a proteasome-associated protein, Ecm29. Using ump1 mutants, we identified Ecm29 as a potent negative regulator of RP assembly and confirmed our previous findings that proper RP assembly requires the CP. Ecm29 was enriched on proteasomes of pocket lysine mutants, as well as those of rpt4-Δ1 and rpt6-Δ1 mutants, in which the C-terminal residue, thought to contact the pocket lysine, is deleted. In both rpt6-Δ1 and α6K62A proteasomes, Ecm29 suppressed opening of the CP substrate translocation channel, which is gated through interactions between Rpt C termini and the α pockets. The ubiquitin ligase Hul5 was recruited to these proteasomes together with Ecm29. Proteasome remodeling through the addition of Ecm29 and Hul5 suggests a new layer of the proteasome stress response and may be a common response to structurally aberrant proteasomes or deficient proteasome function.","DOI":"10.1074/jbc.M111.285924","ISSN":"0021-9258, 1083-351X","note":"PMID: 21878652","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Park","given":"Soyeon"},{"family":"Kim","given":"Woong"},{"family":"Tian","given":"Geng"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2011",10,21]]}}},{"id":148,"uris":["http://zotero.org/users/4604651/items/3RQAMXYY"],"uri":["http://zotero.org/users/4604651/items/3RQAMXYY"],"itemData":{"id":148,"type":"article-journal","title":"The proteasome-associated protein Ecm29 inhibits proteasomal ATPase activity and in vivo protein degradation by the proteasome","container-title":"The Journal of Biological Chemistry","page":"29467-29481","volume":"288","issue":"41","source":"PubMed","abstract":"Several proteasome-associated proteins regulate degradation by the 26 S proteasome using the ubiquitin chains that mark most substrates for degradation. The proteasome-associated protein Ecm29, however, has no ubiquitin-binding or modifying activity, and its direct effect on substrate degradation is unclear. Here, we show that Ecm29 acts as a proteasome inhibitor. Besides inhibiting the proteolytic cleavage of peptide substrates in vitro, it inhibits the degradation of ubiquitin-dependent and -independent substrates in vivo. Binding of Ecm29 to the proteasome induces a closed conformation of the substrate entry channel of the core particle. Furthermore, Ecm29 inhibits proteasomal ATPase activity, suggesting that the mechanism of inhibition and gate

regulation by Ecm29 is through regulation of the proteasomal ATPases. Consistent with this, we identified through chemical cross-linking that Ecm29 binds to, or in close proximity to, the proteasomal ATPase subunit Rpt5. Additionally, we show that Ecm29 preferentially associates with both mutant and nucleotide depleted proteasomes. We propose that the inhibitory ability of Ecm29 is important for its function as a proteasome quality control factor by ensuring that aberrant proteasomes recognized by Ecm29 are inactive.","DOI":"10.1074/jbc.M113.491662","ISSN":"1083-351X","note":"PMID: 23995839\nPMCID: PMC3795246","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"De La Mota-Peynado","given":"Alina"},{"family":"Lee","given":"Stella Yu-Chien"},{"family":"Pierce","given":"Brianne Marie"},{"family":"Wani","given":"Prashant"},{"family":"Singh","given":"Chingakham Ranjit"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2013",10,11]]}},{"id":147,"uris":["http://zotero.org/users/4604651/items/QPYKYRAL"],"uri":["http://zotero.org/users/4604651/items/QPYKYRAL"],"itemData":{"id":147,"type":"article-journal","title":"Loss of Rpt5 Protein Interactions with the Core Particle and Nas2 Protein Causes the Formation of Faulty Proteasomes That Are Inhibited by Ecm29 Protein","container-title":"Journal of Biological Chemistry","page":"36641-36651","volume":"286","issue":"42","source":"www.jbc.org","abstract":"The proteasome is a large and complex protease formed by 66 polypeptides. The assembly of the proteasome is assisted by at least nine chaperones. One of these chaperones, Nas2/p27, binds to the C-terminal region of the AAA-ATPase Rpt5. We report here that the tail of Rpt5 provides two functions. First, it facilitates the previously reported interaction with the proteasome core particle (CP). Second, it is essential for the interaction with Nas2. Deletion of the C-terminal amino acid of Rpt5 disrupts the CP interaction, but not the binding to Nas2. The latter is surprising considering Nas2 contains a PDZ domain, which is often involved in binding to C termini. Interestingly, deletion of the last three amino acids interferes with both functions. The disruption of the Rpt5-CP interactions gave distinct phenotypes different from disruption of the Nas2-Rpt5 interaction. Additionally, proteasomes purified from a Saccharomyces cerevisiae rpt5-Δ3 strain show a strong enrichment of Ecm29. The function of Ecm29, a proteasome-associated protein, is not well understood. Our data show that Ecm29 can inhibit proteasomes, because our Ecm29-containing proteasomes have reduced suc-LLVY-AMC hydrolytic activity. Consistent with this apparent role as negative regulator, the deletion of ECM29 rescues the phenotypes of rpt5-Δ3 and nas2Δ in an hsm3Δ background. In sum, the interactions facilitated by the tail of Rpt5 act synergistically to minimize the formation of faulty proteasomes, thereby preventing recognition and inhibition by Ecm29.","DOI":"10.1074/jbc.M111.280875","ISSN":"0021-9258, 1083-351X","note":"PMID: 21878651","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Lee","given":"Stella Yu-Chien"},{"family":"Mota-Peynado","given":"Alina De La"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2011",10,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2anscuo7ki","properties":{"formattedCitation":"{\\rtf \\super 129\\uc0\\u8211{}131\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":153,"uris":["http://zotero.org/users/4604651/items/2LGUUWAE"],"uri":["http://zotero.org/users/4604651/items/2LGUUWAE"],"itemData":{"id":153,"type":"article-journal","title":"Ecm29 Fulfils Quality Control Functions in Proteasome Assembly","container-title":"Molecular Cell","page":"879-888","volume":"38","issue":"6","source":"ScienceDirect","abstract":"Summary\nThe proteasome, the central protease of eukaryotic cells, is composed of one core particle (CP) and one or two adjacent regulatory particles (RP), which contain multiple subunits. Several proteasome-

dedicated chaperones govern the assembly of CP and RP, respectively. We sought for proteins that regulate final steps of RP-CP assembly in yeast and found Ecm29, a conserved HEAT-like repeat protein. Here, we show that Ecm29 controls the integrity of RP-CP assemblies. Ecm29 recognizes RP-CP species in which CP maturation is stalled due to the lack of distinct β subunits. Reconstitution assays revealed that Ecm29 functions as scaffold protein during the remodeling of incompletely matured RP-CP assemblies into regular enzymes. Upon the completion of CP maturation, Ecm29 is degraded and RP-CP is dissociated.","DOI":"10.1016/j.molcel.2010.06.016","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Lehmann","given":"Andrea"},{"family":"Niewienda","given":"Agathe"},{"family":"Jechow","given":"Katharina"},{"family":"Janek","given":"Katharina"},{"family":"Enenkel","given":"Cordula"}],"issued":{"date-parts":[["2010",6,25]]}},{"id":149,"uris":["http://zotero.org/users/4604651/items/GBJBLYTD"],"uri":["http://zotero.org/users/4604651/items/GBJBLYTD"],"itemData":{"id":149,"type":"article-journal","title":"Structural Defects in the Regulatory Particle-Core Particle Interface of the Proteasome Induce a Novel Proteasome Stress Response","container-title":"Journal of Biological Chemistry","page":"36652-36666","volume":"286","issue":"42","source":"www.jbc.org","abstract":"Proteasomes consist of a 19-subunit regulatory particle (RP) and 28-subunit core particle (CP), an α7β7β7α7 structure. The RP recognizes substrates and translocates them into the CP for degradation. At the RP-CP interface, a heterohexameric Rpt ring joins to a heteroheptameric CP α ring. Rpt C termini insert individually into the α ring pockets to form a salt bridge with a pocket lysine residue. We report that substitutions of α pocket lysine residues produce an unexpected block to CP assembly, arising from a late stage defect in β ring assembly. Substitutions α5K66A and α6K62A resulted in abundant incorporation of immature CP β subunits, associated with a complete β ring, into proteasome holoenzymes. Incorporation of immature CP into the proteasome depended on a proteasome-associated protein, Ecm29. Using ump1 mutants, we identified Ecm29 as a potent negative regulator of RP assembly and confirmed our previous findings that proper RP assembly requires the CP. Ecm29 was enriched on proteasomes of pocket lysine mutants, as well as those of rpt4-Δ1 and rpt6-Δ1 mutants, in which the C-terminal residue, thought to contact the pocket lysine, is deleted. In both rpt6-Δ1 and α6K62A proteasomes, Ecm29 suppressed opening of the CP substrate translocation channel, which is gated through interactions between Rpt C termini and the α pockets. The ubiquitin ligase Hul5 was recruited to these proteasomes together with Ecm29. Proteasome remodeling through the addition of Ecm29 and Hul5 suggests a new layer of the proteasome stress response and may be a common response to structurally aberrant proteasomes or deficient proteasome function.","DOI":"10.1074/jbc.M111.285924","ISSN":"0021-9258, 1083-351X","note":"PMID: 21878652","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Park","given":"Soyeon"},{"family":"Kim","given":"Woong"},{"family":"Tian","given":"Geng"},{"family":"Gygi","given":"Steven P."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2011",10,21]]}},{"id":148,"uris":["http://zotero.org/users/4604651/items/3RQAMXYY"],"uri":["http://zotero.org/users/4604651/items/3RQAMXYY"],"itemData":{"id":148,"type":"article-journal","title":"The proteasome-associated protein Ecm29 inhibits proteasomal ATPase activity and in vivo protein degradation by the proteasome","container-title":"The Journal of Biological Chemistry","page":"29467-29481","volume":"288","issue":"41","source":"PubMed","abstract":"Several proteasome-associated proteins regulate degradation by the 26 S proteasome using the ubiquitin chains that mark most substrates for degradation. The proteasome-associated protein Ecm29, however, has no ubiquitin-binding or modifying activity, and its direct effect on substrate degradation is unclear. Here, we show that Ecm29 acts as a proteasome inhibitor. Besides inhibiting the proteolytic cleavage of peptide substrates in vitro, it inhibits the degradation of ubiquitin-

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Ecm29 within itself and with proteasome subunits and determined the architecture of the Ecm29-proteasome complex with integrative structure modeling. These results enabled us to propose a structural model in which Ecm29 intrudes on the interaction between the 20S core particle and the 19S regulatory particle in the 26S proteasome, disrupting the proteasome structure in response to oxidative stress.","DOI":"10.1074/jbc.M117.803619","ISSN":"1083-351X","note":"PMID: 28821611\nPMCID: PMC5625060","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Wang","given":"Xiaorong"},{"family":"Chemmama","given":"Ilan E."},{"family":"Yu","given":"Clinton"},{"family":"Huszagh","given":"Alexander"},{"family":"Xu","given":"Yue"},{"family":"Viner","given":"Rosa"},{"family":"Block","given":"Sarah A."},{"family":"Cimermancic","given":"Peter"},{"family":"Rychnovsky","given":"Scott D."},{"family":"Ye","given":"Yihong"},{"family":"Sali","given":"Andrej"},{"family":"Huang","given":"Lan"}],"issued":{"date-parts":[["2017"]],"season":"29"}}},{"id":159,"uris":["http://zotero.org/users/4604651/items/KLANFWSB"],"uri":["http://zotero.org/users/4604651/items/KLANFWSB"],"itemData":{"id":159,"type":"article-journal","title":"Regulation of the 26S Proteasome Complex During Oxidative Stress","container-title":"Sci. Signal.","page":"ra88-ra88","volume":"3","issue":"151","source":"stke.sciencemag.org","abstract":"Separation of Powers\nThe proteasome is a large, multicatalytic complex that degrades proteins in an ATP- and ubiquitin-dependent manner. The 26S proteasome is composed of the 20S catalytic core and the 19S regulatory particle. The 19S particle consists of two subcomplexes that constitute the base and lid structures around the catalytic core. When separated from the 26S proteasome, the 20S core degrades oxidized (nonubiquitinated) proteins. Oxidative stress results in the accumulation of damaged proteins in the cell, which are removed by proteasomes. Wang et al. used mass spectrometry to examine the effects of hydrogen peroxide (H2O2)–induced stress on the 26S proteasome in yeast. H2O2 triggered recruitment to the 19S particle of the proteasome-binding protein Ecm29 and disassembly of the 26S proteasome into its 20S and 19S constituents. Yeast strains deficient in Ecm29 did not exhibit 26S disassembly and were more sensitive to H2O2 than were wild-type cells. Indeed, an efficient response to H2O2 required disassembly of the 26S proteasome to generate sufficient amounts of free 20S core to degrade oxidized proteins. Similar results were obtained in experiments with a human cell line, which suggests that dissociation of the 26S proteasome in response to oxidative stress may be a conserved cellular response in eukaryotes.\nThe proteasome plays a pivotal role in the cellular response to oxidative stress. Here, we used biochemical and mass spectrometric

methods to investigate structural changes in the 26S proteasomes from yeast and mammalian cells exposed to hydrogen peroxide (H2O2). Oxidative stress induced the dissociation of the 20S core particle from the 19S regulatory particle of the 26S proteasome, which resulted in loss of the activities of the 26S proteasome and accumulation of ubiquitinated proteins. H2O2 triggered the increased association of the proteasome-interacting protein Ecm29 with the purified 19S particle. Deletion of ECM29 in yeast cells prevented the disassembly of the 26S proteasome in response to oxidative stress, and ecm29 mutants were more sensitive to H2O2 than were wild-type cells, suggesting that separation of the 19S and 20S particles is important for cellular recovery from oxidative stress. The increased amount of free 20S core particles was required to degrade oxidized proteins. The Ecm29-dependent dissociation of the proteasome was independent of Yap1, a transcription factor that is critical for the oxidative stress response in yeast, and thus functions as a parallel defense pathway against H2O2-induced stress.\nOxidative stress triggers release of the core catalytic subunit of the yeast 26S proteasome, enabling degradation of toxic oxidized proteins.\nOxidative stress triggers release of the core catalytic subunit of the yeast 26S proteasome, enabling degradation of toxic oxidized proteins.","DOI":"10.1126/scisignal.2001232","ISSN":"1945-0877, 1937-9145","note":"PMID: 21139140","journalAbbreviation":"Sci. Signal.","language":"en","author":[{"family":"Wang","given":"Xiaorong"},{"family":"Yen","given":"James"},{"family":"Kaiser","given":"Peter"},{"family":"Huang","given":"Lan"}],"issued":{"date-parts":[["2010",12,7]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. Some interesting questions to address in future studies include how Ecm29 is specifically recruited to the 26S proteasome under oxidative stress and whether Ecm29-bound aberrant proteasomes are disassembled or degraded.

The tightly regulated degradation of the majority of cellular proteins is executed by the 26S proteasome. It has also been proposed that the CP could degrade proteins that are inherently unstable or unstructured, and that degradation of such proteins occurs 'by default'[134]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ql6h1h33m","properties":{"formattedCitation":"{\\rtf \\super 134\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":515,"uris":["http://zotero.org/users/4604651/items/XCRAJ656"],"uri":["http://zotero.org/users/4604651/items/XCRAJ656"],"itemData":{"id":515,"type":"article-journal","title":"20S proteasomes and protein degradation \"by default\"","container-title":"BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology","page":"844-

849","volume":"28","issue":"8","source":"PubMed","abstract":"The degradation of the majority of cellular proteins is mediated by the proteasomes. Ubiquitin-dependent proteasomal protein degradation is executed by a number of enzymes that interact to modify the substrates prior to their engagement with the 26S proteasomes. Alternatively, certain proteins are inherently unstable and undergo \"default\" degradation by the 20S proteasomes. Puzzlingly, proteins are by large subjected to both degradation pathways. Proteins with unstructured regions have been found to be substrates of the 20S proteasomes in vitro and, therefore, unstructured regions may serve as signals for protein degradation \"by default\" in the cell. The literature is loaded with examples where engagement of a protein into larger complexes increases protein stability, possibly by escaping degradation \"by default\". Our model suggests that formation of protein complexes masks the unstructured regions, making them inaccessible to the 20S proteasomes. This model not only provides molecular explanations for a recent theoretical \"cooperative stability\" principle, but also provokes new predictions and explanations in the field of protein regulation and functionality.","DOI":"10.1002/bies.20447","ISSN":"0265-9247","note":"PMID: 16927316","journalAbbreviation":"Bioessays","language":"eng","author":[{"family":"Asher","given":"Gad"},{"family":"Reuven","given":"Nina"},{"family":"Shaul","given":"Yosef"}],"issued":{"date-parts":[["2006",8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. It was shown that degradation by the CP proteasome does not require ubiquitin tagging but is dependent on the presence of unstructured regions in proteins, however to date little is known about CP-mediated protein degradation[87]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a25fomocc8j","properties":{"formattedCitation":"{\\rtf \\super 87\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":395,"uris":["http://zotero.org/users/4604651/items/3FT542GQ"],"uri":["http://zotero.org/users/4604651/items/3FT542GQ"],"itemData":{"id":395,"type":"article-journal","title":"Regulating the 20S proteasome ubiquitin-independent degradation pathway","container-title":"Biomolecules","page":"862-884","volume":"4","issue":"3","source":"PubMed","abstract":"For many years, the ubiquitin-26S proteasome degradation pathway was considered the primary route for proteasomal degradation. However, it is now becoming clear that proteins can also be targeted for degradation by the core 20S proteasome itself. Degradation by the 20S proteasome does not require ubiquitin tagging or the presence of the 19S regulatory particle; rather, it relies on the inherent structural disorder of the protein being degraded. Thus, proteins that contain unstructured regions due to oxidation, mutation, or aging, as well as naturally, intrinsically

unfolded proteins, are susceptible to 20S degradation. Unlike the extensive knowledge acquired over the years concerning degradation by the 26S proteasome, relatively little is known about the means by which 20S-mediated proteolysis is controlled. Here, we describe our current understanding of the regulatory mechanisms that coordinate 20S proteasome-mediated degradation, and highlight the gaps in knowledge that remain to be bridged.","DOI":"10.3390/biom4030862","ISSN":"2218-273X","note":"PMID: 25250704\nPMCID: PMC4192676","journalAbbreviation":"Biomolecules","language":"eng","author":[{"family":"Ben-Nissan","given":"Gili"},{"family":"Sharon","given":"Michal"}],"issued":{"date-parts":[["2014",9,23]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

[H2] Regulation of RP-CP association by post-translational modifications

Post-translational modifications of the proteasome offer additional possibilities to regulate proteasomal degradation, as reviewed elsewhere[135,136]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1eil1cjubu","properties":{"formattedCitation":"{\\rtf \\super 135,136\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":140,"uris":["http://zotero.org/users/4604651/items/KVI7IF9Y"],"uri":["http://zotero.org/users/4604651/items/KVI7IF9Y"],"itemData":{"id":140,"type":"article-journal","title":"Precise assembly and regulation of 26S proteasome and correlation between proteasome dysfunction and neurodegenerative diseases","container-title":"BMB Reports","page":"459-473","volume":"49","issue":"9","source":"PubMed Central","abstract":"Neurodegenerative diseases (NDs) often involve the formation of abnormal and toxic protein aggregates, which are thought to be the primary factor in ND occurrence and progression. Aged neurons exhibit marked increases in aggregated protein levels, which can lead to increased cell death in specific brain regions. As no specific drugs/therapies for treating the symptoms or/and progression of NDs are available, obtaining a complete understanding of the mechanism underlying the formation of protein aggregates is needed for designing a novel and efficient removal strategy. Intracellular proteolysis generally involves either the lysosomal or ubiquitin-proteasome system. In this review, we focus on the structure and assembly of the proteasome, proteasome-mediated protein degradation, and the multiple dynamic regulatory mechanisms governing proteasome activity. We also discuss the plausibility of the correlation between changes in proteasome activity and the occurrence of NDs. [BMB Reports 2016; 49(9): 459-473]","DOI":"10.5483/BMBRep.2016.49.9.094","ISSN":"1976-6696","note":"PMID: 27312603\nPMCID: PMC5227139","journalAbbreviation":"BMB Rep","author":[{"family":"Im","given":"Eunju"},{"family":"Chung","given":"Kwang Chul"}],"issued":{"date-parts":[["2016",9,30]]}}},{"id":409,"uris":["http://zotero.org/users/4604651/items/6X6VK7HW"],"uri":["http://zotero.org/users/4604651/items/6X6VK7HW"],"itemData":{"id":409,"type":"article-journal","title":"The life cycle of the 26S proteasome: from birth, through regulation and function, and onto its death","container-title":"Cell Research","page":"869","volume":"26","issue":"8","source":"www.nature.com","abstract":"The life cycle of the 26S proteasome: from birth,

through regulation and function, and onto its death","DOI":"10.1038/cr.2016.86","ISSN":"1748-7838","shortTitle":"The life cycle of the 26S proteasome","language":"En","author":[{"family":"Livneh","given":"Ido"},{"family":"Cohen-Kaplan","given":"Victoria"},{"family":"Cohen-Rosenzweig","given":"Chen"},{"family":"Avni","given":"Noa"},{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2016",8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Protein phosphorylation is one of the most abundant post-translational modifications, and diverse kinases and phosphatases regulate the proteasome[137]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1thoun78g2","properties":{"formattedCitation":"{\\rtf \\super 137\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":28,"uris":["http://zotero.org/users/4604651/items/K3BZ4TM7"],"uri":["http://zotero.org/users/4604651/items/K3BZ4TM7"],"itemData":{"id":28,"type":"article-journal","title":"Reversible phosphorylation of the 26S proteasome","container-title":"Protein & Cell","page":"255-272","volume":"8","issue":"4","source":"PubMed","abstract":"The 26S proteasome at the center of the ubiquitin-proteasome system (UPS) is essential for virtually all cellular processes of eukaryotes. A common misconception about the proteasome is that, once made, it remains as a static and uniform complex with spontaneous and constitutive activity for protein degradation. Recent discoveries have provided compelling evidence to support the exact opposite insomuch as the 26S proteasome undergoes dynamic and reversible phosphorylation under a variety of physiopathological conditions. In this review, we summarize the history and current understanding of proteasome phosphorylation, and advocate the idea of targeting proteasome kinases/phosphatases as a new strategy for clinical interventions of several human diseases.","DOI":"10.1007/s13238-017-0382-x","ISSN":"1674-8018","note":"PMID: 28258412\nPMCID: PMC5359188","journalAbbreviation":"Protein Cell","language":"eng","author":[{"family":"Guo","given":"Xing"},{"family":"Huang","given":"Xiuliang"},{"family":"Chen","given":"Mark J."}],"issued":{"date-parts":[["2017",4]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Attesting the importance of this modification for proteasome assembly, treatment of purified proteasome with alkaline phosphatase leads to its dissociation into CP and RP[138]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aonbuk4fmo","properties":{"formattedCitation":"{\\rtf \\super 138\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":145,"uris":["http://zotero.org/users/4604651/items/86Q428AM"],"uri":["http://zotero.org/users/4604651/items/86Q428AM"],"itemData":{"id":145,"type":"article-journal","title":"Assembly of the 26S Proteasome Is Regulated by Phosphorylation of the p45/Rpt6 ATPase Subunit","container-title":"Biochemistry","page":"314-319","volume":"40","issue":"2","source":"ACS Publications","abstract":"We investigated whether the assembly/disassembly of the 26S proteasome is regulated by phosphorylation/dephosphorylation. The regulatory complex disassembled from the 26S proteasome was capable of phosphorylating the p45/Sug1/Rpt6 subunit, suggesting that the protein kinase is activated upon dissociation of the 26S proteasome or that the phosphorylation site of p45 becomes susceptible to the protein kinase. In addition, the p45-phosphorylated regulatory complex was found to be incorporated into the 26S proteasome. When the 26S proteasome was treated with alkaline phosphatase, it was dissociated into the 20S proteasome and the regulatory complex. Furthermore, the p45 subunit and the C3/α2 subunit were cross-linked with DTBP, whereas these subunits were not cross-linked by dephosphorylating the 26S proteasome. These results indicate that the 26S proteasome is disassembled into the constituent subcomplexes by dephosphorylation and that it is assembled by phosphorylation of p45 by a protein kinase, which is tightly

associated with the regulatory complex. It was also revealed that the p45 subunit is directly associated with the 20S proteasome α-subunit C3 in a phosphorylation-dependent manner.","DOI":"10.1021/bi001815n","ISSN":"0006-2960","journalAbbreviation":"Biochemistry","author":[{"family":"Satoh","given":"Kazuki"},{"family":"Sasajima","given":"Hitoshi"},{"family":"Nyoumura","given":"Ken-ichi"},{"family":"Yokosawa","given":"Hideyoshi"},{"family":"Sawada","given":"Hitoshi"}],"issued":{"date-parts":[["2001",1,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. One of the first kinase reported to phosphorylate proteasome subunits is the cAMP-dependent protein kinase A (PKA)[139]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a289v1e4aqp","properties":{"formattedCitation":"{\\rtf \\super 139\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":144,"uris":["http://zotero.org/users/4604651/items/YACUBCKD"],"uri":["http://zotero.org/users/4604651/items/YACUBCKD"],"itemData":{"id":144,"type":"article-journal","title":"Phosphorylation of the multicatalytic proteinase complex from bovine pituitaries by a copurifying cAMP-dependent protein kinase","container-title":"Archives of Biochemistry and Biophysics","page":"68-74","volume":"283","issue":"1","source":"PubMed","abstract":"The multicatalytic proteinase complex (MPC) constitutes a major nonlysosomal proteolytic system that may play an important role in the processing of biologically active peptides and enzymes, as well as in intracellular metabolism. We report that at least two of its subunits of MW 28,800 (S2) and 27,000 (S3) are phosphorylated by a cAMP-dependent protein kinase (PK-A) that copurifies with the complex isolated from bovine pituitaries. The cAMP-induced phosphorylation was time dependent and inhibited by a PK-A inhibitor. Although not an integral part of the complex, PK-A activity was still present even in 1700-fold-purified and apparently homogeneous preparations by criteria of nondissociating polyacrylamide gel electrophoresis. Furthermore, we present evidence that the copurification of the two enzymes is not species or tissue specific, or dependent on a single method of purification. The copurifying kinase was stimulated 10-fold by cAMP (10 microM) and 2- to 3-fold by a peptide substrate of the MPC, but was unaffected by protein kinase C activators (calcium and a phospholipid mixture). These findings suggest that protein phosphorylation may represent a mechanism for regulating the activity of the multicatalytic proteinase complex.","ISSN":"0003-9861","note":"PMID: 2173492","journalAbbreviation":"Arch. Biochem. Biophys.","language":"eng","author":[{"family":"Pereira","given":"M. E."},{"family":"Wilk","given":"S."}],"issued":{"date-parts":[["1990",11,15]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The serine 120 (S120) of Rpt6 was first shown to be key in this process, phosphorylated by PKA and dephosphorylated by protein phosphatase 1 gamma (PP1γ). Rpt6 phosphorylation by PKA regulates the 26S proteasome[138,140,141]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a28bc67hhb4","properties":{"formattedCitation":"{\\rtf \\super 138,140,141\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":145,"uris":["http://zotero.org/users/4604651/items/86Q428AM"],"uri":["http://zotero.org/users/4604651/items/86Q428AM"],"itemData":{"id":145,"type":"article-journal","title":"Assembly of the 26S Proteasome Is Regulated by Phosphorylation of the p45/Rpt6 ATPase Subunit","container-title":"Biochemistry","page":"314-319","volume":"40","issue":"2","source":"ACS Publications","abstract":"We investigated whether the assembly/disassembly of the 26S proteasome is regulated by phosphorylation/dephosphorylation. The regulatory complex disassembled from the 26S proteasome was capable

of phosphorylating the p45/Sug1/Rpt6 subunit, suggesting that the protein kinase is activated upon dissociation of the 26S proteasome or that the phosphorylation site of p45 becomes susceptible to the protein kinase. In addition, the p45-phosphorylated regulatory complex was found to be incorporated into the 26S proteasome. When the 26S proteasome was treated with alkaline phosphatase, it was dissociated into the 20S proteasome and the regulatory complex. Furthermore, the p45 subunit and the C3/α2 subunit were cross-linked with DTBP, whereas these subunits were not cross-linked by dephosphorylating the 26S proteasome. These results indicate that the 26S proteasome is disassembled into the constituent subcomplexes by dephosphorylation and that it is assembled by phosphorylation of p45 by a protein kinase, which is tightly associated with the regulatory complex. It was also revealed that the p45 subunit is directly associated with the 20S proteasome α-subunit C3 in a phosphorylation-dependent manner.","DOI":"10.1021/bi001815n","ISSN":"0006-2960","journalAbbreviation":"Biochemistry","author":[{"family":"Satoh","given":"Kazuki"},{"family":"Sasajima","given":"Hitoshi"},{"family":"Nyoumura","given":"Ken-ichi"},{"family":"Yokosawa","given":"Hideyoshi"},{"family":"Sawada","given":"Hitoshi"}],"issued":{"date-parts":[["2001",1,1]]}},{"id":139,"uris":["http://zotero.org/users/4604651/items/5QRHQ2RV"],"uri":["http://zotero.org/users/4604651/items/5QRHQ2RV"],"itemData":{"id":139,"type":"article-journal","title":"Regulation of Feedback between Protein Kinase A and the Proteasome System Worsens Huntington's Disease","container-title":"Molecular and Cellular Biology","page":"1073-1084","volume":"33","issue":"5","source":"mcb.asm.org","abstract":"Huntington's disease (HD) is a neurodegenerative disease caused by the expansion of a CAG repeat in the Huntingtin (HTT) gene. Abnormal regulation of the cyclic AMP (cAMP)/protein kinase A (PKA) pathway occurs during HD progression. Here we found that lower PKA activity was associated with proteasome impairment in the striatum for two HD mouse models (R6/2 and N171-82Q) and in mutant HTT (mHTT)-expressing striatal cells. Because PKA regulatory subunits (PKA-Rs) are proteasome substrates, the mHTT-evoked proteasome impairment caused accumulation of PKA-Rs and subsequently inhibited PKA activity. Conversely, activation of PKA enhanced the phosphorylation of Rpt6 (a component of the proteasome), rescued the impaired proteasome activity, and reduced mHTT aggregates. The dominant-negative Rpt6 mutant (Rpt6S120A) blocked the ability of a cAMP-elevating reagent to enhance proteasome activity, whereas the phosphomimetic Rpt6 mutant (Rpt6S120D) increased proteasome activity, reduced HTT aggregates, and ameliorated motor impairment. Collectively, our data demonstrated that positive feedback regulation between PKA and the proteasome is critical for HD pathogenesis.","DOI":"10.1128/MCB.01434-12","ISSN":"0270-7306, 1098-5549","note":"PMID: 23275441","journalAbbreviation":"Mol. Cell. Biol.","language":"en","author":[{"family":"Lin","given":"Jiun-Tsai"},{"family":"Chang","given":"Wei-Cheng"},{"family":"Chen","given":"Hui-Mei"},{"family":"Lai","given":"Hsing-Lin"},{"family":"Chen","given":"Chih-Yeh"},{"family":"Tao","given":"Mi-Hua"},{"family":"Chern","given":"Yijuang"}],"issued":{"date-parts":[["2013",3,1]]}},{"id":138,"uris":["http://zotero.org/users/4604651/items/IGZWD7AM"],"uri":["http://zotero.org/users/4604651/items/IGZWD7AM"],"itemData":{"id":138,"type":"article-journal","title":"PKA rapidly enhances proteasome assembly and activity in in vivo canine hearts","container-title":"Journal of Molecular and Cellular Cardiology","page":"452-462","volume":"46","issue":"4","source":"PubMed","abstract":"Proteasome regulates diverse cellular functions by eliminating ubiquitinated proteins. Protein kinase A (PKA) is a key regulator of proteasome activity. However, it remains unknown how PKA regulates proteasome activity and whether it controls proteasome activity in in vivo hearts. Both the in vitro peptidase assay and the in-gel peptidase assays showed that the treatment with PKA for 30 min dose-dependently activated purified 26S proteasome. Simultaneously, PKA treatment enhanced

phosphorylation and assembly of purified 26S proteasome evaluated by non-reducing native polyacrylamide gel electrophoresis, either of which was blunted by the pretreatment with a PKA inhibitor, H-89. In in vivo canine hearts, proteasome assembly and activity were enhanced 30 min after the exogenous or endogenous stimulation of PKA by the intracoronary administration of isoproterenol or forskolin for 30 min or by ischemic preconditioning (IP) with 4 times of repeated 5 min of ischemia. The intracoronary administration of H-89 blunted the enhancement of proteasome assembly and activity by IP. Myocardial proteasome activity at the end of ischemia was decreased compared with the control, however, it did not differ from the control in dogs with IP. IP decreased the accumulation of ubiquitinated proteins in the canine ischemia/reperfusion myocardium, which was blunted by the intracoronary administration of a proteasome inhibitor, epoxomicin. However, proteasome activation by IP was not involved in its infarct size-limiting effects. These findings indicate that PKA rapidly enhances proteasome assembly and activity in in vivo hearts. Further investigation will be needed to clarify pathophysiological roles of PKA-mediated proteasome activation in ischemia/reperfusion hearts.","DOI":"10.1016/j.yjmcc.2008.11.001","ISSN":"1095-8584","note":"PMID: 19059265","journalAbbreviation":"J. Mol. Cell. Cardiol.","language":"eng","author":[{"family":"Asai","given":"Mitsutoshi"},{"family":"Tsukamoto","given":"Osamu"},{"family":"Minamino","given":"Tetsuo"},{"family":"Asanuma","given":"Hiroshi"},{"family":"Fujita","given":"Masashi"},{"family":"Asano","given":"Yoshihiro"},{"family":"Takahama","given":"Hiroyuki"},{"family":"Sasaki","given":"Hideyuki"},{"family":"Higo","given":"Shuichiro"},{"family":"Asakura","given":"Masanori"},{"family":"Takashima","given":"Seiji"},{"family":"Hori","given":"Masatsugu"},{"family":"Kitakaze","given":"Masafumi"}],"issued":{"date-parts":[["2009",4]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }, possibly by facilitating the interaction between Rpt6 and the CP subunit α2[138]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"acofdp8qt9","properties":{"formattedCitation":"{\\rtf \\super 138\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":145,"uris":["http://zotero.org/users/4604651/items/86Q428AM"],"uri":["http://zotero.org/users/4604651/items/86Q428AM"],"itemData":{"id":145,"type":"article-journal","title":"Assembly of the 26S Proteasome Is Regulated by Phosphorylation of the p45/Rpt6 ATPase Subunit","container-title":"Biochemistry","page":"314-319","volume":"40","issue":"2","source":"ACS Publications","abstract":"We investigated whether the assembly/disassembly of the 26S proteasome is regulated by phosphorylation/dephosphorylation. The regulatory complex disassembled from the 26S proteasome was capable of phosphorylating the p45/Sug1/Rpt6 subunit, suggesting that the protein kinase is activated upon dissociation of the 26S proteasome or that the phosphorylation site of p45 becomes susceptible to the protein kinase. In addition, the p45-phosphorylated regulatory complex was found to be incorporated into the 26S proteasome. When the 26S proteasome was treated with alkaline phosphatase, it was dissociated into the 20S proteasome and the regulatory complex. Furthermore, the p45 subunit and the C3/α2 subunit were cross-linked with DTBP, whereas these subunits were not cross-linked by dephosphorylating the 26S proteasome. These results indicate that the 26S proteasome is disassembled into the constituent subcomplexes by dephosphorylation and that it is assembled by phosphorylation of p45 by a protein kinase, which is tightly associated with the regulatory complex. It was also revealed that the p45 subunit is directly associated with the 20S proteasome α-subunit C3 in a phosphorylation-dependent manner.","DOI":"10.1021/bi001815n","ISSN":"0006-2960","journalAbbreviation":"Biochemistry","author":[{"family":"Satoh","given":"Kazuki"},{"family":"Sasajima","given":"Hitoshi"},{"family":"Nyoumura","given":"Ken-

ichi"},{"family":"Yokosawa","given":"Hideyoshi"},{"family":"Sawada","given":"Hitoshi"}],"issued":{"date-parts":[["2001",1,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

PKA activation has been shown to increase proteasome activity and as a consequence to have a protective effect in several models of neurodegenerative diseases[140,142,143]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1b78jvju3p","properties":{"formattedCitation":"{\\rtf \\super 140,142,143\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":139,"uris":["http://zotero.org/users/4604651/items/5QRHQ2RV"],"uri":["http://zotero.org/users/4604651/items/5QRHQ2RV"],"itemData":{"id":139,"type":"article-journal","title":"Regulation of Feedback between Protein Kinase A and the Proteasome System Worsens Huntington's Disease","container-title":"Molecular and Cellular Biology","page":"1073-1084","volume":"33","issue":"5","source":"mcb.asm.org","abstract":"Huntington's disease (HD) is a neurodegenerative disease caused by the expansion of a CAG repeat in the Huntingtin (HTT) gene. Abnormal regulation of the cyclic AMP (cAMP)/protein kinase A (PKA) pathway occurs during HD progression. Here we found that lower PKA activity was associated with proteasome impairment in the striatum for two HD mouse models (R6/2 and N171-82Q) and in mutant HTT (mHTT)-expressing striatal cells. Because PKA regulatory subunits (PKA-Rs) are proteasome substrates, the mHTT-evoked proteasome impairment caused accumulation of PKA-Rs and subsequently inhibited PKA activity. Conversely, activation of PKA enhanced the phosphorylation of Rpt6 (a component of the proteasome), rescued the impaired proteasome activity, and reduced mHTT aggregates. The dominant-negative Rpt6 mutant (Rpt6S120A) blocked the ability of a cAMP-elevating reagent to enhance proteasome activity, whereas the phosphomimetic Rpt6 mutant (Rpt6S120D) increased proteasome activity, reduced HTT aggregates, and ameliorated motor impairment. Collectively, our data demonstrated that positive feedback regulation between PKA and the proteasome is critical for HD pathogenesis.","DOI":"10.1128/MCB.01434-12","ISSN":"0270-7306, 1098-5549","note":"PMID: 23275441","journalAbbreviation":"Mol. Cell. Biol.","language":"en","author":[{"family":"Lin","given":"Jiun-Tsai"},{"family":"Chang","given":"Wei-Cheng"},{"family":"Chen","given":"Hui-Mei"},{"family":"Lai","given":"Hsing-Lin"},{"family":"Chen","given":"Chih-Yeh"},{"family":"Tao","given":"Mi-Hua"},{"family":"Chern","given":"Yijuang"}],"issued":{"date-parts":[["2013",3,1]]}}},{"id":136,"uris":["http://zotero.org/users/4604651/items/ESMDWXA2"],"uri":["http://zotero.org/users/4604651/items/ESMDWXA2"],"itemData":{"id":136,"type":"article-journal","title":"Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling","container-title":"Nature Medicine","page":"46-53","volume":"22","issue":"1","source":"www.nature.com","abstract":"The ubiquitin proteasome system (UPS) degrades misfolded proteins including those implicated in neurodegenerative diseases. We investigated the effects of tau accumulation on proteasome function in a mouse model of tauopathy and in a cross to a UPS reporter mouse (line Ub-G76V-GFP). Accumulation of insoluble tau was associated with a decrease in the peptidase activity of brain 26S proteasomes, higher levels of ubiquitinated proteins and undegraded Ub-G76V-GFP. 26S proteasomes from mice with tauopathy were physically associated with tau and were less active in hydrolyzing ubiquitinated proteins, small peptides and ATP. 26S proteasomes from normal mice incubated with recombinant oligomers or fibrils also showed lower hydrolyzing capacity in the same assays, implicating tau as a proteotoxin. Administration of an agent that activates cAMP–protein kinase A (PKA) signaling led to attenuation of proteasome dysfunction, probably through proteasome subunit phosphorylation. In vivo, this led to lower levels of aggregated tau and improvements in cognitive performance.","DOI":"10.1038/nm.4011","ISSN":"1078-8956","journalAbbreviation":"Nat

Med","language":"en","author":[{"family":"Myeku","given":"Natura"},{"family":"Clelland","given":"Catherine L."},{"family":"Emrani","given":"Sheina"},{"family":"Kukushkin","given":"Nikolay V."},{"family":"Yu","given":"Wai Haung"},{"family":"Goldberg","given":"Alfred L."},{"family":"Duff","given":"Karen E."}],"issued":{"date-parts":[["2016",1]]}},{"id":137,"uris":["http://zotero.org/users/4604651/items/9VPNI88G"],"uri":["http://zotero.org/users/4604651/items/9VPNI88G"],"itemData":{"id":137,"type":"article-journal","title":"cAMP stimulates the ubiquitin/proteasome pathway in rat spinal cord neurons","container-title":"Neuroscience Letters","page":"126-131","volume":"527","issue":"2","source":"PubMed","abstract":"Proteasome impairment and accumulation of ubiquitinated proteins are implicated in neurodegeneration associated with different forms of spinal cord injury. We show herein that elevating cAMP in rat spinal cord neurons increases 26S proteasome activity in a protein kinase A-dependent manner. Treating spinal cord neurons with dibutyryl-cAMP (db-cAMP) also raised the levels of various components of the UPP including proteasome subunits Rpt6 and β5, polyubiquitin shuttling factor p62/sequestosome1, E3 ligase CHIP, AAA-ATPase p97 and the ubiquitin gene ubB. Finally, db-cAMP reduced the accumulation of ubiquitinated proteins, proteasome inhibition, and neurotoxicity triggered by the endogenous product of inflammation prostaglandin J2. We propose that optimizing the effects of cAMP/PKA-signaling on the UPP could offer an effective therapeutic approach to prevent UPP-related proteotoxicity in spinal cord neurons.","DOI":"10.1016/j.neulet.2012.08.051","ISSN":"1872-7972","note":"PMID: 22982149\nPMCID: PMC3464398","journalAbbreviation":"Neurosci. Lett.","language":"eng","author":[{"family":"Myeku","given":"Natura"},{"family":"Wang","given":"Hu"},{"family":"Figueiredo-Pereira","given":"Maria E."}],"issued":{"date-parts":[["2012",10,11]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Howver, these findings have been contradicted by the observation that Rpt6 phosphorylation did not occur following rolipram-mediated PKA activation, whereas the RP subunit Rpn6 was selectively phosphorylated at serine 14[144]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1jh95m03nh","properties":{"formattedCitation":"{\\rtf \\super 144\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":135,"uris":["http://zotero.org/users/4604651/items/AIFXQXHB"],"uri":["http://zotero.org/users/4604651/items/AIFXQXHB"],"itemData":{"id":135,"type":"article-journal","title":"cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins","container-title":"Proceedings of the National Academy of Sciences","page":"E7176-E7185","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Although rates of protein degradation by the ubiquitin-proteasome pathway (UPS) are determined by their rates of ubiquitination, we show here that the proteasome's capacity to degrade ubiquitinated proteins is also tightly regulated. We studied the effects of cAMP-dependent protein kinase (PKA) on proteolysis by the UPS in several mammalian cell lines. Various agents that raise intracellular cAMP and activate PKA (activators of adenylate cyclase or inhibitors of phosphodiesterase 4) promoted degradation of short-lived (but not long-lived) cell proteins generally, model UPS substrates having different degrons, and aggregation-prone proteins associated with major neurodegenerative diseases, including mutant FUS (Fused in sarcoma), SOD1 (superoxide dismutase 1), TDP43 (TAR DNA-binding protein 43), and tau. 26S proteasomes purified from these treated cells or from control cells and treated with PKA degraded ubiquitinated proteins, small peptides, and ATP more rapidly than controls, but not when treated with protein phosphatase. Raising cAMP levels also increased amounts of doubly capped 26S proteasomes. Activated PKA phosphorylates the 19S subunit, Rpn6/PSMD11 (regulatory particle non-ATPase 6/proteasome subunit D11) at Ser14.

Overexpression of a phosphomimetic Rpn6 mutant activated proteasomes similarly, whereas a nonphosphorylatable mutant decreased activity. Thus, proteasome function and protein degradation are regulated by cAMP through PKA and Rpn6, and activation of proteasomes by this mechanism may be useful in treating proteotoxic diseases.","DOI":"10.1073/pnas.1522332112","ISSN":"0027-8424, 1091-6490","note":"PMID: 26669444","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Lokireddy","given":"Sudarsanareddy"},{"family":"Kukushkin","given":"Nikolay Vadimovich"},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Overexpression of the phosphomimetic Rpn6-S14D mutant stimulated the degradation of short-lived proteasome substrates and aggregation-prone proteins while the phospho-dead mutant Rpn6-S14A had the opposite effect[144]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3ilh3cmk9","properties":{"formattedCitation":"{\\rtf \\super 144\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":135,"uris":["http://zotero.org/users/4604651/items/AIFXQXHB"],"uri":["http://zotero.org/users/4604651/items/AIFXQXHB"],"itemData":{"id":135,"type":"article-journal","title":"cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins","container-title":"Proceedings of the National Academy of Sciences","page":"E7176-E7185","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Although rates of protein degradation by the ubiquitin-proteasome pathway (UPS) are determined by their rates of ubiquitination, we show here that the proteasome's capacity to degrade ubiquitinated proteins is also tightly regulated. We studied the effects of cAMP-dependent protein kinase (PKA) on proteolysis by the UPS in several mammalian cell lines. Various agents that raise intracellular cAMP and activate PKA (activators of adenylate cyclase or inhibitors of phosphodiesterase 4) promoted degradation of short-lived (but not long-lived) cell proteins generally, model UPS substrates having different degrons, and aggregation-prone proteins associated with major neurodegenerative diseases, including mutant FUS (Fused in sarcoma), SOD1 (superoxide dismutase 1), TDP43 (TAR DNA-binding protein 43), and tau. 26S proteasomes purified from these treated cells or from control cells and treated with PKA degraded ubiquitinated proteins, small peptides, and ATP more rapidly than controls, but not when treated with protein phosphatase. Raising cAMP levels also increased amounts of doubly capped 26S proteasomes. Activated PKA phosphorylates the 19S subunit, Rpn6/PSMD11 (regulatory particle non-ATPase 6/proteasome subunit D11) at Ser14. Overexpression of a phosphomimetic Rpn6 mutant activated proteasomes similarly, whereas a nonphosphorylatable mutant decreased activity. Thus, proteasome function and protein degradation are regulated by cAMP through PKA and Rpn6, and activation of proteasomes by this mechanism may be useful in treating proteotoxic diseases.","DOI":"10.1073/pnas.1522332112","ISSN":"0027-8424, 1091-6490","note":"PMID: 26669444","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Lokireddy","given":"Sudarsanareddy"},{"family":"Kukushkin","given":"Nikolay Vadimovich"},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Rpn6 phosphorylation was associated with increased levels of 26S proteasome, especially the RP_2-CP[144]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2i704mnf8t","properties":{"formattedCitation":"{\\rtf \\super 144\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":135,"uris":["http://zotero.org/users/4604651/items/AIFXQXHB"],"uri":["htt

p://zotero.org/users/4604651/items/AIFXQXHB"],"itemData":{"id":135,"type":"article-journal","title":"cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins","container-title":"Proceedings of the National Academy of Sciences","page":"E7176-E7185","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Although rates of protein degradation by the ubiquitin-proteasome pathway (UPS) are determined by their rates of ubiquitination, we show here that the proteasome's capacity to degrade ubiquitinated proteins is also tightly regulated. We studied the effects of cAMP-dependent protein kinase (PKA) on proteolysis by the UPS in several mammalian cell lines. Various agents that raise intracellular cAMP and activate PKA (activators of adenylate cyclase or inhibitors of phosphodiesterase 4) promoted degradation of short-lived (but not long-lived) cell proteins generally, model UPS substrates having different degrons, and aggregation-prone proteins associated with major neurodegenerative diseases, including mutant FUS (Fused in sarcoma), SOD1 (superoxide dismutase 1), TDP43 (TAR DNA-binding protein 43), and tau. 26S proteasomes purified from these treated cells or from control cells and treated with PKA degraded ubiquitinated proteins, small peptides, and ATP more rapidly than controls, but not when treated with protein phosphatase. Raising cAMP levels also increased amounts of doubly capped 26S proteasomes. Activated PKA phosphorylates the 19S subunit, Rpn6/PSMD11 (regulatory particle non-ATPase 6/proteasome subunit D11) at Ser14. Overexpression of a phosphomimetic Rpn6 mutant activated proteasomes similarly, whereas a nonphosphorylatable mutant decreased activity. Thus, proteasome function and protein degradation are regulated by cAMP through PKA and Rpn6, and activation of proteasomes by this mechanism may be useful in treating proteotoxic diseases.","DOI":"10.1073/pnas.1522332112","ISSN":"0027-8424, 1091-6490","note":"PMID: 26669444","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Lokireddy","given":"Sudarsanareddy"},{"family":"Kukushkin","given":"Nikolay Vadimovich"},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , consistent with the proposed function of Rpn6 as a mediator of RP-CP association[22]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1qoemvcdqh","properties":{"formattedCitation":"{\\rtf \\super 22\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":83,"uris":["http://zotero.org/users/4604651/items/M9PEIPYN"],"uri":["http://zotero.org/users/4604651/items/M9PEIPYN"],"itemData":{"id":83,"type":"article-journal","title":"Complete subunit architecture of the proteasome regulatory particle","container-title":"Nature","page":"186-191","volume":"482","issue":"7384","source":"www.nature.com","abstract":"The proteasome is the major ATP-dependent protease in eukaryotic cells, but limited structural information restricts a mechanistic understanding of its activities. The proteasome regulatory particle, consisting of the lid and base subcomplexes, recognizes and processes polyubiquitinated substrates. Here we used electron microscopy and a new heterologous expression system for the lid to delineate the complete subunit architecture of the regulatory particle from yeast. Our studies reveal the spatial arrangement of ubiquitin receptors, deubiquitinating enzymes and the protein unfolding machinery at subnanometre resolution, outlining the substrate's path to degradation. Unexpectedly, the ATPase subunits within the base unfoldase are arranged in a spiral staircase, providing insight into potential mechanisms for substrate translocation through the central pore. Large conformational rearrangements of the lid upon holoenzyme formation suggest allosteric regulation of deubiquitination. We provide a structural basis for the ability of the proteasome to degrade a diverse set of substrates and thus regulate vital cellular processes.","DOI":"10.1038/nature10774","ISSN":"0028-

0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Lander","given":"Gabriel C."},{"family":"Estrin","given":"Eric"},{"family":"Matyskiela","given":"Mary E."},{"family":"Bashore","given":"Charlene"},{"family":"Nogales","given":"Eva"},{"family":"Martin","given":"Andreas"}],"issued":{"date-parts":[["2012",2,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. In light of these discrepancies, it will be important to clarify the contribution of each PKA target in PKA-mediated increase of RP-CP proteasome.

Another illustration of phosphorylation/dephosphorylation regulating the proteasome is the ubiquitin-like domain-containing C-terminal domain phosphatase 1 (UBLCP1)[145]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a4aigb589f","properties":{"formattedCitation":"{\\rtf \\super 145\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":143,"uris":["http://zotero.org/users/4604651/items/AC4HHCPU"],"uri":["http://zotero.org/users/4604651/items/AC4HHCPU"],"itemData":{"id":143,"type":"article-journal","title":"UBLCP1 is a 26S proteasome phosphatase that regulates nuclear proteasome activity","container-title":"Proceedings of the National Academy of Sciences of the United States of America","page":"18649-18654","volume":"108","issue":"46","source":"PubMed","abstract":"Protein degradation by the 26S proteasome is a fundamental process involved in a broad range of cellular activities, yet how proteasome activity is regulated remains poorly understood. We report here that ubiquitin-like domain-containing C-terminal domain phosphatase 1 (UBLCP1) is a 26S proteasome phosphatase that regulates nuclear proteasome activity. UBLCP1 directly interacts with the proteasome via its UBL domain and is exclusively localized in the nucleus. UBLCP1 dephosphorylates the 26S proteasome and inhibits proteasome activity in vitro. Knockdown of UBLCP1 in cells promotes 26S proteasome assembly and selectively enhances nuclear proteasome activity. Our results describe the first identified proteasome-specific phosphatase and uncover a unique mechanism for phosphoregulation of the proteasome.","DOI":"10.1073/pnas.1113170108","ISSN":"1091-6490","note":"PMID: 21949367\nPMCID: PMC3219150","journalAbbreviation":"Proc. Natl. Acad. Sci. U.S.A.","language":"eng","author":[{"family":"Guo","given":"Xing"},{"family":"Engel","given":"James L."},{"family":"Xiao","given":"Junyu"},{"family":"Tagliabracci","given":"Vincent S."},{"family":"Wang","given":"Xiaorong"},{"family":"Huang","given":"Lan"},{"family":"Dixon","given":"Jack E."}],"issued":{"date-parts":[["2011",11,15]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. UBLCP1 was shown to bind Rpn1 via its ubiquitin-like (UBL) domain and to subsequently dephosphorylate the AAA^+-ATPase Rpt1 subunit. UBLCP1 is a proteasome phosphatase regulating nuclear proteasome assembly, especially the association between the RP and the CP[145,146]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"af4pvv987f","properties":{"formattedCitation":"{\\rtf \\super 145,146\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":143,"uris":["http://zotero.org/users/4604651/items/AC4HHCPU"],"uri":["http://zotero.org/users/4604651/items/AC4HHCPU"],"itemData":{"id":143,"type":"article-journal","title":"UBLCP1 is a 26S proteasome phosphatase that regulates nuclear proteasome activity","container-title":"Proceedings of the National Academy of Sciences of the United States of America","page":"18649-18654","volume":"108","issue":"46","source":"PubMed","abstract":"Protein degradation by the 26S proteasome is a fundamental process involved in a broad range of cellular activities, yet how proteasome activity is regulated remains poorly

understood. We report here that ubiquitin-like domain-containing C-terminal domain phosphatase 1 (UBLCP1) is a 26S proteasome phosphatase that regulates nuclear proteasome activity. UBLCP1 directly interacts with the proteasome via its UBL domain and is exclusively localized in the nucleus. UBLCP1 dephosphorylates the 26S proteasome and inhibits proteasome activity in vitro. Knockdown of UBLCP1 in cells promotes 26S proteasome assembly and selectively enhances nuclear proteasome activity. Our results describe the first identified proteasome-specific phosphatase and uncover a unique mechanism for phosphoregulation of the proteasome.","DOI":"10.1073/pnas.1113170108","ISSN":"1091-6490","note":"PMID: 21949367\nPMCID: PMC3219150","journalAbbreviation":"Proc. Natl. Acad. Sci. U.S.A.","language":"eng","author":[{"family":"Guo","given":"Xing"},{"family":"Engel","given":"James L."},{"family":"Xiao","given":"Junyu"},{"family":"Tagliabracci","given":"Vincent S."},{"family":"Wang","given":"Xiaorong"},{"family":"Huang","given":"Lan"},{"family":"Dixon","given":"Jack E."}],"issued":{"date-parts":[["2011",11,15]]}}},{"id":142,"uris":["http://zotero.org/users/4604651/items/UTGQTVJ7"],"uri":["http://zotero.org/users/4604651/items/UTGQTVJ7"],"itemData":{"id":142,"type":"article-journal","title":"Phosphatase UBLCP1 controls proteasome assembly","container-title":"Open Biology","volume":"7","issue":"5","source":"PubMed","abstract":"Ubiquitin-like domain-containing C-terminal domain phosphatase 1 (UBLCP1), an FCP/SCP phosphatase family member, was identified as the first proteasome phosphatase. UBLCP1 binds to proteasome subunit Rpn1 and dephosphorylates the proteasome in vitro However, it is still unclear which proteasome subunit(s) are the bona fide substrate(s) of UBLCP1 and the precise mechanism for proteasome regulation remains elusive. Here, we show that UBLCP1 selectively binds to the 19S regulatory particle (RP) through its interaction with Rpn1, but not the 20S core particle (CP) or the 26S proteasome holoenzyme. In the RP, UBLCP1 dephosphorylates the subunit Rpt1, impairs its ATPase activity, and consequently disrupts the 26S proteasome assembly, yet it has no effects on the RP assembly from precursor complexes. The Rpn1-binding and phosphatase activities of UBLCP1 are essential for its function on Rpt1 dephosphorylation and proteasome activity both in vivo and in vitro Our study establishes the essential role of the UBLCP1/Rpn1/Rpt1 complex in regulating proteasome assembly.","DOI":"10.1098/rsob.170042","ISSN":"2046-2441","note":"PMID: 28539385","journalAbbreviation":"Open Biol","language":"eng","author":[{"family":"Sun","given":"Shuangwu"},{"family":"Liu","given":"Sisi"},{"family":"Zhang","given":"Zhengmao"},{"family":"Zeng","given":"Wang"},{"family":"Sun","given":"Chuang"},{"family":"Tao","given":"Tao"},{"family":"Lin","given":"Xia"},{"family":"Feng","given":"Xin-Hua"}],"issued":{"date-parts":[["2017",5]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. A screen using a salicylic fragment-based library identified a potent UBLCP1 inhibitor (compound 13; IC50 of 1 μM), which increases nuclear proteasome activity in cells. The therapeutic potential of this compound to correct conditions caused by protein misfolding remains to be determined.

ADP-ribosylation is another post-translational modification that regulates a proteasome-binding protein, PI31. ADP-ribose bound PI31 has been proposed to selectively interacts with two RACs, dp27 and dS5b (the fly homolog of the yeast Nas2 and Hsm3, respectively), to promote 26S proteasome assembly[147]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"athar1ihgu","properties":{"formattedCitation":"{\\rtf \\super

147\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":134,"uris":["http://zotero.org/users/4604651/items/YTASG8CX"],"uri":["http://zotero.org/users/4604651/items/YTASG8CX"],"itemData":{"id":134,"type":"article-journal","title":"Proteasome regulation by ADP-ribosylation","container-title":"Cell","page":"614-627","volume":"153","issue":"3","source":"PubMed Central","abstract":"Protein degradation by the ubiquitin-proteasome system is central to cell homeostasis and survival. Defects in this process are associated with diseases such as cancer and neurodegenerative disorders. The 26S proteasome is a large protease complex that degrades ubiquitinated proteins. Here we show that ADP-ribosylation promotes 26S proteasome activity in both Drosophila and human cells. We identify the ADP-ribosyl transferase Tankyrase (TNKS) and the 19S assembly chaperones dp27 and dS5b as direct binding partners of the proteasome regulator PI31. TNKS-mediated ADP-ribosylation of PI31 drastically reduces its affinity for 20S proteasome α-subunits to relieve 20S repression by PI31. Additionally, PI31 modification increases binding to and sequestration of dp27 and dS5b from 19S regulatory particles, promoting 26S assembly. Inhibition of TNKS by either RNAi or a small-molecule inhibitor, XAV939, blocks this process to reduce 26S assembly. These results unravel a mechanism of proteasome regulation that can be targeted with existing small-molecule inhibitors.","DOI":"10.1016/j.cell.2013.03.040","ISSN":"0092-8674","note":"PMID: 23622245\nPMCID: PMC3676968","journalAbbreviation":"Cell","author":[{"family":"Cho-Park","given":"Park F."},{"family":"Steller","given":"Hermann"}],"issued":{"date-parts":[["2013",4,25]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. However, another work failed to recapitulate these findings *in vivo*[148]*{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2mm8cp7ron","properties":{"formattedCitation":"{\\rtf \\super 148\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":437,"uris":["http://zotero.org/users/4604651/items/LBZRWMBV"],"uri":["http://zotero.org/users/4604651/items/LBZRWMBV"],"itemData":{"id":437,"type":"article-journal","title":"Molecular and cellular roles of PI31 (PSMF1) protein in regulation of proteasome function","container-title":"The Journal of Biological Chemistry","page":"17392-17405","volume":"289","issue":"25","source":"PubMed","abstract":"We investigated molecular features and cellular roles of PI31 (PSMF1) on regulation of proteasome function. PI31 has a C-terminal HbYX (where Hb is a hydrophobic amino acid, Y is tyrosine, and X is any amino acid) motif characteristic of several proteasome activators. Peptides corresponding to the PI31 C terminus also bind to and activate the 20 S proteasome in an HbYX-dependent manner, but intact PI31protein inhibits in vitro 20 S activity. Binding to and inhibition of the proteasome by PI31 are conferred by the HbYX-containing proline-rich C-terminal domain but do not require HbYX residues. Thus, multiple regions of PI31 bind independently to the proteasome and collectively determine effects on activity. PI31 blocks the ATP-dependent in vitro assembly of 26 S proteasome from 20 S proteasome and PA700 subcomplexes but has no effect on in vitro activity of the intact 26 S proteasome. To determine the physiologic significance of these in vitro effects, we assessed multiple aspects of cellular proteasome*

content and function after altering PI31 levels. We detected no change in overall cellular proteasome content or function when PI31 levels were either increased by moderate ectopic overexpression or decreased by RNA interference (RNAi). We also failed to identify a role of PI31 ADP-ribosylation as a mechanism for regulation of overall 26 S proteasome content and function, as recently proposed. Thus, despite its in vitro effects on various proteasome activities and its structural relationship to established proteasome regulators, cellular roles and mechanisms of PI31 in regulation of proteasome function remain unclear and require future definition.","DOI":"10.1074/jbc.M114.561183","ISSN":"1083-351X","note":"PMID: 24770418\nPMCID: PMC4067172","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Li","given":"Xiaohua"},{"family":"Thompson","given":"David"},{"family":"Kumar","given":"Brajesh"},{"family":"DeMartino","given":"George N."}],"issued":{"date-parts":[["2014",6,20]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }, thereby questioning the physiological relevance of PI31 in the regulation of the 26S proteasome.

Large-scale analyses of post-translational modifications of the proteasome have revealed more than 345 post-translational modifications on the 26S proteasome which can be divided into 11 different types: phosphorylation, ubiquitination, succinylation, N-acetylation, N-myristoylation, N-methylation, oxidation, O-glycosylation, SUMOylation, poly-ADP ribosylation and truncation[149]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2evuk721kt","properties":{"formattedCitation":"{\\rtf \\super 149\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":520,"uris":["http://zotero.org/users/4604651/items/46J654MC"],"uri":["http://zotero.org/users/4604651/items/46J654MC"],"itemData":{"id":520,"type":"article-journal","title":"Co- and post-translational modifications of the 26S proteasome in yeast","container-title":"Proteomics","page":"2769-2779","volume":"10","issue":"15","source":"PubMed","abstract":"The yeast (Saccharomyces cerevisiae) 26S proteasome consists of the 19S regulatory particle (19S RP) and 20S proteasome subunits. We detected comprehensively co- and post-translational modifications of these subunits using proteomic techniques. First, using MS/MS, we investigated the N-terminal modifications of three 19S RP subunits, Rpt1, Rpn13, and Rpn15, which had been unclear, and found that the N-terminus of Rpt1 is not modified, whereas that of Rpn13 and Rpn15 is acetylated. Second, we identified a total of 33 Ser/Thr phosphorylation sites in 15 subunits of the proteasome. The data obtained by us and other groups reveal that the 26S proteasome contains at least 88 phospho-amino acids including 63 pSer, 23 pThr, and 2 pTyr residues.

Dephosphorylation treatment of the 19S RP with lambda phosphatase resulted in a 30% decrease in ATPase activity, demonstrating that phosphorylation is involved in the regulation of ATPase activity in the proteasome. Third, we tried to detect glycosylated subunits of the 26S proteasome. However, we identified neither N- and O-linked oligosaccharides nor O-linked beta-N-acetylglucosamine in the 19S RP and 20S proteasome subunits. To date, a total of 110 co- and post-translational modifications, including N(alpha)-acetylation, N(alpha)-myristoylation, and phosphorylation, in the yeast 26S proteasome have been identified.","DOI":"10.1002/pmic.200900283","ISSN":"1615-9861","note":"PMID: 20486117","journalAbbreviation":"Proteomics","language":"eng","author":[{"family":"Kikuchi","given":"Julia"},{"family":"Iwafune","given":"Yuko"},{"family":"Akiyama","given":"Tomoko"},{"family":"Okayama","given":"Akiko"},{"family":"Nakamura","given":"Hiroki"},{"family":"Arakawa","given":"Noriaki"},{"family":"Kimura","given":"Yayoi"},{"family":"Hirano","given":"Hisashi"}],"issued":{"date-parts":[["2010",8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. The functional consequences of these modifications remain, for the majority, completely unknown and their characterization will be an important subject of future studies[149]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1hkvggo3ri","properties":{"formattedCitation":"{\\rtf \\super 149\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":520,"uris":["http://zotero.org/users/4604651/items/46J654MC"],"uri":["http://zotero.org/users/4604651/items/46J654MC"],"itemData":{"id":520,"type":"article-journal","title":"Co- and post-translational modifications of the 26S proteasome in yeast","container-title":"Proteomics","page":"2769-2779","volume":"10","issue":"15","source":"PubMed","abstract":"The yeast (Saccharomyces cerevisiae) 26S proteasome consists of the 19S regulatory particle (19S RP) and 20S proteasome subunits. We detected comprehensively co- and post-translational modifications of these subunits using proteomic techniques. First, using MS/MS, we investigated the N-terminal modifications of three 19S RP subunits, Rpt1, Rpn13, and Rpn15, which had been unclear, and found that the N-terminus of Rpt1 is not modified, whereas that of Rpn13 and Rpn15 is acetylated. Second, we identified a total of 33 Ser/Thr phosphorylation sites in 15 subunits of the proteasome. The data obtained by us and other groups reveal that the 26S proteasome contains at least 88 phospho-amino acids including 63 pSer, 23 pThr, and 2 pTyr residues. Dephosphorylation treatment of the 19S RP with lambda phosphatase resulted in a 30% decrease in ATPase activity, demonstrating that phosphorylation is involved in the regulation of ATPase activity in the proteasome. Third, we tried to detect glycosylated subunits of the

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[H1] Proteasomal degradation and autophagy

It has been known for a long time that impairment of proteasomal degradation induces autophagy. This has been seen in numerous experimental systems, from cells to organisms and from yeast to mammals[150]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2jt1ad3kf9","properties":{"formattedCitation":"{\\rtf \\super 150\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":401,"uris":["http://zotero.org/users/4604651/items/C2ICVNGH"],"uri":["http://zotero.org/users/4604651/items/C2ICVNGH"],"itemData":{"id":401,"type":"article-journal","title":"Proteostasis and neurodegeneration: the roles of proteasomal degradation and autophagy","container-title":"Biochimica Et Biophysica Acta","page":"197-204","volume":"1843","issue":"1","source":"PubMed","abstract":"All proteins in a cell continuously turn over, each at its own rate, contributing to a cell's development, differentiation, or aging. Of course, unnecessary protein(s), or those synthesized in excess, that hamper cellular homeostasis should be discarded rapidly. Furthermore, cells that have been subjected to various environmental stresses, e.g., reactive oxygen species (ROS) and UV irradiation, may incur various types of protein damage, which vitiate normal and homeostatic functions in the cell. Thereby, the prompt elimination of impaired proteins is essential for cell viability. This housekeeping is accomplished by two major catabolic routes-proteasomal digestion and autophagy. Strict maintenance of proteostasis is particularly important in non-proliferative cells, especially neurons, and it is plausible that its failure leads to a number of the neurodegenerative diseases becoming prominent in the growing elderly population. This article is part of a Special Issue entitled: Ubiquitin-Proteasome System. Guest Editors: Thomas Sommer and Dieter H. Wolf.","DOI":"10.1016/j.bbamcr.2013.03.012","ISSN":"0006-3002","note":"PMID: 23523933","shortTitle":"Proteostasis and neurodegeneration","journalAbbreviation":"Biochim. Biophys. Acta","language":"eng","author":[{"family":"Tanaka","given":"Keiji"},{"family":"Matsuda","given":"Noriyuki"}],"issued":{"date-parts":[["2014",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. The molecular connections between these two degradation systems occur at multiple levels. One example is

the accumulation of proteasome substrates, where impairment of proteasomal degradation may be compensated by autophagic degradation.

In addition to bulk autophagy, which is induced upon nutrient starvation and is regarded as non-selective, autophagy can also be selective. Importantly, ubiquitin serves as a signal to target proteins for degradation by both systems[151]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1vejsgh9l0","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a22rg2704vp","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1dhfoib679","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular

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28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2jo1vdeagt","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1m5mu00n0r","properties":{"formattedCitation":"{\\rtf \\super 152\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":403,"uris":["http://zotero.org/users/4604651/items/86VBRJ2R"],"uri":["http://zotero.org/users/4604651/items/86VBRJ2R"],"itemData":{"id":403,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","source":"PubMed","abstract":"Autophagy and the ubiquitin-proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","ISSN":"1545-4509","note":"PMID: 28460188","journalAbbreviation":"Annu. Rev. Biochem.","language":"eng","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017",6,20]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a7u83amnah","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems

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Because { ADDIN ZOTERO_TEMP }unfolding of proteins is required for proteasomal degradation, it is believed that the proteasome degrades soluble proteins whilst organelles or protein aggregates are degraded by autophagy. One well-established illustration of concerted actions between these two degradative machineries, is the clearance of multiple aggregation-prone proteins such as huntingtin{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"anpr6g1rkk","properties":{"formattedCitation":"{\\rtf \\super 153\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":253,"uris":["http://zotero.org/users/4604651/items/3PKBCZG9"],"uri":["http://zotero.org/users/4604651/items/3PKBCZG9"],"itemData":{"id":253,"type":"article-journal","title":"Coping with Protein Quality Control Failure","container-title":"Annual Review of Cell and Developmental Biology","page":"439-465","volume":"33","issue":"1","source":"Annual Reviews","abstract":"Cells and organisms have evolved numerous mechanisms to cope with and to adapt to unexpected challenges and harsh conditions. Proteins are essential to perform the vast majority of cellular and organismal functions. To maintain a healthy proteome, cells rely on a network of factors and pathways collectively known as protein quality control (PQC) systems, which not only ensure that newly synthesized proteins reach a functional conformation but also are essential for surveillance, prevention, and rescue of protein defects. The main players of PQC systems are chaperones and protein degradation systems: the ubiquitin-proteasome system and autophagy. Here we provide an integrated overview of the diverse PQC systems in eukaryotic cells in health and diseases, with an emphasis on the key regulatory aspects and their cross talks. We also highlight how PQC regulation may be exploited for potential therapeutic benefit.","DOI":"10.1146/annurev-cellbio-111315-125334","note":"PMID: 28992440","author":[{"family":"Pilla","given":"Esther"},{"family":"Schneider","given":"Kim"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }, or α-synuclein[152]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a167gvu4v02","properties":{"formattedCitation":"{\\rtf \\super 153\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":253,"uris":["http://zotero.org/users/4604651/items/3PKBCZG9"],"uri":["http

://zotero.org/users/4604651/items/3PKBCZG9"],"itemData":{"id":253,"type":"article-journal","title":"Coping with Protein Quality Control Failure","container-title":"Annual Review of Cell and Developmental Biology","page":"439-465","volume":"33","issue":"1","source":"Annual Reviews","abstract":"Cells and organisms have evolved numerous mechanisms to cope with and to adapt to unexpected challenges and harsh conditions. Proteins are essential to perform the vast majority of cellular and organismal functions. To maintain a healthy proteome, cells rely on a network of factors and pathways collectively known as protein quality control (PQC) systems, which not only ensure that newly synthesized proteins reach a functional conformation but also are essential for surveillance, prevention, and rescue of protein defects. The main players of PQC systems are chaperones and protein degradation systems: the ubiquitin-proteasome system and autophagy. Here we provide an integrated overview of the diverse PQC systems in eukaryotic cells in health and diseases, with an emphasis on the key regulatory aspects and their cross talks. We also highlight how PQC regulation may be exploited for potential therapeutic benefit.","DOI":"10.1146/annurev-cellbio-111315-125334","note":"PMID: 28992440","author":[{"family":"Pilla","given":"Esther"},{"family":"Schneider","given":"Kim"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}{**

ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2g19l1v7kt","properties":{"formattedCitation":"{\\rtf \\super 153\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":253,"uris":["http://zotero.org/users/4604651/items/3PKBCZG9"],"uri":["http://zotero.org/users/4604651/items/3PKBCZG9"],"itemData":{"id":253,"type":"article-journal","title":"Coping with Protein Quality Control Failure","container-title":"Annual Review of Cell and Developmental Biology","page":"439-465","volume":"33","issue":"1","source":"Annual Reviews","abstract":"Cells and organisms have evolved numerous mechanisms to cope with and to adapt to unexpected challenges and harsh conditions. Proteins are essential to perform the vast majority of cellular and organismal functions. To maintain a healthy proteome, cells rely on a network of factors and pathways collectively known as protein quality control (PQC) systems, which not only ensure that newly synthesized proteins reach a functional conformation but also are essential for surveillance, prevention, and rescue of protein defects. The main players of PQC systems are chaperones and protein degradation systems: the ubiquitin-proteasome system and autophagy. Here we provide an integrated overview of the diverse PQC systems in eukaryotic cells in health and diseases, with an emphasis on the key regulatory aspects and their cross talks. We also highlight how PQC regulation may be exploited for potential therapeutic benefit.","DOI":"10.1146/annurev-cellbio-111315-125334","note":"PMID: 28992440","author":[{"family":"Pilla","given":"Esther"},{"family":"Schneider","given":"Kim"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. The proteasome is responsible for the

degradation of most misfolded proteins to prevent them from forming large aggregates. When the proteasome is defective or overwhelmed, misfolded proteins accumulate and form large oligomers and aggregates which are targeted by autophagy[151]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3ihdelrhk","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a17obj74ajr","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a21dcs35ucf","properties":{"formattedCitation":"{\\rtf \\super 152\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":403,"uris":["http://zotero.org/users/4604651/items/86VBRJ2R"],"uri":["http://zotero.org/users/4604651/items/86VBRJ2R"],"itemData":{"id":403,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","source":"PubMed","abstract":"Autophagy and the ubiquitin-proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and

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It remains unclear whether autophagy inhibition can induce compensatory proteasome activation. With the popular notion that proteasome degrades soluble substrates and autophagy degrades larger cellular structures, it is difficult to imagine that proteasomal degradation could functionally replace autophagy. A form of autophagy–proteasome crosstalk occurs when the 26S proteasome is degraded by autophagy; a process that was discovered in plants and referred to as proteaphagy[153]. Proteaphagy occurs in plants upon nitrogen starvation and proteasome inhibition, and is mediated by Rpn10, which binds to both ubiquitinated proteasome and ATG8, acting as a proteaphagy receptor[153]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a19fuvmnkei","properties":{"formattedCitation":"{\\rtf \\super 154\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":119,"uris":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"uri":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"itemData":{"id":119,"type":"article-journal","title":"Autophagic Degradation of the 26S Proteasome Is Mediated by the Dual ATG8/Ubiquitin Receptor RPN10 in Arabidopsis","container-title":"Molecular Cell","page":"1053-1066","volume":"58","issue":"6","source":"PubMed","abstract":"Autophagic turnover of intracellular constituents is critical for cellular housekeeping, nutrient recycling, and various aspects of growth and development in eukaryotes. Here we show that autophagy impacts the other major degradative route involving the ubiquitin-proteasome system by eliminating 26S proteasomes, a process we termed proteaphagy. Using Arabidopsis proteasomes tagged with GFP, we observed their deposition into vacuoles via a route requiring components of the autophagy machinery. This transport can be initiated separately by nitrogen starvation and chemical or genetic inhibition of the proteasome, implying distinct induction mechanisms. Proteasome inhibition stimulates comprehensive ubiquitylation of the complex, with the ensuing proteaphagy requiring the proteasome subunit RPN10, which can simultaneously bind

both ATG8 and ubiquitin. Collectively, we propose that Arabidopsis RPN10 acts as a selective autophagy receptor that targets inactive 26S proteasomes by concurrent interactions with ubiquitylated proteasome subunits/targets and lipidated ATG8 lining the enveloping autophagic membranes.","DOI":"10.1016/j.molcel.2015.04.023","ISSN":"1097-4164","note":"PMID: 26004230\nPMCID: PMC4903074","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"Li","given":"Faqiang"},{"family":"Gemperline","given":"David C."},{"family":"Book","given":"Adam J."},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2015",6,18]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a20vdjc88ua","properties":{"formattedCitation":"{\\rtf \\super 154\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":119,"uris":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"uri":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"itemData":{"id":119,"type":"article-journal","title":"Autophagic Degradation of the 26S Proteasome Is Mediated by the Dual ATG8/Ubiquitin Receptor RPN10 in Arabidopsis","container-title":"Molecular Cell","page":"1053-1066","volume":"58","issue":"6","source":"PubMed","abstract":"Autophagic turnover of intracellular constituents is critical for cellular housekeeping, nutrient recycling, and various aspects of growth and development in eukaryotes. Here we show that autophagy impacts the other major degradative route involving the ubiquitin-proteasome system by eliminating 26S proteasomes, a process we termed proteaphagy. Using Arabidopsis proteasomes tagged with GFP, we observed their deposition into vacuoles via a route requiring components of the autophagy machinery. This transport can be initiated separately by nitrogen starvation and chemical or genetic inhibition of the proteasome, implying distinct induction mechanisms. Proteasome inhibition stimulates comprehensive ubiquitylation of the complex, with the ensuing proteaphagy requiring the proteasome subunit RPN10, which can simultaneously bind both ATG8 and ubiquitin. Collectively, we propose that Arabidopsis RPN10 acts as a selective autophagy receptor that targets inactive 26S proteasomes by concurrent interactions with ubiquitylated proteasome subunits/targets and lipidated ATG8 lining the enveloping autophagic membranes.","DOI":"10.1016/j.molcel.2015.04.023","ISSN":"1097-4164","note":"PMID: 26004230\nPMCID: PMC4903074","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"Li","given":"Faqiang"},{"family":"Gemperline","given":"David C."},{"family":"Book","given":"Adam J."},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2015",6,18]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a8vmv9829m","properties":{"formattedCitation":"{\\rtf \\super 155\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-

3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID: PMC4751371","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Waite","given":"Kenrick A."},{"family":"De-La Mota-Peynado","given":"Alina"},{"family":"Vontz","given":"Gabrielle"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2016",2,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a24slijfcng","properties":{"formattedCitation":"{\\rtf \\super 155\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID:

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S."},{"family":"Li","given":"Faqiang"},{"family":"Gemperline","given":"David C."},{"family":"Book","given":"Adam J."},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2015",6,18]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Similar results have been observed in yeast, whereby Cue5 is the proteaphagy receptor[154,155]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2aheblrbqs","properties":{"formattedCitation":"{\\rtf \\super 155,156\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID: PMC4751371","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Waite","given":"Kenrick A."},{"family":"De-La Mota-Peynado","given":"Alina"},{"family":"Vontz","given":"Gabrielle"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2016",2,12]]}}},{"id":126,"uris":["http://zotero.org/users/4604651/items/6ELTIFZH"],"uri":["http://zotero.org/users/4604651/items/6ELTIFZH"],"itemData":{"id":126,"type":"article-journal","title":"Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone","container-title":"Cell Reports","page":"1717-1732","volume":"16","issue":"6","source":"PubMed","abstract":"The autophagic clearance of 26S proteasomes (proteaphagy) is an important homeostatic mechanism within the ubiquitin system that modulates proteolytic capacity and eliminates damaged particles. Here, we define two proteaphagy routes in yeast that respond to either nitrogen starvation or particle inactivation. Whereas the core autophagic machineries required for Atg8 lipidation and vesiculation are essential for both routes, the upstream Atg1 kinase participates only in starvation-induced proteaphagy. Following inactivation, 26S proteasomes become extensively modified with ubiquitin. Although prior studies with Arabidopsis implicated RPN10 in tethering ubiquitylated proteasomes to ATG8 lining the autophagic membranes, yeast proteaphagy employs the evolutionarily distinct receptor Cue5, which simultaneously binds ubiquitin and Atg8. Proteaphagy of inactivated proteasomes also requires the oligomeric Hsp42 chaperone, suggesting that ubiquitylated proteasomes are directed by Hsp42 to insoluble protein deposit (IPOD)-type structures before encapsulation. Together, Cue5 and Hsp42 provide a quality control checkpoint in yeast directed at recycling dysfunctional 26S proteasomes.","DOI":"10.1016/j.celrep.2016.07.015","ISSN":"2211-1247","note":"PMID: 27477278","journalAbbreviation":"Cell Rep","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"McLoughlin","given":"Fionn"},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-

parts":[["2016",8,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2o18u0gdf0","properties":{"formattedCitation":"{\\rtf \\super 154,155\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID: PMC4751371","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Waite","given":"Kenrick A."},{"family":"De-La Mota-Peynado","given":"Alina"},{"family":"Vontz","given":"Gabrielle"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2016",2,12]]}},{"id":119,"uris":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"uri":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"itemData":{"id":119,"type":"article-journal","title":"Autophagic Degradation of the 26S Proteasome Is Mediated by the Dual ATG8/Ubiquitin Receptor RPN10 in Arabidopsis","container-title":"Molecular Cell","page":"1053-1066","volume":"58","issue":"6","source":"PubMed","abstract":"Autophagic turnover of intracellular constituents is critical for cellular housekeeping, nutrient recycling, and various

aspects of growth and development in eukaryotes. Here we show that autophagy impacts the other major degradative route involving the ubiquitin-proteasome system by eliminating 26S proteasomes, a process we termed proteaphagy. Using Arabidopsis proteasomes tagged with GFP, we observed their deposition into vacuoles via a route requiring components of the autophagy machinery. This transport can be initiated separately by nitrogen starvation and chemical or genetic inhibition of the proteasome, implying distinct induction mechanisms. Proteasome inhibition stimulates comprehensive ubiquitylation of the complex, with the ensuing proteaphagy requiring the proteasome subunit RPN10, which can simultaneously bind both ATG8 and ubiquitin. Collectively, we propose that Arabidopsis RPN10 acts as a selective autophagy receptor that targets inactive 26S proteasomes by concurrent interactions with ubiquitylated proteasome subunits/targets and lipidated ATG8 lining the enveloping autophagic membranes.","DOI":"10.1016/j.molcel.2015.04.023","ISSN":"1097-4164","note":"PMID: 26004230\nPMCID: PMC4903074","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"Li","given":"Faqiang"},{"family":"Gemperline","given":"David C."},{"family":"Book","given":"Adam J."},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2015",6,18]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1omhtcabkt","properties":{"formattedCitation":"{\\rtf \\super 155,156\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID: PMC4751371","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Waite","given":"Kenrick A."},{"family":"De-La Mota-Peynado","given":"Alina"},{"family":"Vontz","given":"Gabrielle"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-parts":[["2016",2,12]]}}},{"id":126,"uris":["http://zotero.org/users/4604651/items/6ELTIFZH"],"uri":["http://zotero.org/users/4604651/item

s/6ELTIFZH"],"itemData":{"id":126,"type":"article-journal","title":"Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone","container-title":"Cell Reports","page":"1717-1732","volume":"16","issue":"6","source":"PubMed","abstract":"The autophagic clearance of 26S proteasomes (proteaphagy) is an important homeostatic mechanism within the ubiquitin system that modulates proteolytic capacity and eliminates damaged particles. Here, we define two proteaphagy routes in yeast that respond to either nitrogen starvation or particle inactivation. Whereas the core autophagic machineries required for Atg8 lipidation and vesiculation are essential for both routes, the upstream Atg1 kinase participates only in starvation-induced proteaphagy. Following inactivation, 26S proteasomes become extensively modified with ubiquitin. Although prior studies with Arabidopsis implicated RPN10 in tethering ubiquitylated proteasomes to ATG8 lining the autophagic membranes, yeast proteaphagy employs the evolutionarily distinct receptor Cue5, which simultaneously binds ubiquitin and Atg8. Proteaphagy of inactivated proteasomes also requires the oligomeric Hsp42 chaperone, suggesting that ubiquitylated proteasomes are directed by Hsp42 to insoluble protein deposit (IPOD)-type structures before encapsulation. Together, Cue5 and Hsp42 provide a quality control checkpoint in yeast directed at recycling dysfunctional 26S proteasomes.","DOI":"10.1016/j.celrep.2016.07.015","ISSN":"2211-1247","note":"PMID: 27477278","journalAbbreviation":"Cell Rep","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"McLoughlin","given":"Fionn"},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2016",8,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Proteaphagy has also been described in human cells with p62 being important for autophagic targeting of the 26S proteasome[156]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a20o3udhkag","properties":{"formattedCitation":"{\\rtf \\super 157\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":20,"uris":["http://zotero.org/users/4604651/items/C9GA3FAW"],"uri":["http://zotero.org/users/4604651/items/C9GA3FAW"],"itemData":{"id":20,"type":"article-journal","title":"p62- and ubiquitin-dependent stress-induced autophagy of the mammalian 26S proteasome","container-title":"Proceedings of the National Academy of Sciences","page":"E7490-E7499","volume":"113","issue":"47","source":"www.pnas.org","abstract":"The ubiquitin-proteasome system and autophagy are the two main proteolytic systems involved in, among other functions, the maintenance of cell integrity by eliminating misfolded and damaged proteins and organelles. Both systems remove their targets after their conjugation with ubiquitin. An interesting, yet incompletely understood problem relates to the fate of the components of the two systems. Here we provide evidence that amino acid starvation enhances polyubiquitination on specific sites of the proteasome, a modification essential for its targeting to the autophagic machinery. The uptake of the ubiquitinated proteasome is mediated by its interaction with the ubiquitin-associated domain of p62/SQSTM1, a process that also requires interaction with LC3. Importantly, deletion of the PB1 domain of p62, which is important for the targeting of ubiquitinated substrates to the proteasome, has no effect on stress-induced

autophagy of this proteolytic machinery, suggesting that the domain of p62 that binds to the proteasome determines the function of p62 in either targeting substrates to the proteasome or targeting the proteasome to autophagy.","DOI":"10.1073/pnas.1615455113","ISSN":"0027-8424, 1091-6490","note":"PMID: 27791183","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Cohen-Kaplan","given":"Victoria"},{"family":"Livneh","given":"Ido"},{"family":"Avni","given":"Noa"},{"family":"Fabre","given":"Bertrand"},{"family":"Ziv","given":"Tamar"},{"family":"Kwon","given":"Yong Tae"},{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2016",11,22]]}},"locator":"-"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1nqh71kfq9","properties":{"formattedCitation":"{\\rtf \\super 157\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":20,"uris":["http://zotero.org/users/4604651/items/C9GA3FAW"],"uri":["http://zotero.org/users/4604651/items/C9GA3FAW"],"itemData":{"id":20,"type":"article-journal","title":"p62- and ubiquitin-dependent stress-induced autophagy of the mammalian 26S proteasome","container-title":"Proceedings of the National Academy of Sciences","page":"E7490-E7499","volume":"113","issue":"47","source":"www.pnas.org","abstract":"The ubiquitin-proteasome system and autophagy are the two main proteolytic systems involved in, among other functions, the maintenance of cell integrity by eliminating misfolded and damaged proteins and organelles. Both systems remove their targets after their conjugation with ubiquitin. An interesting, yet incompletely understood problem relates to the fate of the components of the two systems. Here we provide evidence that amino acid starvation enhances polyubiquitination on specific sites of the proteasome, a modification essential for its targeting to the autophagic machinery. The uptake of the ubiquitinated proteasome is mediated by its interaction with the ubiquitin-associated domain of p62/SQSTM1, a process that also requires interaction with LC3. Importantly, deletion of the PB1 domain of p62, which is important for the targeting of ubiquitinated substrates to the proteasome, has no effect on stress-induced autophagy of this proteolytic machinery, suggesting that the domain of p62 that binds to the proteasome determines the function of p62 in either targeting substrates to the proteasome or targeting the proteasome to autophagy.","DOI":"10.1073/pnas.1615455113","ISSN":"0027-8424, 1091-6490","note":"PMID: 27791183","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Cohen-Kaplan","given":"Victoria"},{"family":"Livneh","given":"Ido"},{"family":"Avni","given":"Noa"},{"family":"Fabre","given":"Bertrand"},{"family":"Ziv","given":"Tamar"},{"family":"Kwon","given":"Yong Tae"},{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2016",11,22]]}},"locator":"-"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Thus, autophagy may control proteasome levels and, in this way, may impact, albeit indirectly, on proteasomal degradation.

The mechanisms described highlight the crosstalk between the proteasome and autophagy at the level of substrate degradation. However, because degradation of substrates recycles amino acids, an important component of the crosstalk between these two degradative pathways is orchestrated by amino-acid homeostasis. As we discuss below, TORC1 integrates

amino acid metabolism and levels of protein degradation via both the proteasome and autophagy.

[H1] TORC1 links proteasome biogenesis to metabolism

A high supply of nutrients favours growth and anabolic processes whereas a scarcity of nutrients promotes catabolic processes to spare and recycle existing resources for cell survival. TORC1 is a central controller of cell growth and cellular homeostasis in all eukaryotes[157,158]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1f93sr0k2b","properties":{"formattedCitation":"{\\rtf \\super 158,159\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}}},{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-title":"The EMBO journal","page":"397-408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"a23ofqfbt7k","properties":{"formattedCitation":"{\\rtf \\super 158,159\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}}},{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-title":"The EMBO journal","page":"397-408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a25u5tm27pm","properties":{"formattedCitation":"{\\rtf \\super 158\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. TORC1 senses amino acid availability to balance protein synthesis and degradation (FIG. 6). In nutrient-rich conditions, TORC1 activation favours growth in part by promoting the synthesis of new proteins (FIG. 6 and Box 2). This increase of anabolic processes is associated with a repression of cellular catabolism through the phosphorylation and inhibition of the kinase ULK1 and the transcription factor EB (TFEB), which are involved in autophagosome formation and transcription of autophagy-lysosome genes, respectively[159–162]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1j0q3jhl3g","properties":{"formattedCitation":"{\\rtf \\super 160\\uc0\\u8211{}163\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":132,"uris":["http://zotero.org/users/4604651/items/EKME3IRF"],"uri":["http://zotero.org/users/4604651

/items/EKME3IRF"],"itemData":{"id":132,"type":"article-journal","title":"AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1","container-title":"Nature Cell Biology","page":"132-
141","volume":"13","issue":"2","source":"PubMed","abstract":"Autophagy is a process by which components of the cell are degraded to maintain essential activity and viability in response to nutrient limitation. Extensive genetic studies have shown that the yeast ATG1 kinase has an essential role in autophagy induction. Furthermore, autophagy is promoted by AMP activated protein kinase (AMPK), which is a key energy sensor and regulates cellular metabolism to maintain energy homeostasis. Conversely, autophagy is inhibited by the mammalian target of rapamycin (mTOR), a central cell-growth regulator that integrates growth factor and nutrient signals. Here we demonstrate a molecular mechanism for regulation of the mammalian autophagy-initiating kinase Ulk1, a homologue of yeast ATG1. Under glucose starvation, AMPK promotes autophagy by directly activating Ulk1 through phosphorylation of Ser 317 and Ser 777. Under nutrient sufficiency, high mTOR activity prevents Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. This coordinated phosphorylation is important for Ulk1 in autophagy induction. Our study has revealed a signalling mechanism for Ulk1 regulation and autophagy induction in response to nutrient signalling.","DOI":"10.1038/ncb2152","ISSN":"1476-4679","note":"PMID: 21258367\nPMCID: PMC3987946","journalAbbreviation":"Nat. Cell Biol.","language":"eng","author":[{"family":"Kim","given":"Joungmok"},{"family":"Kundu","given":"Mondira"},{"family":"Viollet","given":"Benoit"},{"family":"Guan","given":"Kun-Liang"}],"issued":{"date-
parts":[["2011",2]]}}},{"id":129,"uris":["http://zotero.org/users/4604651/items/L4DFXHYC"],"uri":["http://zotero.org/users/4604651/items/L4DFXHYC"],"itemData":{"id":129,"type":"article-journal","title":"MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB","container-title":"Autophagy","page":"903-914","volume":"8","issue":"6","source":"PubMed","abstract":"The mammalian target of rapamycin (MTOR) protein kinase complex is a key component of a pathway that regulates cell growth and proliferation in response to energy levels, hypoxia, nutrients and insulin. Inhibition of MTORC1 strongly induces autophagy by regulating the activity of the ULK protein kinase complex that is required for the formation of autophagosomes. However, the participation of MTORC1 in the expression of autophagy genes has not been characterized. Here we show that MTORC1 regulates nuclear localization and activity of the transcription factor EB (TFEB), a member of the bHLH leucine-zipper family of transcription factors that

drives expression of autophagy and lysosomal genes. Under normal nutrient conditions, TFEB is phosphorylated in Ser211 in an MTORC1-dependent manner. This phosphorylation promotes association of TFEB with members of the YWHA (14-3-3) family of proteins and retention of the transcription factor in the cytosol. Pharmacological or genetic inhibition of MTORC1 causes dissociation of the TFEB/YWHA complex and rapid transport of TFEB to the nucleus where it increases transcription of multiple genes implicated in autophagy and lysosomal function. Active TFEB also associates with late endosomal/lysosomal membranes through interaction with the LAMTOR/RRAG/MTORC1 complex. Our results unveil a novel role for MTORC1 in the maintenance of cellular homeostasis by regulating autophagy at the transcriptional level.","DOI":"10.4161/auto.19653","ISSN":"1554-8635","note":"PMID: 22576015\nPMCID: PMC3427256","journalAbbreviation":"Autophagy","language":"eng","author":[{"family":"Martina","given":"Jose A."},{"family":"Chen","given":"Yong"},{"family":"Gucek","given":"Marjan"},{"family":"Puertollano","given":"Rosa"}],"issued":{"date-parts":[["2012",6]]}}},{"id":131,"uris":["http://zotero.org/users/4604651/items/SDZ5PCZD"],"uri":["http://zotero.org/users/4604651/items/SDZ5PCZD"],"itemData":{"id":131,"type":"article-journal","title":"The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis","container-title":"Science Signaling","page":"ra42","volume":"5","issue":"228","source":"PubMed","abstract":"Lysosomes are the major cellular site for clearance of defective organelles and digestion of internalized material. Demand on lysosomal capacity can vary greatly, and lysosomal function must be adjusted to maintain cellular homeostasis. Here, we identified an interaction between the lysosome-localized mechanistic target of rapamycin complex 1 (mTORC1) and the transcription factor TFEB (transcription factor EB), which promotes lysosome biogenesis. When lysosomal activity was adequate, mTOR-dependent phosphorylation of TFEB on Ser(211) triggered the binding of 14-3-3 proteins to TFEB, resulting in retention of the transcription factor in the cytoplasm. Inhibition of lysosomal function reduced the mTOR-dependent phosphorylation of TFEB, resulting in diminished interactions between TFEB and 14-3-3 proteins and the translocation of TFEB into the nucleus, where it could stimulate genes involved in lysosomal biogenesis. These results identify TFEB as a target of mTOR and suggest a mechanism for matching the transcriptional regulation of genes encoding proteins of autophagosomes and lysosomes to cellular need. The closely related transcription factors MITF (microphthalmia transcription factor) and TFE3 (transcription factor E3) also localized to

lysosomes and accumulated in the nucleus when lysosome function was inhibited, thus broadening the range of physiological contexts under which this regulatory mechanism may prove important.","DOI":"10.1126/scisignal.2002790","ISSN":"1937-9145","note":"PMID: 22692423\nPMCID: PMC3437338","journalAbbreviation":"Sci Signal","language":"eng","author":[{"family":"Roczniak-Ferguson","given":"Agnes"},{"family":"Petit","given":"Constance S."},{"family":"Froehlich","given":"Florian"},{"family":"Qian","given":"Sharon"},{"family":"Ky","given":"Jennifer"},{"family":"Angarola","given":"Brittany"},{"family":"Walther","given":"Tobias C."},{"family":"Ferguson","given":"Shawn M."}],"issued":{"date-parts":[["2012",6,12]]}},{"id":130,"uris":["http://zotero.org/users/4604651/items/QRALJC7M"],"uri":["http://zotero.org/users/4604651/items/QRALJC7M"],"itemData":{"id":130,"type":"article-journal","title":"A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB","container-title":"The EMBO journal","page":"1095-1108","volume":"31","issue":"5","source":"PubMed","abstract":"The lysosome plays a key role in cellular homeostasis by controlling both cellular clearance and energy production to respond to environmental cues. However, the mechanisms mediating lysosomal adaptation are largely unknown. Here, we show that the Transcription Factor EB (TFEB), a master regulator of lysosomal biogenesis, colocalizes with master growth regulator mTOR complex 1 (mTORC1) on the lysosomal membrane. When nutrients are present, phosphorylation of TFEB by mTORC1 inhibits TFEB activity. Conversely, pharmacological inhibition of mTORC1, as well as starvation and lysosomal disruption, activates TFEB by promoting its nuclear translocation. In addition, the transcriptional response of lysosomal and autophagic genes to either lysosomal dysfunction or pharmacological inhibition of mTORC1 is suppressed in TFEB-/- cells. Interestingly, the Rag GTPase complex, which senses lysosomal amino acids and activates mTORC1, is both necessary and sufficient to regulate starvation- and stress-induced nuclear translocation of TFEB. These data indicate that the lysosome senses its content and regulates its own biogenesis by a lysosome-to-nucleus signalling mechanism that involves TFEB and mTOR.","DOI":"10.1038/emboj.2012.32","ISSN":"1460-2075","note":"PMID: 22343943\nPMCID: PMC3298007","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"Settembre","given":"Carmine"},{"family":"Zoncu","given":"Roberto"},{"family":"Medina","given":"Diego L."},{"family":"Vetrini","given":"Francesco"},{"family":"Erdin","given":"Serkan"},{"family":"Erdin","given":"SerpilUckac"},{"family":"Huynh","given":"Tuong"},{"family":"Ferron","given":"Mathieu"},{"family":"Karsenty","given":"Gerard"},{"family":"Vellard","given":"

Michel C."},{"family":"Facchinetti","given":"Valeria"},{"family":"Sabatini","given":"David M."},{"family":"Ballabio","given":"Andrea"}],"issued":{"date-parts":[["2012",3,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a21hqa9ft5o","properties":{"formattedCitation":"{\\rtf \\super 160\\uc0\\u8211{}163\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":132,"uris":["http://zotero.org/users/4604651/items/EKME3IRF"],"uri":["http://zotero.org/users/4604651/items/EKME3IRF"],"itemData":{"id":132,"type":"article-journal","title":"AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1","container-title":"Nature Cell Biology","page":"132-141","volume":"13","issue":"2","source":"PubMed","abstract":"Autophagy is a process by which components of the cell are degraded to maintain essential activity and viability in response to nutrient limitation. Extensive genetic studies have shown that the yeast ATG1 kinase has an essential role in autophagy induction. Furthermore, autophagy is promoted by AMP activated protein kinase (AMPK), which is a key energy sensor and regulates cellular metabolism to maintain energy homeostasis. Conversely, autophagy is inhibited by the mammalian target of rapamycin (mTOR), a central cell-growth regulator that integrates growth factor and nutrient signals. Here we demonstrate a molecular mechanism for regulation of the mammalian autophagy-initiating kinase Ulk1, a homologue of yeast ATG1. Under glucose starvation, AMPK promotes autophagy by directly activating Ulk1 through phosphorylation of Ser 317 and Ser 777. Under nutrient sufficiency, high mTOR activity prevents Ulk1 activation by phosphorylating Ulk1 Ser 757 and disrupting the interaction between Ulk1 and AMPK. This coordinated phosphorylation is important for Ulk1 in autophagy induction. Our study has revealed a signalling mechanism for Ulk1 regulation and autophagy induction in response to nutrient signalling.","DOI":"10.1038/ncb2152","ISSN":"1476-4679","note":"PMID: 21258367\nPMCID: PMC3987946","journalAbbreviation":"Nat. Cell Biol.","language":"eng","author":[{"family":"Kim","given":"Joungmok"},{"family":"Kundu","given":"Mondira"},{"family":"Viollet","given":"Benoit"},{"family":"Guan","given":"Kun-Liang"}],"issued":{"date-parts":[["2011",2]]}}},{"id":129,"uris":["http://zotero.org/users/4604651/items/L4DFXHYC"],"uri":["http://zotero.org/users/4604651/items/L4DFXHYC"],"itemData":{"id":129,"type":"article-journal","title":"MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB","container-title":"Autophagy","page":"903-914","volume":"8","issue":"6","source":"PubMed","abstract":"The mammalian target of rapamycin (MTOR) protein kinase complex is a key component of a pathway that regulates cell growth and proliferation in response to energy levels, hypoxia, nutrients and insulin. Inhibition of MTORC1 strongly induces autophagy by regulating the activity of the ULK protein kinase complex that is required for the formation of autophagosomes. However, the participation of MTORC1 in the expression of autophagy genes has not been characterized. Here we show that MTORC1 regulates nuclear localization and activity of the transcription factor EB (TFEB), a member of the bHLH leucine-zipper family of transcription factors that drives expression of autophagy and lysosomal genes. Under normal nutrient conditions, TFEB is phosphorylated in Ser211 in an MTORC1-dependent manner. This phosphorylation promotes association of TFEB with members of the YWHA (14-3-3) family of proteins and retention of the transcription factor in the cytosol. Pharmacological or genetic inhibition of MTORC1 causes dissociation of the TFEB/YWHA complex and rapid transport of TFEB to the nucleus where it increases transcription of multiple genes implicated in autophagy and lysosomal function. Active TFEB also associates with late endosomal/lysosomal membranes through interaction with the

LAMTOR/RRAG/MTORC1 complex. Our results unveil a novel role for MTORC1 in the maintenance of cellular homeostasis by regulating autophagy at the transcriptional level.","DOI":"10.4161/auto.19653","ISSN":"1554-8635","note":"PMID: 22576015\nPMCID: PMC3427256","journalAbbreviation":"Autophagy","language":"eng","author":[{"family":"Martina","given":"Jose A."},{"family":"Chen","given":"Yong"},{"family":"Gucek","given":"Marjan"},{"family":"Puertollano","given":"Rosa"}],"issued":{"date-parts":[["2012",6]]}}},{"id":131,"uris":["http://zotero.org/users/4604651/items/SDZ5PCZD"],"uri":["http://zotero.org/users/4604651/items/SDZ5PCZD"],"itemData":{"id":131,"type":"article-journal","title":"The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis","container-title":"Science Signaling","page":"ra42","volume":"5","issue":"228","source":"PubMed","abstract":"Lysosomes are the major cellular site for clearance of defective organelles and digestion of internalized material. Demand on lysosomal capacity can vary greatly, and lysosomal function must be adjusted to maintain cellular homeostasis. Here, we identified an interaction between the lysosome-localized mechanistic target of rapamycin complex 1 (mTORC1) and the transcription factor TFEB (transcription factor EB), which promotes lysosome biogenesis. When lysosomal activity was adequate, mTOR-dependent phosphorylation of TFEB on Ser(211) triggered the binding of 14-3-3 proteins to TFEB, resulting in retention of the transcription factor in the cytoplasm. Inhibition of lysosomal function reduced the mTOR-dependent phosphorylation of TFEB, resulting in diminished interactions between TFEB and 14-3-3 proteins and the translocation of TFEB into the nucleus, where it could stimulate genes involved in lysosomal biogenesis. These results identify TFEB as a target of mTOR and suggest a mechanism for matching the transcriptional regulation of genes encoding proteins of autophagosomes and lysosomes to cellular need. The closely related transcription factors MITF (microphthalmia transcription factor) and TFE3 (transcription factor E3) also localized to lysosomes and accumulated in the nucleus when lysosome function was inhibited, thus broadening the range of physiological contexts under which this regulatory mechanism may prove important.","DOI":"10.1126/scisignal.2002790","ISSN":"1937-9145","note":"PMID: 22692423\nPMCID: PMC3437338","journalAbbreviation":"Sci Signal","language":"eng","author":[{"family":"Roczniak-Ferguson","given":"Agnes"},{"family":"Petit","given":"Constance S."},{"family":"Froehlich","given":"Florian"},{"family":"Qian","given":"Sharon"},{"family":"Ky","given":"Jennifer"},{"family":"Angarola","given":"Brittany"},{"family":"Walther","given":"Tobias C."},{"family":"Ferguson","given":"Shawn M."}],"issued":{"date-parts":[["2012",6,12]]}}},{"id":130,"uris":["http://zotero.org/users/4604651/items/QRALJC7M"],"uri":["http://zotero.org/users/4604651/items/QRALJC7M"],"itemData":{"id":130,"type":"article-journal","title":"A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB","container-title":"The EMBO journal","page":"1095-1108","volume":"31","issue":"5","source":"PubMed","abstract":"The lysosome plays a key role in cellular homeostasis by controlling both cellular clearance and energy production to respond to environmental cues. However, the mechanisms mediating lysosomal adaptation are largely unknown. Here, we show that the Transcription Factor EB (TFEB), a master regulator of lysosomal biogenesis, colocalizes with master growth regulator mTOR complex 1 (mTORC1) on the lysosomal membrane. When nutrients are present, phosphorylation of TFEB by mTORC1 inhibits TFEB activity. Conversely, pharmacological inhibition of mTORC1, as well as starvation and lysosomal disruption, activates TFEB by promoting its nuclear translocation. In addition, the transcriptional response of lysosomal and autophagic genes to either lysosomal dysfunction or pharmacological inhibition of mTORC1 is suppressed in TFEB-/- cells. Interestingly, the Rag GTPase complex, which senses lysosomal amino acids and activates mTORC1, is both necessary and sufficient to regulate starvation- and stress-induced nuclear

translocation of TFEB. These data indicate that the lysosome senses its content and regulates its own biogenesis by a lysosome-to-nucleus signalling mechanism that involves TFEB and mTOR.","DOI":"10.1038/emboj.2012.32","ISSN":"1460-2075","note":"PMID: 22343943\nPMCID: PMC3298007","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"Settembre","given":"Carmine"},{"family":"Zoncu","given":"Roberto"},{"family":"Medina","given":"Diego L."},{"family":"Vetrini","given":"Francesco"},{"family":"Erdin","given":"Serkan"},{"family":"Erdin","given":"SerpilUckac"},{"family":"Huynh","given":"Tuong"},{"family":"Ferron","given":"Mathieu"},{"family":"Karsenty","given":"Gerard"},{"family":"Vellard","given":"Michel C."},{"family":"Facchinetti","given":"Valeria"},{"family":"Sabatini","given":"David M."},{"family":"Ballabio","given":"Andrea"}],"issued":{"date-parts":[["2012",3,7]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Conversely, in nutrient-limiting conditions TORC1 inhibition represses anabolic processes and cell growth while stimulating catabolism in order to mobilize stored energy and resources to maintain essential cellular processes and ensure cell survival (FIG. 6).

It is well established that TORC1 inhibition induces autophagy[151,163]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3he1gr44c","properties":{"formattedCitation":"{\\rtf \\super 151,164\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}},{"id":121,"uris":["http://zotero.org/users/4604651/items/KG6ZVPWB"],"uri":["http://zotero.org/users/4604651/items/KG6ZVPWB"],"itemData":{"id":121,"type":"article-journal","title":"Autophagy at the crossroads of catabolism and anabolism","container-

title":"Nature Reviews Molecular Cell Biology","page":"461-472","volume":"16","issue":"8","source":"www.nature.com","abstract":"Autophagy is a conserved catabolic process that degrades cytoplasmic constituents and organelles in the lysosome. Starvation-induced protein degradation is a salient feature of autophagy but recent progress has illuminated how autophagy, during both starvation and nutrient-replete conditions, can mobilize diverse cellular energy and nutrient stores such as lipids, carbohydrates and iron. Processes such as lipophagy, glycophagy and ferritinophagy enable cells to salvage key metabolites to sustain and facilitate core anabolic functions. Here, we discuss the established and emerging roles of autophagy in fuelling biosynthetic capacity and in promoting metabolic and nutrient homeostasis.","DOI":"10.1038/nrm4024","ISSN":"1471-0072","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Kaur","given":"Jasvinder"},{"family":"Debnath","given":"Jayanta"}],"issued":{"date-parts":[["2015",8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1nqn2nl89u","properties":{"formattedCitation":"{\\rtf \\super 151,164\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}},{"id":121,"uris":["http://zotero.org/users/4604651/items/KG6ZVPWB"],"uri":["http://zotero.org/users/4604651/items/KG6ZVPWB"],"itemData":{"id":121,"type":"article-journal","title":"Autophagy at the crossroads of catabolism and anabolism","container-title":"Nature Reviews Molecular Cell Biology","page":"461-472","volume":"16","issue":"8","source":"www.nature.com","abstract":"Autophagy is a conserved catabolic process that degrades cytoplasmic constituents and organelles in the lysosome. Starvation-induced protein degradation is a salient feature of autophagy but recent progress has illuminated how autophagy, during both starvation and nutrient-replete conditions, can mobilize diverse cellular energy and nutrient stores such as lipids, carbohydrates and iron. Processes such as lipophagy, glycophagy and ferritinophagy enable cells to salvage key metabolites to sustain and facilitate core anabolic functions. Here, we discuss the established and emerging roles of autophagy in fuelling

biosynthetic capacity and in promoting metabolic and nutrient homeostasis.","DOI":"10.1038/nrm4024","ISSN":"1471-0072","journalAbbreviation":"Nat Rev Mol Cell Biol","language":"en","author":[{"family":"Kaur","given":"Jasvinder"},{"family":"Debnath","given":"Jayanta"}],"issued":{"date-parts":[["2015",8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. In addition, it has recently been shown that the inhibition of TORC1 increases proteasome assembly and abundance[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"agft4adibg","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. These findings indicate that TORC1 coordinates proteasome assembly and abundance with growth and cellular metabolism (Fig. 6). It is noteworthy that this increase proteasome assembly and abundance following TORC1 inhibition is transient[106]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ldarpuuh7","properties":{"formattedCitation":"{\\rtf \\super 106\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5

controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. A similar transient increase of proteasome activity has been observed following starvation-mediated inhibition of TORC1[164]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"abv09ufpbu","properties":{"formattedCitation":"{\\rtf \\super 165\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":120,"uris":["http://zotero.org/users/4604651/items/2R47CEJ9"],"uri":["http://zotero.org/users/4604651/items/2R47CEJ9"],"itemData":{"id":120,"type":"article-journal","title":"PSMD10/gankyrin induces autophagy to promote tumor progression through cytoplasmic interaction with ATG7 and nuclear transactivation of ATG7 expression","container-title":"Autophagy","page":"1355-1371","volume":"12","issue":"8","source":"PubMed","abstract":"Although autophagy is most critical for survival of cancer cells, especially in fast-growing tumors, the mechanism remains to be fully characterized. Herein we report that PSMD10/gankyrin promotes autophagy in hepatocellular carcinoma (HCC) in response to starvation or stress through 2 complementary routes. PSMD10 was physically associated with ATG7 in the cytoplasm, and this association was enhanced by initial nutrient deprivation. Subsequently, PSMD10 translocated into the nucleus and bound cooperatively with nuclear HSF1 (heat shock transcription factor 1) onto the ATG7 promoter, upregulated ATG7 expression in the advanced stage of starvation. Intriguingly, the type of PSMD10-mediated autophagy was independent of the proteasome system, although PSMD10 has been believed to be an indispensable chaperone for assembly of the 26S proteasome. A significant correlation between PSMD10 expression and ATG7 levels was detected in human HCC biopsies, and the combination of these 2 parameters is a powerful predictor of poor prognosis. The median survival of sorafenib-treated HCC patients with high expression of PSMD10 was much shorter than those with low expression of PSMD10. Furthermore, PSMD10 augmented autophagic flux to resist sorafenib or conventional chemotherapy, and inhibition of autophagy suppressed PSMD10-mediated resistance. We conclude that these results present a novel mechanism involving modulation of ATG7 by PSMD10 in sustaining autophagy, promoting HCC cell survival against starvation or chemotherapy. Targeting of PSMD10 might therefore be an attractive strategy in HCC treatment by suppressing autophagy and inducing HCC cell sensitivity to drugs.","DOI":"10.1080/15548627.2015.1034405","ISSN":"1554-8635","note":"PMID: 25905985","journalAbbreviation":"Autophagy","language":"eng","author":[{"family":"Luo","given":"Tao"},{"family":"Fu","given":"Jing"},{"family":"Xu","given":"An"},{"family":"Su","given":"Bo"},{"family":"Ren","given":"Yibing"},{"family":"Li","given":"Ning"},{"family":"Zhu","given":"Junjie"},{"family":"Zhao","given":"Xiaofang"},{"family":"Dai","given":"Rongyang"},{"family":"Cao","given":"Jie"},{"family":"Wang","given":"Bibo"},{"family":"Qin","given":"Wenhao"},{"family":"Jiang","given":"Jinhua"},{"family":"Li","given":"Juan"},{"family":"Wu","given":"Mengchao"},{"family":"Feng","given":"Gensheng"},{"family":"Chen","given":"Yao"},{"family":"Wang","given":"Hongyang"}],"issued":{"date-parts":[["2016",8,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Interestingly, the return to basal levels of proteasome following TORC1 inhibition is accompanied by an increase of autophagy, suggesting that autophagic degradation of the

proteasome or proteaphagy might be one of the causes for proteasome increase being transient. In agreement with this model, the proteasome was recently found to be a substrate of the autophagy-lysosome system[153–156]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1sn1iq73lo","properties":{"formattedCitation":"{\\rtf \\super 154\\uc0\\u8211{}157\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":119,"uris":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"uri":["http://zotero.org/users/4604651/items/VRJIK5FQ"],"itemData":{"id":119,"type":"article-journal","title":"Autophagic Degradation of the 26S Proteasome Is Mediated by the Dual ATG8/Ubiquitin Receptor RPN10 in Arabidopsis","container-title":"Molecular Cell","page":"1053-1066","volume":"58","issue":"6","source":"PubMed","abstract":"Autophagic turnover of intracellular constituents is critical for cellular housekeeping, nutrient recycling, and various aspects of growth and development in eukaryotes. Here we show that autophagy impacts the other major degradative route involving the ubiquitin-proteasome system by eliminating 26S proteasomes, a process we termed proteaphagy. Using Arabidopsis proteasomes tagged with GFP, we observed their deposition into vacuoles via a route requiring components of the autophagy machinery. This transport can be initiated separately by nitrogen starvation and chemical or genetic inhibition of the proteasome, implying distinct induction mechanisms. Proteasome inhibition stimulates comprehensive ubiquitylation of the complex, with the ensuing proteaphagy requiring the proteasome subunit RPN10, which can simultaneously bind both ATG8 and ubiquitin. Collectively, we propose that Arabidopsis RPN10 acts as a selective autophagy receptor that targets inactive 26S proteasomes by concurrent interactions with ubiquitylated proteasome subunits/targets and lipidated ATG8 lining the enveloping autophagic membranes.","DOI":"10.1016/j.molcel.2015.04.023","ISSN":"1097-4164","note":"PMID: 26004230\nPMCID: PMC4903074","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"Li","given":"Faqiang"},{"family":"Gemperline","given":"David C."},{"family":"Book","given":"Adam J."},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2015",6,18]]}}},{"id":127,"uris":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"uri":["http://zotero.org/users/4604651/items/ZVQGSSN8"],"itemData":{"id":127,"type":"article-journal","title":"Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles","container-title":"The Journal of Biological Chemistry","page":"3239-3253","volume":"291","issue":"7","source":"PubMed","abstract":"The proteasome is responsible for the degradation of many cellular proteins. If and how this abundant and normally stable complex is degraded by cells is largely unknown. Here we show that in yeast, upon nitrogen starvation, proteasomes are targeted for vacuolar degradation through autophagy. Using GFP-tagged proteasome subunits, we observed that autophagy of a core particle (CP) subunit depends on the deubiquitinating enzyme Ubp3, although a regulatory particle (RP) subunit does not. Furthermore, upon blocking of autophagy, RP remained largely nuclear, although CP largely localized to the cytosol as well as granular structures within the cytosol. In all, our data reveal a regulated process for the removal of proteasomes upon nitrogen starvation. This process involves CP and RP dissociation, nuclear export, and independent vacuolar targeting of CP and RP. Thus, in addition to the well characterized transcriptional up-regulation of genes encoding proteasome subunits, cells are also capable of down-regulating cellular levels of proteasomes through proteaphagy.","DOI":"10.1074/jbc.M115.699124","ISSN":"1083-351X","note":"PMID: 26670610\nPMCID: PMC4751371","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Waite","given":"Kenrick A."},{"family":"De-La Mota-Peynado","given":"Alina"},{"family":"Vontz","given":"Gabrielle"},{"family":"Roelofs","given":"Jeroen"}],"issued":{"date-

parts":[["2016",2,12]]}},{"id":20,"uris":["http://zotero.org/users/4604651/items/C9GA3FAW"],"uri":["http://zotero.org/users/4604651/items/C9GA3FAW"],"itemData":{"id":20,"type":"article-journal","title":"p62- and ubiquitin-dependent stress-induced autophagy of the mammalian 26S proteasome","container-title":"Proceedings of the National Academy of Sciences","page":"E7490-E7499","volume":"113","issue":"47","source":"www.pnas.org","abstract":"The ubiquitin-proteasome system and autophagy are the two main proteolytic systems involved in, among other functions, the maintenance of cell integrity by eliminating misfolded and damaged proteins and organelles. Both systems remove their targets after their conjugation with ubiquitin. An interesting, yet incompletely understood problem relates to the fate of the components of the two systems. Here we provide evidence that amino acid starvation enhances polyubiquitination on specific sites of the proteasome, a modification essential for its targeting to the autophagic machinery. The uptake of the ubiquitinated proteasome is mediated by its interaction with the ubiquitin-associated domain of p62/SQSTM1, a process that also requires interaction with LC3. Importantly, deletion of the PB1 domain of p62, which is important for the targeting of ubiquitinated substrates to the proteasome, has no effect on stress-induced autophagy of this proteolytic machinery, suggesting that the domain of p62 that binds to the proteasome determines the function of p62 in either targeting substrates to the proteasome or targeting the proteasome to autophagy.","DOI":"10.1073/pnas.1615455113","ISSN":"0027-8424, 1091-6490","note":"PMID: 27791183","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Cohen-Kaplan","given":"Victoria"},{"family":"Livneh","given":"Ido"},{"family":"Avni","given":"Noa"},{"family":"Fabre","given":"Bertrand"},{"family":"Ziv","given":"Tamar"},{"family":"Kwon","given":"Yong Tae"},{"family":"Ciechanover","given":"Aaron"}],"issued":{"date-parts":[["2016",11,22]]}},"locator":"-"},{"id":126,"uris":["http://zotero.org/users/4604651/items/6ELTIFZH"],"uri":["http://zotero.org/users/4604651/items/6ELTIFZH"],"itemData":{"id":126,"type":"article-journal","title":"Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone","container-title":"Cell Reports","page":"1717-1732","volume":"16","issue":"6","source":"PubMed","abstract":"The autophagic clearance of 26S proteasomes (proteaphagy) is an important homeostatic mechanism within the ubiquitin system that modulates proteolytic capacity and eliminates damaged particles. Here, we define two proteaphagy routes in yeast that respond to either nitrogen starvation or particle inactivation. Whereas the core autophagic machineries required for Atg8 lipidation and vesiculation are essential for both routes, the upstream Atg1 kinase participates only in starvation-induced proteaphagy. Following inactivation, 26S proteasomes become extensively modified with ubiquitin. Although prior studies with Arabidopsis implicated RPN10 in tethering ubiquitylated proteasomes to ATG8 lining the autophagic membranes, yeast proteaphagy employs the evolutionarily distinct receptor Cue5, which simultaneously binds ubiquitin and Atg8. Proteaphagy of inactivated proteasomes also requires the oligomeric Hsp42 chaperone, suggesting that ubiquitylated proteasomes are directed by Hsp42 to insoluble protein deposit (IPOD)-type structures before encapsulation. Together, Cue5 and Hsp42 provide a quality control checkpoint in yeast directed at recycling dysfunctional 26S proteasomes.","DOI":"10.1016/j.celrep.2016.07.015","ISSN":"2211-1247","note":"PMID: 27477278","journalAbbreviation":"Cell Rep","language":"eng","author":[{"family":"Marshall","given":"Richard S."},{"family":"McLoughlin","given":"Fionn"},{"family":"Vierstra","given":"Richard D."}],"issued":{"date-parts":[["2016",8,9]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

Another study has reported that uncontrolled activation of TORC1 in mammalian cells depleted of *TSC2* (encoding a negative regulator of TORC1) and subjected to serum starvation increases the levels of active proteasomes in an Nrf1-dependent manner[165]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a138m3k3iie","properties":{"formattedCitation":"{\\rtf \\super 166\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":125,"uris":["http://zotero.org/users/4604651/items/Q4QKWPRR"],"uri":["http://zotero.org/users/4604651/items/Q4QKWPRR"],"itemData":{"id":125,"type":"article-journal","title":"Coordinated regulation of protein synthesis and degradation by mTORC1","container-title":"Nature","page":"440-443","volume":"513","issue":"7518","source":"www.nature.com","abstract":"Eukaryotic cells coordinately control anabolic and catabolic processes to maintain cell and tissue homeostasis. Mechanistic target of rapamycin complex 1 (mTORC1) promotes nutrient-consuming anabolic processes, such as protein synthesis. Here we show that as well as increasing protein synthesis, mTORC1 activation in mouse and human cells also promotes an increased capacity for protein degradation. Cells with activated mTORC1 exhibited elevated levels of intact and active proteasomes through a global increase in the expression of genes encoding proteasome subunits. The increase in proteasome gene expression, cellular proteasome content, and rates of protein turnover downstream of mTORC1 were all dependent on induction of the transcription factor nuclear factor erythroid-derived 2-related factor 1 (NRF1; also known as NFE2L1). Genetic activation of mTORC1 through loss of the tuberous sclerosis complex tumour suppressors, TSC1 or TSC2, or physiological activation of mTORC1 in response to growth factors or feeding resulted in increased NRF1 expression in cells and tissues. We find that this NRF1-dependent elevation in proteasome levels serves to increase the intracellular pool of amino acids, which thereby influences rates of new protein synthesis. Therefore, mTORC1 signalling increases the efficiency of proteasome-mediated protein degradation for both quality control and as a mechanism to supply substrate for sustained protein synthesis.","DOI":"10.1038/nature13492","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Zhang","given":"Yinan"},{"family":"Nicholatos","given":"Justin"},{"family":"Dreier","given":"John R."},{"family":"Ricoult","given":"Stéphane J. H."},{"family":"Widenmaier","given":"Scott B."},{"family":"Hotamisligil","given":"Gökhan S."},{"family":"Kwiatkowski","given":"David J."},{"family":"Manning","given":"Brendan D."}],"issued":{"date-parts":[["2014",9,18]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. One possible explanation for these contradicting observations lies within the specific experimental conditions used[165], as prolonged hyperactivation of TORC1 in cells cultured in the absence of serum could have elicited adaptive mechanisms leading to increased levels of proteasome.

In line with TORC1 repressing diverse catabolic processes, mTORC1 inhibition increases protein ubiquitination and degradation in human cells. mTORC1-dependent ubiquitination is rather selective as it preferentially targets growth-related factors, such as the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase[166,167]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"acvkg4icq4","properties":{"formattedCitation":"{\\rtf \\super 167,168\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":118,"uris":["http://zotero.org/users/4604651/items/42SRD4WN"],"uri":["http://zotero.org/users/4604651/items/42SRD4WN"],"itemData":{"id":118,"type":"article-journal","title":"mTOR inhibition activates

overall protein degradation by the ubiquitin proteasome system as well as by autophagy","container-title":"Proceedings of the National Academy of Sciences","page":"15790-15797","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Growth factors and nutrients enhance protein synthesis and suppress overall protein degradation by activating the protein kinase mammalian target of rapamycin (mTOR). Conversely, nutrient or serum deprivation inhibits mTOR and stimulates protein breakdown by inducing autophagy, which provides the starved cells with amino acids for protein synthesis and energy production. However, it is unclear whether proteolysis by the ubiquitin proteasome system (UPS), which catalyzes most protein degradation in mammalian cells, also increases when mTOR activity decreases. Here we show that inhibiting mTOR with rapamycin or Torin1 rapidly increases the degradation of long-lived cell proteins, but not short-lived ones, by stimulating proteolysis by proteasomes, in addition to autophagy. This enhanced proteasomal degradation required protein ubiquitination, and within 30 min after mTOR inhibition, the cellular content of K48-linked ubiquitinated proteins increased without any change in proteasome content or activity. This rapid increase in UPS-mediated proteolysis continued for many hours and resulted primarily from inhibition of mTORC1 (not mTORC2), but did not require new protein synthesis or key mTOR targets: S6Ks, 4E-BPs, or Ulks. These findings do not support the recent report that mTORC1 inhibition reduces proteolysis by suppressing proteasome expression [Zhang Y, et al. (2014) Nature 513(7518):440–443]. Several growth-related proteins were identified that were ubiquitinated and degraded more rapidly after mTOR inhibition, including HMG-CoA synthase, whose enhanced degradation probably limits cholesterol biosynthesis upon insulin deficiency. Thus, mTOR inhibition coordinately activates the UPS and autophagy, which provide essential amino acids and, together with the enhanced ubiquitination of anabolic proteins, help slow growth.","DOI":"10.1073/pnas.1521919112","ISSN":"0027-8424, 1091-6490","note":"PMID:
26669439","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Zhao","given":"Jinghui"},{"family":"Zhai","given":"Bo"},{"family":"Gygi","given":"Steven P."},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}},{"id":117,"uris":["http://zotero.org/users/4604651/items/2PG8K5D4"],"uri":["http://zotero.org/users/4604651/items/2PG8K5D4"],"itemData":{"id":117,"type":"article-journal","title":"Coordinate regulation of autophagy and the ubiquitin proteasome system by MTOR","container-title":"Autophagy","page":"1967-1970","volume":"12","issue":"10","source":"Taylor and Francis+NEJM","abstract":"Proteins in eukaryotic cells are continually being degraded to amino acids either by the ubiquitin proteasome system (UPS) or by the autophagic-lysosomal pathway. The breakdown of proteins by these 2 degradative pathways involves totally different enzymes that function in distinct subcellular compartments. While most studies of the UPS have focused on the selective ubiquitination and breakdown of specific cell proteins, macroautophagy/autophagy is a more global nonselective process. Consequently, the UPS and autophagy were traditionally assumed to serve distinct physiological functions and to be regulated in quite different manners. However, recent findings indicate that protein breakdown by these 2 systems is coordinately regulated by important physiological stimuli. The activation of MTORC1 by nutrients and hormones rapidly suppresses proteolysis by both proteasomes and autophagy, which helps promote protein accumulation, whereas in nutrient-poor conditions, MTORC1 inactivation causes the simultaneous activation of these 2 degradative pathways to supply the deprived cells with a source of amino acids. Also this selective breakdown of key anabolic proteins by the UPS upon MTORC1 inhibition can help limit growth-related processes (e.g., cholesterol biosynthesis). Thus, the collaboration of these 2 degradative systems, together with the simultaneous control of protein translation by MTORC1, provide clear advantages to the organism in both growth and starvation conditions.","DOI":"10.1080/15548627.2016.1205770","ISSN":"1554-8627","note":"PMID:

27459110","author":[{"family":"Zhao","given":"Jinghui"},{"family":"Goldberg","given":"Alfred L."}],"issued":{"date-parts":[["2016",10,2]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

Amino acid homeostasis plays a central role integrating proteasome assembly and abundance with growth and cellular metabolism. The proteasome is not only important as a protein destruction machine but also to recycle amino acids, and proteasome inhibition results in a shortage of amino acids [12,168]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a8lb25f6ot","properties":{"formattedCitation":"{\\rtf \\super 12,169\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":97,"uris":["http://zotero.org/users/4604651/items/8GWU56TD"],"uri":["http://zotero.org/users/4604651/items/8GWU56TD"],"itemData":{"id":97,"type":"article-journal","title":"Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition","container-title":"Molecular Cell","page":"242-253","volume":"48","issue":"2","source":"ScienceDirect","abstract":"The ubiquitin-proteasome system targets many cellular proteins for degradation and thereby controls most cellular processes. Although it is well established that proteasome inhibition is lethal, the underlying mechanism is unknown. Here, we show that proteasome inhibition results in a lethal amino acid shortage. In yeast, mammalian cells, and flies, the deleterious consequences of proteasome inhibition are rescued by amino acid supplementation. In all three systems, this rescuing effect occurs without noticeable changes in the levels of proteasome substrates. In mammalian cells, the amino acid scarcity resulting from proteasome inhibition is the signal that causes induction of both the integrated stress response and autophagy, in an unsuccessful attempt to replenish the pool of intracellular amino acids. These results reveal that cells can tolerate protein waste, but not the amino acid scarcity resulting from proteasome inhibition.","DOI":"10.1016/j.molcel.2012.08.003","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Suraweera","given":"Amila"},{"family":"Münch","given":"Christian"},{"family":"Hanssum","given":"Ariane"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2012",10,26]]}}},{"id":533,"uris":["http://zotero.org/users/4604651/items/YKQRN2MT"],"uri":["http://zotero.org/users/4604651/items/YKQRN2MT"],"itemData":{"id":533,"type":"article-journal","title":"Protein synthesis upon acute nutrient restriction relies on proteasome function","container-title":"Science (New York, N.Y.)","page":"1960-1963","volume":"310","issue":"5756","source":"PubMed","abstract":"The mechanisms that protect mammalian cells against amino acid deprivation are only partially understood. We found that during an acute decrease in external amino acid supply, before up-regulation of the autophagosomal-lysosomal pathway, efficient translation was ensured by proteasomal protein degradation. Amino acids for the synthesis of new proteins were supplied by the degradation of preexisting proteins, whereas nascent and newly formed polypeptides remained largely protected from proteolysis. Proteasome inhibition during nutrient deprivation caused rapid amino acid depletion and marked impairment of translation. Thus, the proteasome plays a crucial role in cell survival after acute disruption of amino acid supply.","DOI":"10.1126/science.1121925","ISSN":"1095-9203","note":"PMID: 16373576","journalAbbreviation":"Science","language":"eng","author":[{"family":"Vabulas","given":"Ramunas M."},{"family":"Hartl","given":"F. Ulrich"}],"issued":{"date-parts":[["2005",12,23]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a5bcn9sar8","properties":{"formattedCitation":"{\\rtf \\super

12\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":97,"uris":["http://zotero.org/users/4604651/items/8GWU56TD"],"uri":["http://zotero.org/users/4604651/items/8GWU56TD"],"itemData":{"id":97,"type":"article-journal","title":"Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition","container-title":"Molecular Cell","page":"242-253","volume":"48","issue":"2","source":"ScienceDirect","abstract":"The ubiquitin-proteasome system targets many cellular proteins for degradation and thereby controls most cellular processes. Although it is well established that proteasome inhibition is lethal, the underlying mechanism is unknown. Here, we show that proteasome inhibition results in a lethal amino acid shortage. In yeast, mammalian cells, and flies, the deleterious consequences of proteasome inhibition are rescued by amino acid supplementation. In all three systems, this rescuing effect occurs without noticeable changes in the levels of proteasome substrates. In mammalian cells, the amino acid scarcity resulting from proteasome inhibition is the signal that causes induction of both the integrated stress response and autophagy, in an unsuccessful attempt to replenish the pool of intracellular amino acids. These results reveal that cells can tolerate protein waste, but not the amino acid scarcity resulting from proteasome inhibition.","DOI":"10.1016/j.molcel.2012.08.003","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Suraweera","given":"Amila"},{"family":"Münch","given":"Christian"},{"family":"Hanssum","given":"Ariane"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2012",10,26]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (FIG. 6). The importance of supplying amino acids is highlighted by the observation that proteasome inhibition is lethal for cells and organisms[83,169,170]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a10rekcg88k","properties":{"formattedCitation":"{\\rtf \\super 83,170,171\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":124,"uris":["http://zotero.org/users/4604651/items/VTMZAJQ7"],"uri":["http://zotero.org/users/4604651/items/VTMZAJQ7"],"itemData":{"id":124,"type":"article-journal","title":"Rpn10-Mediated Degradation of Ubiquitinated Proteins Is Essential for Mouse Development","container-title":"Molecular and Cellular Biology","page":"6629-6638","volume":"27","issue":"19","source":"mcb.asm.org","abstract":"Rpn10 is a subunit of the 26S proteasome that recognizes polyubiquitinated proteins. The importance of Rpn10 in ubiquitin-mediated proteolysis is debatable, since a deficiency of Rpn10 causes different phenotypes in different organisms. To date, the role of mammalian Rpn10 has not been examined genetically. Moreover, vertebrates have five splice variants of Rpn10 whose expressions are developmentally regulated, but their biological significance is not understood. To address these issues, we generated three kinds of Rpn10 mutant mice. Rpn10 knockout resulted in early-embryonic lethality, demonstrating the essential role of Rpn10 in mouse development. Rpn10a knock-in mice, which exclusively expressed the constitutive type of Rpn10 and did not express vertebrate-specific variants, grew normally, indicating that Rpn10 diversity is not essential for conventional development. Mice expressing the N-terminal portion of Rpn10, which contained a von Willebrand factor A (VWA) domain but lacked ubiquitin-interacting motifs (Rpn10ΔUIM), also exhibited embryonic lethality, suggesting the important contribution of UIM domains to viability, but survived longer than Rpn10-null mice, consistent with a “facilitator” function of the VWA domain. Biochemical analysis of the Rpn10ΔUIM liver showed specific impairment of degradation of ubiquitinated proteins. Our results demonstrate that Rpn10-mediated degradation of ubiquitinated proteins, catalyzed by UIMs, is indispensable for mammalian life.","DOI":"10.1128/MCB.00509-07","ISSN":"0270-7306, 1098-5549","note":"PMID: 17646385","journalAbbreviation":"Mol. Cell. Biol.","language":"en","author":[{"family":"Hamazaki","given":"Jun"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Kawahara","gi

ven":"Hiroyuki"},{"family":"Hisanaga","given":"Shin-ichi"},{"family":"Tanaka","given":"Keiji"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2007",10,1]]}},{"id":116,"uris":["http://zotero.org/users/4604651/items/AR5GLG4U"],"uri":["http://zotero.org/users/4604651/items/AR5GLG4U"],"itemData":{"id":116,"type":"article-journal","title":"Proteasomes are essential for yeast proliferation. cDNA cloning and gene disruption of two major subunits","container-title":"The Journal of Biological Chemistry","page":"16604-16613","volume":"265","issue":"27","source":"PubMed","abstract":"The cDNAs encoding two major subunits, named YC1 and YC7-alpha, of yeast proteasomes (multicatalytic proteinase complexes) were isolated and sequenced. As deduced from their nucleotide sequences, YC1 and YC7-alpha consist of 288 and 252 amino acid residues with calculated molecular weights of 31,534 and 27,999, respectively. They showed marked sequence homology to other eukaryotic proteasome components, suggesting that proteasomes are composed of a family of subunits with the same evolutional origin. To obtain information on the physiological role of proteasomes, we disrupted the chromosomal genes of YC1 and YC7-alpha of yeast cells independently, using isolated cDNA clones. Disruption of the coding region of one copy of the YC1 gene in diploid yeast created a recessive lethal mutation, but disruption of the 3'-noncoding region of the gene had no effect on cell proliferation. Disruption of the YC7-alpha gene also had a lethal effect on haploid yeast cells. These findings demonstrated that YC1 and YC7-alpha are both encoded by a single copy gene and that these genes are essential for proliferation of yeast cells.","ISSN":"0021-9258","note":"PMID: 1697860","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Fujiwara","given":"T."},{"family":"Tanaka","given":"K."},{"family":"Orino","given":"E."},{"family":"Yoshimura","given":"T."},{"family":"Kumatori","given":"A."},{"family":"Tamura","given":"T."},{"family":"Chung","given":"C. H."},{"family":"Nakai","given":"T."},{"family":"Yamaguchi","given":"K."},{"family":"Shin","given":"S."}],"issued":{"date-parts":[["1990",9,25]]}},{"id":115,"uris":["http://zotero.org/users/4604651/items/LF6AJ32K"],"uri":["http://zotero.org/users/4604651/items/LF6AJ32K"],"itemData":{"id":115,"type":"webpage","title":"Genetics of Proteasome Diseases","container-title":"Scientifica","genre":"Research article","abstract":"The proteasome is a large, multiple subunit complex that is capable of degrading most intracellular proteins. Polymorphisms in proteasome subunits are associated with cardiovascular diseases, diabetes, neurological diseases, and cancer. One polymorphism in the proteasome gene PSMA6 (−8C/G) is associated with three different diseases: type 2 diabetes, myocardial infarction, and coronary artery disease. One type of proteasome, the immunoproteasome, which contains inducible catalytic subunits, is adapted to generate peptides for antigen presentation. It has recently been shown that mutations and polymorphisms in the immunoproteasome catalytic subunit PSMB8 are associated with several inflammatory and autoinflammatory diseases including Nakajo-Nishimura syndrome, CANDLE syndrome, and intestinal M. tuberculosis infection. This comprehensive review describes the disease-related polymorphisms in proteasome genes associated with human diseases and the physiological modulation of proteasome function by these polymorphisms. Given the large number of subunits and the central importance of the proteasome in human physiology as well as the fast pace of detection of proteasome polymorphisms associated with human diseases, it is likely that other polymorphisms in proteasome genes associated with diseases will be detected in the near future. While disease-associated polymorphisms are now readily discovered, the challenge will be to use this genetic information for clinical benefit.","URL":"https://www.hindawi.com/journals/scientifica/2013/637629/","note":"PMID: 24490108\nDOI: 10.1155/2013/637629","language":"en","author":[{"family":"Gomes","given":"Aldrin V."}],"issued":{"date-parts":[["2013"]]},"accessed":{"date-parts":[["2017",8,15]]}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} }, but yeast and mammalian cells as wells flies survive proteasome inhibition when supplemented with amino acids[12]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1tpqf4lcen","properties":{"formattedCitation":"{\\rtf \\super 12\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":97,"uris":["http://zotero.org/users/4604651/items/8GWU56TD"],"uri":["http://zotero.org/users/4604651/items/8GWU56TD"],"itemData":{"id":97,"type":"article-journal","title":"Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition","container-title":"Molecular Cell","page":"242-253","volume":"48","issue":"2","source":"ScienceDirect","abstract":"The ubiquitin-proteasome system targets many cellular proteins for degradation and thereby controls most cellular processes. Although it is well established that proteasome inhibition is lethal, the underlying mechanism is unknown. Here, we show that proteasome inhibition results in a lethal amino acid shortage. In yeast, mammalian cells, and flies, the deleterious consequences of proteasome inhibition are rescued by amino acid supplementation. In all three systems, this rescuing effect occurs without noticeable changes in the levels of proteasome substrates. In mammalian cells, the amino acid scarcity resulting from proteasome inhibition is the signal that causes induction of both the integrated stress response and autophagy, in an unsuccessful attempt to replenish the pool of intracellular amino acids. These results reveal that cells can tolerate protein waste, but not the amino acid scarcity resulting from proteasome inhibition.","DOI":"10.1016/j.molcel.2012.08.003","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Suraweera","given":"Amila"},{"family":"Münch","given":"Christian"},{"family":"Hanssum","given":"Ariane"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2012",10,26]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }.

The amino acid scarcity resulting from proteasome inhibition causes a starvation-associated stress that signals to induce both the integrated stress response **[G]** and autophagy[12], in an attempt to rescue amino acid homeostasis. The integrated stress response consists in decreasing the rates of protein synthesis, thereby decreasing the consumption of amino acids when the supply is limited. In parallel, cells induce autophagy to recycle intracellular components and thereby provide nutrients to compensate for the shortage resulting from proteasome inhibition (FIG. 6). Thus, amino acid scarcity is a signal that activates autophagy when the proteasome is inhibited and this occurs through TORC1[12]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2hvoueei3e","properties":{"formattedCitation":"{\\rtf \\super 12\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":97,"uris":["http://zotero.org/users/4604651/items/8GWU56TD"],"uri":["http://zotero.org/users/4604651/items/8GWU56TD"],"itemData":{"id":97,"type":"article-journal","title":"Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition","container-title":"Molecular Cell","page":"242-253","volume":"48","issue":"2","source":"ScienceDirect","abstract":"The ubiquitin-proteasome system targets many cellular proteins for degradation and thereby controls most cellular processes. Although it is well established that proteasome inhibition is lethal, the underlying mechanism is unknown. Here, we show that proteasome inhibition results in a lethal amino acid shortage. In yeast, mammalian cells, and flies, the deleterious consequences of proteasome inhibition are rescued by amino acid supplementation. In all three systems, this rescuing effect occurs without noticeable changes in the levels of proteasome substrates. In mammalian cells, the amino acid scarcity resulting from

proteasome inhibition is the signal that causes induction of both the integrated stress response and autophagy, in an unsuccessful attempt to replenish the pool of intracellular amino acids. These results reveal that cells can tolerate protein waste, but not the amino acid scarcity resulting from proteasome inhibition.","DOI":"10.1016/j.molcel.2012.08.003","ISSN":"1097-2765","journalAbbreviation":"Molecular Cell","author":[{"family":"Suraweera","given":"Amila"},{"family":"Münch","given":"Christian"},{"family":"Hanssum","given":"Ariane"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2012",10,26]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Similar to proteasome inhibition, inhibition of the regulator of proteasomal degradation p97 **[G]**, also disturbs amino acid homeostasis and, consequently, protein synthesis[171]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"alpmm0ke01","properties":{"formattedCitation":"{\\rtf \\super 172\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":123,"uris":["http://zotero.org/users/4604651/items/Q24WTW5A"],"uri":["http://zotero.org/users/4604651/items/Q24WTW5A"],"itemData":{"id":123,"type":"article-journal","title":"Inadequate fine-tuning of protein synthesis and failure of amino acid homeostasis following inhibition of the ATPase VCP/p97","container-title":"Cell Death & Disease","page":"e2031","volume":"6","source":"PubMed","abstract":"The cellular mechanisms that control protein degradation may constitute a non-oncogenic cancer cell vulnerability and, therefore, a therapeutic target. Although this proposition is supported by the clinical success of proteasome inhibitors in some malignancies, most cancers are resistant to proteasome inhibition. The ATPase valosin-containing protein (VCP; p97) is an essential regulator of protein degradation in multiple pathways and has emerged as a target for cancer therapy. We found that pharmacological depletion of VCP enzymatic activity with mechanistically different inhibitors robustly induced proteotoxic stress in solid cancer and multiple myeloma cells, including cells that were insensitive, adapted, or clinically resistant to proteasome inhibition. VCP inhibition had an impact on two key regulators of protein synthesis, eukaryotic initiation factor 2α (eIF2α) and mechanistic target of rapamycin complex 1 (mTORC1), and attenuated global protein synthesis. However, a block on protein translation that was itself cytotoxic alleviated stress signaling and reduced cell death triggered by VCP inhibition. Some of the proteotoxic effects of VCP depletion depended on the eIF2α phosphatase, protein phosphatase 1 regulatory subunit 15A (PPP1R15A)/PP1c, but not on mTORC1, although there appeared to be cross-talk between them. Thus, cancer cell death following VCP inhibition was linked to inadequate fine-tuning of protein synthesis and activity of PPP1R15A/PP1c. VCP inhibitors also perturbed intracellular amino acid levels, activated eukaryotic translation initiation factor 2α kinase 4 (EIF2AK4), and enhanced cellular dependence on amino acid supplies, consistent with a failure of amino acid homeostasis. Many of the observed effects of VCP inhibition differed from the effects triggered by proteasome inhibition or by protein misfolding. Thus, depletion of VCP enzymatic activity triggers cancer cell death in part through inadequate regulation of protein synthesis and amino acid metabolism. The data provide novel insights into the maintenance of intracellular proteostasis by VCP and may have implications for the development of anti-cancer therapies.","DOI":"10.1038/cddis.2015.373","ISSN":"2041-4889","note":"PMID: 26720340\nPMCID: PMC4720905","journalAbbreviation":"Cell Death Dis","language":"eng","author":[{"family":"Parzych","given":"K."},{"family":"Chinn","given":"T. M."},{"family":"Chen","given":"Z."},{"family":"Loaiza","given":"S."},{"family":"Porsch","given":"F."},{"family":"Valbuena","given":"G. N."},{"family":"Kleijnen","given":"M. F."},{"family":"Karadimitris","given":"A."},{"family":"Gentleman","given":"E."},{"family":"Keun","given":"H.

C."},{"family":"Auner","given":"H. W."}],"issued":{"date-parts":[["2015",12,31]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. This further supports the notion that one of the vital functions of the proteasome is to recycle amino acids.

[H1] Proteasome deregulation in aging and disease

The proteasome degrades a very large number of cellular proteins and in this way, control many cellular processes. With such a central role, it is not surprising that dysfunction of the proteasome is associated with diverse diseases.

[H2] Neurodegeneration

Dysfunctions of the proteasome have been associated with a broad range of diseases. Failure to degrade abnormal, misfolded, mutant or damaged proteins leads to their accumulation, which can be deleterious for cells. The accumulation of proteins of abnormal conformation in the form of insoluble aggregates is associated with age-related and is hallmark of neurodegenerative diseases[153,172], suggesting that the cellular capacity to neutralize aggregation-prone proteins declines with age. Indeed, although aging is probably a multi-component problem, a decline in proteasomal degradation has been associated with ageing (see references[173–175] for excellent reviews on this topic){ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a23n27fadpr","properties":{"formattedCitation":"{\\rtf \\super 173\\uc0\\u8211{}176\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":114,"uris":["http://zotero.org/users/4604651/items/PBMQ36JN"],"uri":["http://zotero.org/users/4604651/items/PBMQ36JN"],"itemData":{"id":114,"type":"article-journal","title":"Proteasome activation delays aging in vitro and in vivo","container-title":"Free Radical Biology & Medicine","page":"303-320","volume":"71","source":"PubMed","abstract":"Aging is a natural biological process that is characterized by a progressive accumulation of macromolecular damage. In the proteome, aging is accompanied by decreased protein homeostasis and function of the major cellular proteolytic systems, leading to the accumulation of unfolded, misfolded, or aggregated proteins. In particular, the proteasome is responsible for the removal of normal as well as damaged or misfolded proteins. Extensive work during the past several years has clearly demonstrated that proteasome activation by either genetic means or use of compounds significantly retards aging. Importantly, this represents a common feature across evolution, thereby suggesting proteasome activation to be an evolutionarily conserved mechanism of aging and longevity regulation. This review article reports on the means of function of these proteasome activators and how they regulate aging in various species.","DOI":"10.1016/j.freeradbiomed.2014.03.031","ISSN":"1873-4596","note":"PMID: 24681338","journalAbbreviation":"Free Radic. Biol. Med.","language":"eng","author":[{"family":"Chondrogianni","given":"Niki"},{"family":"Sakellari","given":"Marianthi"},{"family":"Lefaki","given":"Maria"},{"family":"Papaevgeniou","given":"Nikoletta"},{"family":"Gonos","given":"Efstathios S."}],"issued":{"date-parts":[["2014",6]]}}},{"id":113,"uris":["http://zotero.org/users/4604651/items/Y3UZEV4P"],"uri":["http://zotero.org/users/4604651/items/

Y3UZEV4P"],"itemData":{"id":113,"type":"article-journal","title":"The Mechanistic Links Between Proteasome Activity, Aging and Age-related Diseases","container-title":"Current Genomics","page":"38-51","volume":"15","issue":"1","source":"PubMed","abstract":"Damaged and misfolded proteins accumulate during the aging process, impairing cell function and tissue homeostasis. These perturbations to protein homeostasis (proteostasis) are hallmarks of age-related neurodegenerative disorders such as Alzheimer's, Parkinson's or Huntington's disease. Damaged proteins are degraded by cellular clearance mechanisms such as the proteasome, a key component of the proteostasis network. Proteasome activity declines during aging, and proteasomal dysfunction is associated with late-onset disorders. Modulation of proteasome activity extends lifespan and protects organisms from symptoms associated with proteostasis disorders. Here we review the links between proteasome activity, aging and neurodegeneration. Additionally, strategies to modulate proteasome activity and delay the onset of diseases associated to proteasomal dysfunction are discussed herein.","DOI":"10.2174/1389202915011403061133 44","ISSN":"1389-2029","note":"PMID: 24653662\nPMCID: PMC3958958","journalAbbreviation":"Curr. Genomics","language":"eng","author":[{"family":"Saez","given":"Isabel"},{"family":"Vilchez","given":"David"}],"issued":{"date-parts":[["2014",2]]}},{"id":122,"uris":["http://zotero.org/users/4604651/items/JQNS66NI"],"uri":["http://zotero.org/users/4604651/items/JQNS66NI"],"itemData":{"id":122,"type":"article-journal","title":"Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases.","container-title":"Ageing research reviews","page":"37-55","volume":"23","issue":"Pt A","source":"europepmc.org","abstract":"Abstract: Aging is a natural process accompanied by a progressive accumulation of damage in all constituent macromolecules (nucleic acids, lipids and...","DOI":"10.1016/j.arr.2014.12.003","ISSN":"1568-1637","note":"PMID: 25540941","shortTitle":"Proteasome activation","journalAbbreviation":"Ageing Res Rev","language":"eng","author":[{"family":"N","given":"Chondrogianni"},{"family":"K","given":"Voutetakis"},{"family":"M","given":"Kapetanou"},{"family":"V","given":"Delitsikou"},{"family":"N","given":"Papaevgeniou"},{"family":"M","given":"Sakellari"},{"family":"M","given":"Lefaki"},{"family":"K","given":"Filippopoulou"},{"family":"Es","given":"Gonos"}],"issued":{"date-parts":[["2015",9]]}},{"id":108,"uris":["http://zotero.org/users/4604651/items/PNXHG7D5"],"uri":["http://zotero.org/users/4604651/items/PNXHG7D5"],"itemData":{"id":108,"type":"article-journal","title":"The role of protein clearance mechanisms in organismal ageing and age-related diseases","container-title":"Nature Communications","page":"ncomms6659","volume":"5","source":"www.nature.com","abstract":" \nProteins are subject to continuous and complex quality-control mechanisms, which ensure integrity of the proteome. Vilchez et al. review how a demise in these processes, collectively referred to as proteostasis, is linked to organismal ageing and the development o… ","DOI":"10.1038/ncomms6659","ISSN":"2041-1723","language":"en","author":[{"family":"Vilchez","given":"David"},{"family":"Saez","given":"Isabel"},{"family":"Dillin","given":"Andrew"}],"issued":{"date-parts":[["2014",12,8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}.

As protein degradation has a crucial role in preventing the accumulation of aggregation-prone proteins, a lot of effort has been invested in trying to increase the cellular capacity for protein degradation with the view that this could slow down aging or neurodegenerative diseases. For example, increasing the cellular autophagic capacity, by inhibition of mTOR1 for

example, has received a lot of attention[151]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1tkj8v7ko0","properties":{"formattedCitation":"{\\rtf \\super 151\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":128,"uris":["http://zotero.org/users/4604651/items/Q95GN4F3"],"uri":["http://zotero.org/users/4604651/items/Q95GN4F3"],"itemData":{"id":128,"type":"article-journal","title":"Proteasomal and Autophagic Degradation Systems","container-title":"Annual Review of Biochemistry","page":"193-224","volume":"86","issue":"1","source":"Annual Reviews","abstract":"Autophagy and the ubiquitin–proteasome system are the two major quality control pathways responsible for cellular homeostasis. As such, they provide protection against age-associated changes and a plethora of human diseases. Ubiquitination is utilized as a degradation signal by both systems, albeit in different ways, to mark cargoes for proteasomal and lysosomal degradation. Both systems intersect and communicate at multiple points to coordinate their actions in proteostasis and organelle homeostasis. This review summarizes molecular details of how proteasome and autophagy pathways are functionally interconnected in cells and indicates common principles and nodes of communication that can be therapeutically exploited.","DOI":"10.1146/annurev-biochem-061516-044908","note":"PMID: 28460188","author":[{"family":"Dikic","given":"Ivan"}],"issued":{"date-parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. This is because protein aggregates associated with neurodegenerative diseases are thought to be too big to be degraded by the proteasome. However, as discussed above, inhibition of TORC1 not only increases autophagy but also proteasomal degradation[106,167]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"avhf1birif","properties":{"formattedCitation":"{\\rtf \\super 106,167\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}}},{"id":118,"uris":["http://zotero.org/users/4604651/items/42SRD4WN"],"uri":["http://zotero.org/users/4604651/items/42SRD4WN"],"itemData":{"id":118,"type":"article-journal","title":"mTOR inhibition activates overall protein degradation by the

ubiquitin proteasome system as well as by autophagy","container-title":"Proceedings of the National Academy of Sciences","page":"15790-15797","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Growth factors and nutrients enhance protein synthesis and suppress overall protein degradation by activating the protein kinase mammalian target of rapamycin (mTOR). Conversely, nutrient or serum deprivation inhibits mTOR and stimulates protein breakdown by inducing autophagy, which provides the starved cells with amino acids for protein synthesis and energy production. However, it is unclear whether proteolysis by the ubiquitin proteasome system (UPS), which catalyzes most protein degradation in mammalian cells, also increases when mTOR activity decreases. Here we show that inhibiting mTOR with rapamycin or Torin1 rapidly increases the degradation of long-lived cell proteins, but not short-lived ones, by stimulating proteolysis by proteasomes, in addition to autophagy. This enhanced proteasomal degradation required protein ubiquitination, and within 30 min after mTOR inhibition, the cellular content of K48-linked ubiquitinated proteins increased without any change in proteasome content or activity. This rapid increase in UPS-mediated proteolysis continued for many hours and resulted primarily from inhibition of mTORC1 (not mTORC2), but did not require new protein synthesis or key mTOR targets: S6Ks, 4E-BPs, or Ulks. These findings do not support the recent report that mTORC1 inhibition reduces proteolysis by suppressing proteasome expression [Zhang Y, et al. (2014) Nature 513(7518):440–443]. Several growth-related proteins were identified that were ubiquitinated and degraded more rapidly after mTOR inhibition, including HMG-CoA synthase, whose enhanced degradation probably limits cholesterol biosynthesis upon insulin deficiency. Thus, mTOR inhibition coordinately activates the UPS and autophagy, which provide essential amino acids and, together with the enhanced ubiquitination of anabolic proteins, help slow growth.","DOI":"10.1073/pnas.1521919112","ISSN":"0027-8424, 1091-6490","note":"PMID: 26669439","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Zhao","given":"Jinghui"},{"family":"Zhai","given":"Bo"},{"family":"Gygi","given":"Steven P."},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Thus, it will be interesting to re-evaluate the contribution of proteasomal degradation in the reported benefits of TORC1 inhibitors. It is also important to keep in mind that whilst protein aggregates may be too big to be degraded by the proteasome, the precursors of these aggregates, mutant Huntingtin, α-synuclein, SOD1, are proteasome substrates[176]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ars0l5api7","properties":{"formattedCitation":"{\\rtf \\super 177\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":535,"uris":["http://zotero.org/users/4604651/items/IVLLVKNE"],"uri":["http://zotero.org/users/4604651/items/IVLLVKNE"],"itemData":{"id":535,"type":"chapter","title":"The Ubiquitin–Proteasome System in Neurodegenerative Diseases: More than the Usual Suspects","container-title":"Protein Chaperones and Protection from Neurodegenerative Diseases","publisher":"Wiley-Blackwell","page":"179-210","source":"Wiley Online Library","abstract":"This chapter contains sections titled: Ubiquitinated Protein Deposits: The Hallmark of Neurodegenerative Diseases The Proteasome Assessing Proteasome Degradation Monitoring Proteasome Dysfunction The Ubiquitin–Proteasome System in Neurodegenerative Diseases: Facts and Discrepancies Proteasome Impairment by Expanded Polyq-Containing Proteins Proteasome

ATPases and Inclusion Formation: More than the Usual Suspects Concluding Note Acknowledgment References","URL":"https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118063903.ch5","ISBN":"978-1-118-06390-3","note":"DOI: 10.1002/9781118063903.ch5","shortTitle":"The Ubiquitin–Proteasome System in Neurodegenerative Diseases","language":"en","author":[{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2011"]]},"accessed":{"date-parts":[["2018",4,20]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. Thus, increasing proteasomal degradation in a controlled manner to decrease accumulation of misfolded proteins, before they form large inclusions, is an attractive possibility. Inhibitors of the proteasome-associated DUB USP14 have been proposed for such a purpose[85]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"akhbsh9vdp","properties":{"formattedCitation":"{\\rtf \\super 85\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":391,"uris":["http://zotero.org/users/4604651/items/N54J53VP"],"uri":["http://zotero.org/users/4604651/items/N54J53VP"],"itemData":{"id":391,"type":"article-journal","title":"Enhancement of proteasome activity by a small-molecule inhibitor of USP14","container-title":"Nature","page":"179-184","volume":"467","issue":"7312","source":"PubMed","abstract":"Proteasomes, the primary mediators of ubiquitin-protein conjugate degradation, are regulated through complex and poorly understood mechanisms. Here we show that USP14, a proteasome-associated deubiquitinating enzyme, can inhibit the degradation of ubiquitin-protein conjugates both in vitro and in cells. A catalytically inactive variant of USP14 has reduced inhibitory activity, indicating that inhibition is mediated by trimming of the ubiquitin chain on the substrate. A high-throughput screen identified a selective small-molecule inhibitor of the deubiquitinating activity of human USP14. Treatment of cultured cells with this compound enhanced degradation of several proteasome substrates that have been implicated in neurodegenerative disease. USP14 inhibition accelerated the degradation of oxidized proteins and enhanced resistance to oxidative stress. Enhancement of proteasome activity through inhibition of USP14 may offer a strategy to reduce the levels of aberrant proteins in cells under proteotoxic stress.","DOI":"10.1038/nature09299","ISSN":"1476-4687","note":"PMID: 20829789\nPMCID: PMC2939003","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Lee","given":"Byung-Hoon"},{"family":"Lee","given":"Min Jae"},{"family":"Park","given":"Soyeon"},{"family":"Oh","given":"Dong-

Chan"},{"family":"Elsasser","given":"Suzanne"},{"family":"Chen","given":"Ping-Chung"},{"family":"Gartner","given":"Carlos"},{"family":"Dimova","given":"Nevena"},{"family":"Hanna","given":"John"},{"family":"Gygi","given":"Steven P."},{"family":"Wilson","given":"Scott M."},{"family":"King","given":"Randall W."},{"family":"Finley","given":"Daniel"}],"issued":{"date-parts":[["2010",9,9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } , although this has been the subject of controversies[177]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1nk98uq46s","properties":{"formattedCitation":"{\\rtf \\super 178\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":537,"uris":["http://zotero.org/users/4604651/items/8BKXRW4F"],"uri":["http://zotero.org/users/4604651/items/8BKXRW4F"],"itemData":{"id":537,"type":"article-journal","title":"Genetic Background Alters the Severity and Onset of Neuromuscular Disease Caused by the Loss of Ubiquitin-Specific Protease 14 (Usp14)","container-title":"PLOS ONE","page":"e84042","volume":"8","issue":"12","source":"PLoS Journals","abstract":"In this study, we identified and characterized an N-ethyl-N-nitrosourea (ENU) induced mutation in Usp14 (nmf375) that leads to adult-onset neurological disease. The nmf375 mutation causes aberrant splicing of Usp14 mRNA, resulting in a 95% reduction in USP14. We previously showed that loss of USP14 in ataxia (axJ) mice results in reduced ubiquitin levels, motor endplate disease, Purkinje cell axonal dystrophy and decreased hippocampal paired pulse facilitation (PPF) during the first 4-6 weeks of life, and early postnatal lethality by two months of age. Although the loss of USP14 is comparable between the nmf375 and axJ mice, the nmf375 mice did not exhibit these axJ developmental abnormalities. However, by 12 weeks of age the nmf375 mutants present with ubiquitin depletion and motor endplate disease, indicating a continual role for USP14-mediated regulation of ubiquitin pools and neuromuscular junction (NMJ) structure in adult mice. The observation that motor endplate disease was only seen after ubiquitin depletion suggests that the preservation of NMJ structure requires the stable maintenance of synaptic ubiquitin pools. Differences in genetic background were shown to affect ubiquitin expression and dramatically alter the phenotypes caused by USP14 deficiency.","DOI":"10.1371/journal.pone.0084042","ISSN":"1932-6203","journalAbbreviation":"PLOS ONE","language":"en","author":[{"family":"Marshall","given":"Andrea G."},{"family":"Watson","given":"Jennifer A."},{"family":"Hallengren","given":"Jada J."},{"family":"Walters","given":"Brandon J."},{"family":"Dobrunz","given":"Lynn

E."},{"family":"Francillon","given":"Ludwig"},{"family":"Wilson","given":"Julie A."},{"family":"Phillips","given":"Scott E."},{"family":"Wilson","given":"Scott M."}],"issued":{"date-parts":[["2013",12,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. Uncovering new nodes of regulation of proteasomal degradation provides new opportunities to manipulate this system for potential therapeutics.

[H2] Targeting the proteasome in cancer

Age is also one of the greatest risk factors for cancer[178,179] { ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a28ekp5jlic","properties":{"formattedCitation":"{\\rtf \\super 179,180\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":112,"uris":["http://zotero.org/users/4604651/items/MIE65ULG"],"uri":["http://zotero.org/users/4604651/items/MIE65ULG"],"itemData":{"id":112,"type":"article-journal","title":"The Hallmarks of Aging","container-title":"Cell","page":"1194-1217","volume":"153","issue":"6","source":"www.cell.com","abstract":"Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. This deterioration is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Aging research has experienced an unprecedented advance over recent years, particularly with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution. This Review enumerates nine tentative hallmarks that represent common denominators of aging in different organisms, with special emphasis on mammalian aging. These hallmarks are: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A major challenge is to dissect the interconnectedness between the candidate hallmarks and their relative contributions to aging, with the final goal of identifying pharmaceutical targets to improve human health during aging, with minimal side effects.","DOI":"10.1016/j.cell.2013.05.039","ISSN":"0092-8674, 1097-4172","journalAbbreviation":"Cell","language":"English","author":[{"family":"López-Otín","given":"Carlos"},{"family":"Blasco","given":"Maria A."},{"family":"Partridge","given":"Linda"},{"family":"Serrano","given":"Manuel"},{"famil

y":"Kroemer","given":"Guido"}],"issued":{"date-parts":[["2013",6,6]]}},{"id":111,"uris":["http://zotero.org/users/4604651/items/H8QRBS6P"],"uri":["http://zotero.org/users/4604651/items/H8QRBS6P"],"itemData":{"id":111,"type":"article-journal","title":"The common biology of cancer and ageing","container-title":"Nature","page":"767-774","volume":"448","issue":"7155","source":"www.nature.com","abstract":"At first glance, cancer and ageing would seem to be unlikely bedfellows. Yet the origins for this improbable union can actually be traced back to a sequence of tragic—and some say unethical—events that unfolded more than half a century ago. Here we review the series of key observations that has led to a complex but growing convergence between our understanding of the biology of ageing and the mechanisms that underlie cancer.","DOI":"10.1038/nature05985","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Finkel","given":"Toren"},{"family":"Serrano","given":"Manuel"},{"family":"Blasco","given":"Maria A."}],"issued":{"date-parts":[["2007",8,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} owing to the age-dependent accumulation of genomic mutations[180]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a22ruih9h2d","properties":{"formattedCitation":"{\\rtf \\super 180\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":111,"uris":["http://zotero.org/users/4604651/items/H8QRBS6P"],"uri":["http://zotero.org/users/4604651/items/H8QRBS6P"],"itemData":{"id":111,"type":"article-journal","title":"The common biology of cancer and ageing","container-title":"Nature","page":"767-774","volume":"448","issue":"7155","source":"www.nature.com","abstract":"At first glance, cancer and ageing would seem to be unlikely bedfellows. Yet the origins for this improbable union can actually be traced back to a sequence of tragic—and some say unethical—events that unfolded more than half a century ago. Here we review the series of key observations that has led to a complex but growing convergence between our understanding of the biology of ageing and the mechanisms that underlie cancer.","DOI":"10.1038/nature05985","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Finkel","given":"Toren"},{"family":"Serrano","given":"Manuel"},{"family":"Blasco","given":"Maria A."}],"issued":{"date-parts":[["2007",8,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Such mutations may cause a change in the levels of protein expression and/or a stochiometric imbalance in expression of subunits of protein complexes. This in turn may cause the accumulation of misfolded or overproduced proteins, potentially explaining why cancer cells are often ‘addicted’ to high levels of proteasomes. This Achille’s heel has been exploited and proteasome inhibitors are used to treat some cancers[180,181]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2oafb3vje6","properties":{"formattedCitation":"{\\rtf \\super 181,182\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":107,"uris":["http://zotero.org/users/4604651/items/MD8CQ33H"],"uri":["http://zotero.org/users/4604651/items/MD8CQ33H"],"itemData":{"id":107,"type":"article-journal","title":"Proteasome inhibitors in cancer

therapy","container-title":"Nature Reviews Clinical Oncology","page":"417-433","volume":"14","issue":"7","source":"www.nature.com","abstract":"The ubiquitin proteasome pathway was discovered in the 1980s to be a central component of the cellular protein-degradation machinery with essential functions in homeostasis, which include preventing the accumulation of misfolded or deleterious proteins. Cancer cells produce proteins that promote both cell survival and proliferation, and/or inhibit mechanisms of cell death. This notion set the stage for preclinical testing of proteasome inhibitors as a means to shift this fine equilibrium towards cell death. Since the late 1990s, clinical trials have been conducted for a variety of malignancies, leading to regulatory approvals of proteasome inhibitors to treat multiple myeloma and mantle-cell lymphoma. First-generation and second-generation proteasome inhibitors can elicit deep initial responses in patients with myeloma, for whom these drugs have dramatically improved outcomes, but relapses are frequent and acquired resistance to treatment eventually emerges. In addition, promising preclinical data obtained with proteasome inhibitors in models of solid tumours have not been confirmed in the clinic, indicating the importance of primary resistance. Investigation of the mechanisms of resistance is, therefore, essential to further maximize the utility of this class of drugs in the era of personalized medicine. Herein, we discuss the advances and challenges resulting from the introduction of proteasome inhibitors into the clinic.","DOI":"10.1038/nrclinonc.2016.206","ISSN":"1759-4774","journalAbbreviation":"Nat Rev Clin Oncol","language":"en","author":[{"family":"Manasanch","given":"Elisabet E."},{"family":"Orlowski","given":"Robert Z."}],"issued":{"date-parts":[["2017",7]]}},{"id":110,"uris":["http://zotero.org/users/4604651/items/V4KZP8TM"],"uri":["http://zotero.org/users/4604651/items/V4KZP8TM"],"itemData":{"id":110,"type":"article-journal","title":"The 26S proteasome is a multifaceted target for anti-cancer therapies","container-title":"Oncotarget","page":"24733-24749","volume":"6","issue":"28","source":"PubMed","abstract":"Proteasomes play a critical role in the fate of proteins that are involved in major cellular processes, including signal transduction, gene expression, cell cycle, replication, differentiation, immune response, cellular response to stress, etc. In contrast to non-specific degradation by lysosomes, proteasomes are highly selective and destroy only the proteins that are covalently labelled with small proteins, called ubiquitins. Importantly, many diseases, including neurodegenerative diseases and cancers, are intimately connected to the activity of proteasomes making them an important pharmacological target. Currently, the vast majority of inhibitors are aimed at blunting the proteolytic activities of proteasomes. However, recent achievements in solving structures of proteasomes at very high resolution provided opportunities to design new classes of small molecules that target other physiologically-important enzymatic activities of proteasomes, including the de-ubiquitinating one. This review attempts to catalog the information available to date about novel classes of proteasome inhibitors that may have important pharmacological ramifications.","DOI":"10.18632/oncotarget.4619","ISSN":"1949-2553","note":"PMID: 26295307\nPMCID: PMC4694792","journalAbbreviation":"Oncotarget","language":"eng","author":[{"family":"Grigoreva","given":"Tatyana A."},{"family":"Tribulovich","given":"Vyacheslav G."},{"family":"Garabadzhiu","given":"Alexander V."},{"family":"Melino","given":"Gerry"},{"family":"Barlev","given":"Nickolai A."}],"issued":{"date-parts":[["2015",9,22]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Recent advance in the use of proteasome inhibitors in cancer therapy has been comprehensively reviewed elsewhere[180,181].

Bortezomib was the first proteasome inhibitor to be brought to the clinic and is used for the treatment of multiple myeloma[180,181]. { ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ad09tei2gp","properties":{"formattedCitation":"{\\rtf \\super 181,182\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":107,"uris":["http://zotero.org/users/4604651/items/MD8CQ33H"],"uri":["http://zotero.org/users/4604651/items/MD8CQ33H"],"itemData":{"id":107,"type":"article-journal","title":"Proteasome inhibitors in cancer therapy","container-title":"Nature Reviews Clinical Oncology","page":"417-433","volume":"14","issue":"7","source":"www.nature.com","abstract":"The ubiquitin proteasome pathway was discovered in the 1980s to be a central component of the cellular protein-degradation machinery with essential functions in homeostasis, which include preventing the accumulation of misfolded or deleterious proteins. Cancer cells produce proteins that promote both cell survival and proliferation, and/or inhibit mechanisms of cell death. This notion set the stage for preclinical testing of proteasome inhibitors as a means to shift this fine equilibrium towards cell death. Since the late 1990s, clinical trials have been conducted for a variety of malignancies, leading to regulatory approvals of proteasome inhibitors to treat multiple myeloma and mantle-cell lymphoma. First-generation and second-generation proteasome inhibitors can elicit deep initial responses in patients with myeloma, for whom these drugs have dramatically improved outcomes, but relapses are frequent and acquired resistance to treatment eventually emerges. In addition, promising preclinical data obtained with proteasome inhibitors in models of solid tumours have not been confirmed in the clinic, indicating the importance of primary resistance. Investigation of the mechanisms of resistance is, therefore, essential to further maximize the utility of this class of drugs in the era of personalized medicine. Herein, we discuss the advances and challenges resulting from the introduction of proteasome inhibitors into the clinic.","DOI":"10.1038/nrclinonc.2016.206","ISSN":"1759-4774","journalAbbreviation":"Nat Rev Clin Oncol","language":"en","author":[{"family":"Manasanch","given":"Elisabet E."},{"family":"Orlowski","given":"Robert Z."}],"issued":{"date-parts":[["2017",7]]}}},{"id":110,"uris":["http://zotero.org/users/4604651/items/V4KZP8TM"],"uri":["http://zotero.org/users/4604651/items/V4KZP8TM"],"itemData":{"id":110,"type":"article-journal","title":"The 26S proteasome is a multifaceted target for anti-cancer therapies","container-title":"Oncotarget","page":"24733-24749","volume":"6","issue":"28","source":"PubMed","abstract":"Proteasomes play a critical role in the fate of proteins that are involved in major cellular processes, including signal

transduction, gene expression, cell cycle, replication, differentiation, immune response, cellular response to stress, etc. In contrast to non-specific degradation by lysosomes, proteasomes are highly selective and destroy only the proteins that are covalently labelled with small proteins, called ubiquitins. Importantly, many diseases, including neurodegenerative diseases and cancers, are intimately connected to the activity of proteasomes making them an important pharmacological target. Currently, the vast majority of inhibitors are aimed at blunting the proteolytic activities of proteasomes. However, recent achievements in solving structures of proteasomes at very high resolution provided opportunities to design new classes of small molecules that target other physiologically-important enzymatic activities of proteasomes, including the de-ubiquitinating one. This review attempts to catalog the information available to date about novel classes of proteasome inhibitors that may have important pharmacological ramifications.","DOI":"10.18632/oncotarget.4619","ISSN":"1949-2553","note":"PMID: 26295307\nPMCID: PMC4694792","journalAbbreviation":"Oncotarget","language":"eng","author":[{"family":"Grigoreva","given":"Tatyana A."},{"family":"Tribulovich","given":"Vyacheslav G."},{"family":"Garabadzhiu","given":"Alexander V."},{"family":"Melino","given":"Gerry"},{"family":"Barlev","given":"Nickolai A."}],"issued":{"date-parts":[["2015",9,22]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**Whilst proteasome inhibitor drugs have shown benefits, relapses are frequent because resistance to the treatment almost inevitably arises. Thus, understanding the mechanisms underlying resistance to proteasome inhibitors is an area of intense research. Interestingly, knock-down of RP subunits increases resistance to proteasome inhibitors[182]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2qq124ep07","properties":{"formattedCitation":"{\\rtf \\super 183\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":540,"uris":["http://zotero.org/users/4604651/items/RVRU7HFI"],"uri":["http://zotero.org/users/4604651/items/RVRU7HFI"],"itemData":{"id":540,"type":"article-journal","title":"Paradoxical resistance of multiple myeloma to proteasome inhibitors by decreased levels of 19S proteasomal subunits","container-title":"eLife","page":"e08153","volume":"4","source":"elifesciences.org","abstract":"The nodes of the cytosolic proteostasis network can control sensitivity to proteasome inhibitors and decreased levels of the 19S proteasomal regulator can lead to increased resistance to inhibitors.","DOI":"10.7554/eLife.08153","ISSN":"2050-084X","journalAbbreviation":"eLife Sciences","language":"en","author":[{"family":"Acosta-

Alvear","given":"Diego"},{"family":"Cho","given":"Min Y."},{"family":"Wild","given":"Thomas"},{"family":"Buchholz","given":"Tonia J."},{"family":"Lerner","given":"Alana G."},{"family":"Simakova","given":"Olga"},{"family":"Hahn","given":"Jamie"},{"family":"Korde","given":"Neha"},{"family":"Landgren","given":"Ola"},{"family":"Maric","given":"Irina"},{"family":"Choudhary","given":"Chunaram"},{"family":"Walter","given":"Peter"},{"family":"Weissman","given":"Jonathan S."},{"family":"Kampmann","given":"Martin"}],"issued":{"date-parts":[["2015",9,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. In light of the recent findings that cells adjust proteasome abundance to their needs, it is reasonable to speculate that cells adapt to the reduction of RP subunits by inducing a response that leads to resistance to proteasome inhibition. It will be interesting to identify such mechanisms.

Several lines of evidence highlight the notion that the perturbation of proteasome assembly can have an effect on tumorigenesis. The first indication came with the observations that two out of the four RACs, p27 (Nas2 in yeast, also known as PSMD9) and p28 (Nas6 in yeast, also known as PSMD10 or Gankyrin), promote cancer progression[183–186]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a184odba0nj","properties":{"formattedCitation":"{\\rtf \\super 184\\uc0\\u8211{}187\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":109,"uris":["http://zotero.org/users/4604651/items/NRIB4AW9"],"uri":["http://zotero.org/users/4604651/items/NRIB4AW9"],"itemData":{"id":109,"type":"article-journal","title":"PSMD9 expression predicts radiotherapy response in breast cancer","container-title":"Molecular Cancer","page":"73","volume":"13","source":"BioMed Central","abstract":"More than 50% of cancer patients are recommended to receive radiotherapy. Recommendations are based mainly on clinical and pathological factors and not intrinsic tumour radio-sensitivity. Use of radiotherapy according to predictive markers would potentially reduce costly over-treatment, and improve the treatment risk-benefit ratio and cancer outcomes. Tumour expression of the 26S proteasome has been reported to predict radiotherapy response: low expression was associated with higher rates of local recurrence after radiotherapy, suggesting that low proteasome expression and activity was associated with radio-resistance. However, this conclusion is at odds with the emerging use of proteasome inhibitors as radio-sensitizers. Our aim was to further analyse the relevance of 26S proteasome expression, focussing specifically on the PSMD9 subunit, in the largest clinical cohort to date, and to investigate the functional

role of PSMD9 in radio-sensitivity in breast cancer cell lines.","DOI":"10.1186/1476-4598-13-73","ISSN":"1476-4598","journalAbbreviation":"Molecular Cancer","author":[{"family":"Langlands","given":"Fiona E."},{"family":"Dodwell","given":"David"},{"family":"Hanby","given":"Andrew M."},{"family":"Horgan","given":"Kieran"},{"family":"Millican-Slater","given":"Rebecca A."},{"family":"Speirs","given":"Valerie"},{"family":"Verghese","given":"Eldo T."},{"family":"Smith","given":"Laura"},{"family":"Hughes","given":"Thomas A."}],"issued":{"date-parts":[["2014"]]}}},{"id":106,"uris":["http://zotero.org/users/4604651/items/R2NL2JP9"],"uri":["http://zotero.org/users/4604651/items/R2NL2JP9"],"itemData":{"id":106,"type":"article-journal","title":"The role of PSMD9 in human disease: future clinical and therapeutic implications","container-title":"Molecular 2015, Vol. 2, Pages 476-484","source":"www.aimspress.com","abstract":"PSMD9 was first characterized as a component of the PA700 proteasomal regulator, and was found to stimulate association of PA700 with the catalytic 20S proteasomal core to form the active 26S proteasome. It was also independently identified under the name “bridge-1” as a transcriptional co-activator that modulates function of the transcription factors PDX-1, E12, and E47, and interacts with the co-activator histone acetyltransferase p300. Here, we discuss the molecular and genetic data linking PSMD9 to a diverse range of conditions including diabetes, cancer, mental health problems, polycystic ovary syndrome and neurodegenerative diseases, and thereby highlight its potential as a therapeutic target in these multiple settings.","URL":"http://www.aimspress.com/article/10.3934/molsci.2015.4.476/fulltext.html","DOI":"10.3934/molsci.2015.4.476","shortTitle":"The role of PSMD9 in human disease","language":"en","author":[{"family":"Hopper","given":"Joanne L."},{"family":"Begum","given":"Natasha"},{"family":"Smith","given":"Laura"},{"family":"Hughes","given":"Thomas A."}],"issued":{"date-parts":[["2015",11,25]]},"accessed":{"date-parts":[["2017",6,27]]}}},{"id":102,"uris":["http://zotero.org/users/4604651/items/TWPJN2W3"],"uri":["http://zotero.org/users/4604651/items/TWPJN2W3"],"itemData":{"id":102,"type":"article-journal","title":"Gankyrin: a new oncoprotein and regulator of pRb and p53","container-title":"Trends in Cell Biology","page":"229-233","volume":"16","issue":"5","source":"www.cell.com","DOI":"10.1016/j.tcb.2006.03.001","ISSN":"0962-8924, 1879-3088","note":"PMID: 16581249","shortTitle":"Gankyrin","journalAbbreviation":"Trends in Cell

Biology","language":"English","author":[{"family":"Dawson","given":"Simon"},{"family":"Higashitsuji","given":"Hiroaki"},{"family":"Wilkinson","given":"Anthony J."},{"family":"Fujita","given":"Jun"},{"family":"Mayer","given":"R. John"}],"issued":{"date-parts":[["2006",5,1]]}}},{"id":105,"uris":["http://zotero.org/users/4604651/items/MFMLQWKJ"],"uri":["http://zotero.org/users/4604651/items/MFMLQWKJ"],"itemData":{"id":105,"type":"article-journal","title":"The oncoprotein gankyrin binds to MDM2/HDM2, enhancing ubiquitylation and degradation of p53","container-title":"Cancer Cell","page":"75-87","volume":"8","issue":"1","source":"ScienceDirect","abstract":"Summary\nGankyrin is an ankyrin repeat oncoprotein commonly overexpressed in hepatocellular carcinomas. Gankyrin interacts with the S6 proteasomal ATPase and accelerates the degradation of the tumor suppressor Rb. We show here that gankyrin has an antiapoptotic activity in cells exposed to DNA damaging agents. Downregulation of gankyrin induces apoptosis in cells with wild-type p53. In vitro and in vivo experiments revealed that gankyrin binds to Mdm2, facilitating p53-Mdm2 binding, and increases ubiquitylation and degradation of p53. Gankyrin also enhances Mdm2 autoubiquitylation in the absence of p53. Downregulation of gankyrin reduced amounts of Mdm2 and p53 associated with the 26S proteasome. Thus, gankyrin is a cofactor that increases the activities of Mdm2 on p53 and probably targets polyubiquitylated p53 into the 26S proteasome.","DOI":"10.1016/j.ccr.2005.06.006","ISSN":"1535-6108","journalAbbreviation":"Cancer Cell","author":[{"family":"Higashitsuji","given":"Hiroaki"},{"family":"Higashitsuji","given":"Hisako"},{"family":"Itoh","given":"Katsuhiko"},{"family":"Sakurai","given":"Toshiharu"},{"family":"Nagao","given":"Toshikazu"},{"family":"Sumitomo","given":"Haruhiko"},{"family":"Masuda","given":"Tomoko"},{"family":"Dawson","given":"Simon"},{"family":"Shimada","given":"Yutaka"},{"family":"Mayer","given":"R. John"},{"family":"Fujita","given":"Jun"}],"issued":{"date-parts":[["2005",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . For example, the loss of p27 in breast cancer cells decreases cell resistance to radiotherapy[183,184]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"al30gc7kmt","properties":{"formattedCitation":"{\\rtf \\super 184,185\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":109,"uris":["http://zotero.org/users/4604651/items/NRIB4AW9"],"uri":["http://zotero.org/users/4604651/items/NRIB4AW9"],"itemData":{"id":109,"type":"article-journal","title":"PSMD9 expression predicts radiotherapy response in breast cancer","container-title":"Molecular Cancer","page":"73","volume":"13","source":"BioMed Central","abstract":"More than 50% of cancer patients are recommended to receive radiotherapy. Recommendations are based mainly on

clinical and pathological factors and not intrinsic tumour radio-sensitivity. Use of radiotherapy according to predictive markers would potentially reduce costly over-treatment, and improve the treatment risk-benefit ratio and cancer outcomes. Tumour expression of the 26S proteasome has been reported to predict radiotherapy response: low expression was associated with higher rates of local recurrence after radiotherapy, suggesting that low proteasome expression and activity was associated with radio-resistance. However, this conclusion is at odds with the emerging use of proteasome inhibitors as radio-sensitizers. Our aim was to further analyse the relevance of 26S proteasome expression, focussing specifically on the PSMD9 subunit, in the largest clinical cohort to date, and to investigate the functional role of PSMD9 in radio-sensitivity in breast cancer cell lines.","DOI":"10.1186/1476-4598-13-73","ISSN":"1476-4598","journalAbbreviation":"Molecular Cancer","author":[{"family":"Langlands","given":"Fiona E."},{"family":"Dodwell","given":"David"},{"family":"Hanby","given":"Andrew M."},{"family":"Horgan","given":"Kieran"},{"family":"Millican-Slater","given":"Rebecca A."},{"family":"Speirs","given":"Valerie"},{"family":"Verghese","given":"Eldo T."},{"family":"Smith","given":"Laura"},{"family":"Hughes","given":"Thomas A."}],"issued":{"date-parts":[["2014"]]}}},{"id":106,"uris":["http://zotero.org/users/4604651/items/R2NL2JP9"],"uri":["http://zotero.org/users/4604651/items/R2NL2JP9"],"itemData":{"id":106,"type":"article-journal","title":"The role of PSMD9 in human disease: future clinical and therapeutic implications","container-title":"Molecular 2015, Vol. 2, Pages 476-484","source":"www.aimspress.com","abstract":"PSMD9 was first characterized as a component of the PA700 proteasomal regulator, and was found to stimulate association of PA700 with the catalytic 20S proteasomal core to form the active 26S proteasome. It was also independently identified under the name “bridge-1” as a transcriptional co-activator that modulates function of the transcription factors PDX-1, E12, and E47, and interacts with the co-activator histone acetyltransferase p300. Here, we discuss the molecular and genetic data linking PSMD9 to a diverse range of conditions including diabetes, cancer, mental health problems, polycystic ovary syndrome and neurodegenerative diseases, and thereby highlight its potential as a therapeutic target in these multiple settings.","URL":"http://www.aimspress.com/article/10.3934/molsci.2015.4.476/fulltext.html","DOI":"10.3934/molsci.2015.4.476","shortTitle":"The role of PSMD9 in human disease","language":"en","author":[{"family":"Hopper","given":"Joanne L."},{"family":"Begum","given":"Natasha"},{"family":"Smith","given":"Laura"},{"family":"Hughes","given":"Thomas A."}],"issued":{"date-parts":[["2015",11,25]]},"accessed":{"date-parts":[["2017",6,27]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }, which is in agreement with RACs being regulated by different stresses[97]. There are also robust links between the RAC p28 and cancer, p28 being considered an oncoprotein[185,186]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1f029quobe","properties":{"formattedCitation":"{\\rtf \\super 186,187\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":105,"uris":["http://zotero.org/users/4604651/items/MFMLQWKJ"],"uri":["http://zotero.org/users/4604651/items/MFMLQWKJ"],"itemData":{"id":105,"type":"article-journal","title":"The oncoprotein gankyrin binds to MDM2/HDM2, enhancing ubiquitylation and degradation of p53","container-title":"Cancer Cell","page":"75-87","volume":"8","issue":"1","source":"ScienceDirect","abstract":"Summary\nGankyrin is an ankyrin repeat oncoprotein commonly overexpressed in hepatocellular carcinomas. Gankyrin interacts with the S6 proteasomal ATPase and accelerates the degradation of the tumor suppressor Rb. We show here that gankyrin has an antiapoptotic activity in cells exposed to DNA damaging agents. Downregulation of

gankyrin induces apoptosis in cells with wild-type p53. In vitro and in vivo experiments revealed that gankyrin binds to Mdm2, facilitating p53-Mdm2 binding, and increases ubiquitylation and degradation of p53. Gankyrin also enhances Mdm2 autoubiquitylation in the absence of p53. Downregulation of gankyrin reduced amounts of Mdm2 and p53 associated with the 26S proteasome. Thus, gankyrin is a cofactor that increases the activities of Mdm2 on p53 and probably targets polyubiquitylated p53 into the 26S proteasome.","DOI":"10.1016/j.ccr.2005.06.006","ISSN":"1535-6108","journalAbbreviation":"Cancer Cell","author":[{"family":"Higashitsuji","given":"Hiroaki"},{"family":"Higashitsuji","given":"Hisako"},{"family":"Itoh","given":"Katsuhiko"},{"family":"Sakurai","given":"Toshiharu"},{"family":"Nagao","given":"Toshikazu"},{"family":"Sumitomo","given":"Haruhiko"},{"family":"Masuda","given":"Tomoko"},{"family":"Dawson","given":"Simon"},{"family":"Shimada","given":"Yutaka"},{"family":"Mayer","given":"R. John"},{"family":"Fujita","given":"Jun"}],"issued":{"date-parts":[["2005",7]]}},{"id":102,"uris":["http://zotero.org/users/4604651/items/TWPJN2W3"],"uri":["http://zotero.org/users/4604651/items/TWPJN2W3"],"itemData":{"id":102,"type":"article-journal","title":"Gankyrin: a new oncoprotein and regulator of pRb and p53","container-title":"Trends in Cell Biology","page":"229-233","volume":"16","issue":"5","source":"www.cell.com","DOI":"10.1016/j.tcb.2006.03.001","ISSN":"0962-8924, 1879-3088","note":"PMID: 16581249","shortTitle":"Gankyrin","journalAbbreviation":"Trends in Cell Biology","language":"English","author":[{"family":"Dawson","given":"Simon"},{"family":"Higashitsuji","given":"Hiroaki"},{"family":"Wilkinson","given":"Anthony J."},{"family":"Fujita","given":"Jun"},{"family":"Mayer","given":"R. John"}],"issued":{"date-parts":[["2006",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The role of p28 in cancer was highlighted long before its function as a proteasome assembly chaperone was identified and the interpretation of some early studies may need to be revisited accordingly. More recently, it has been reported that p53 missense mutants cooperate with Nrf2 in activating the transcription of proteasome genes as well as those encoding the RACs leading to higher levels of proteasome activity[187]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ac34o6e85t","properties":{"formattedCitation":"{\\rtf \\super 188\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":101,"uris":["http://zotero.org/users/4604651/items/DFELVKGC"],"uri":["http://zotero.org/users/4604651/items/DFELVKGC"],"itemData":{"id":101,"type":"article-journal","title":"Proteasome machinery is instrumental in a common gain-of-function program of the p53 missense mutants in cancer","container-title":"Nature Cell Biology","page":"897-909","volume":"18","issue":"8","source":"www.nature.com","abstract":"In cancer, the tumour suppressor gene TP53 undergoes frequent missense mutations that endow mutant p53 proteins with oncogenic properties. Until now, a universal mutant p53 gain-of-function program has not been defined. By means of multi-omics: proteome, DNA interactome (chromatin immunoprecipitation followed by sequencing) and transcriptome (RNA sequencing/microarray) analyses, we identified the proteasome machinery as a common target of p53 missense mutants. The mutant p53–proteasome axis globally affects protein homeostasis, inhibiting multiple tumour-suppressive pathways, including the anti-oncogenic KSRP–microRNA pathway. In cancer cells, p53 missense mutants cooperate with Nrf2 (NFE2L2) to activate proteasome gene transcription, resulting in resistance to the proteasome inhibitor carfilzomib. Combining the mutant p53-inactivating agent APR-246 (PRIMA-1MET) with the proteasome inhibitor carfilzomib is effective in overcoming chemoresistance in triple-negative

breast cancer cells, creating a therapeutic opportunity for treatment of solid tumours and metastasis with mutant p53.","DOI":"10.1038/ncb3380","ISSN":"1465-7392","journalAbbreviation":"Nat Cell Biol","language":"en","author":[{"family":"Walerych","given":"Dawid"},{"family":"Lisek","given":"Kamil"},{"family":"Sommaggio","given":"Roberta"},{"family":"Piazza","given":"Silvano"},{"family":"Ciani","given":"Yari"},{"family":"Dalla","given":"Emiliano"},{"family":"Rajkowska","given":"Katarzyna"},{"family":"Gaweda-Walerych","given":"Katarzyna"},{"family":"Ingallina","given":"Eleonora"},{"family":"Tonelli","given":"Claudia"},{"family":"Morelli","given":"Marco J."},{"family":"Amato","given":"Angela"},{"family":"Eterno","given":"Vincenzo"},{"family":"Zambelli","given":"Alberto"},{"family":"Rosato","given":"Antonio"},{"family":"Amati","given":"Bruno"},{"family":"Wiśniewski","given":"Jacek R."},{"family":"Del Sal","given":"Giannino"}],"issued":{"date-parts":[["2016",8]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. These findings highlight the importance of the regulation of proteasome assembly in cancer.

miR-101, that targets the CP chaperone POMP mRNA to rapidly decrease POMP protein, is a potent tumor-suppressor which is downregulated in a variety of cancers[188]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1ri9i46d3h","properties":{"formattedCitation":"{\\rtf \\super 189\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":104,"uris":["http://zotero.org/users/4604651/items/XJB672ZL"],"uri":["http://zotero.org/users/4604651/items/XJB672ZL"],"itemData":{"id":104,"type":"article-journal","title":"Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer","container-title":"Science (New York, N.Y.)","page":"1695-1699","volume":"322","issue":"5908","source":"PubMed","abstract":"Enhancer of zeste homolog 2 (EZH2) is a mammalian histone methyltransferase that contributes to the epigenetic silencing of target genes and regulates the survival and metastasis of cancer cells. EZH2 is overexpressed in aggressive solid tumors by mechanisms that remain unclear. Here we show that the expression and function of EZH2 in cancer cell lines are inhibited by microRNA-101 (miR-101). Analysis of human prostate tumors revealed that miR-101 expression decreases during cancer progression, paralleling an increase in EZH2 expression. One or both of the two genomic loci encoding miR-101 were somatically lost in 37.5% of clinically localized prostate cancer cells (6 of 16) and 66.7% of metastatic disease cells (22 of 33). We propose that the genomic loss of miR-101 in cancer leads to overexpression of EZH2 and concomitant dysregulation of epigenetic pathways, resulting in cancer progression.","DOI":"10.1126/science.1165395","ISSN":"1095-9203","note":"PMID: 19008416\nPMCID: PMC2684823","journalAbbreviation":"Science","language":"eng","author":[{"family":"Varambally","given":"Sooryanarayana"},{"family":"Cao","given":"Qi"},{"family":"Mani","given":"Ram-Shankar"},{"family":"Shankar","given":"Sunita"},{"family":"Wang","given":"Xiaosong"},{"family":"Ateeq","given":"Bushra"},{"family":"Laxman","given":"Bharathi"},{"family":"Cao","given":"Xuhong"},{"family":"Jing","given":"Xiaojun"},{"family":"Ramnarayanan","given":"Kalpana"},{"family":"Brenner","given":"J. Chad"},{"family":"Yu","given":"Jindan"},{"family":"Kim","given":"Jung H."},{"family":"Han","given":"Bo"},{"family":"Tan","given":"Patrick"},{"family":"Kumar-Sinha","given":"Chandan"},{"family":"Lonigro","given":"Robert J."},{"family":"Palanisamy","given":"Nallasivam"},{"family":"Maher","given":"Christopher A."},{"family":"Chinnaiyan","given":"Arul

M."}],"issued":{"date-parts":[["2008",12,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . The tumor suppressor function of miR-101 is completely abrogated by the expression of miR-101-resistent POMP showing that POMP targeting is necessary for miR-101-mediated tumor suppression[109]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a24gtt4p0po","properties":{"formattedCitation":"{\\rtf \\super 115\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":172,"uris":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"uri":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"itemData":{"id":172,"type":"article-journal","title":"MicroRNA-101 Suppresses Tumor Cell Proliferation by Acting as an Endogenous Proteasome Inhibitor via Targeting the Proteasome Assembly Factor POMP","container-title":"Molecular Cell","page":"243-257","volume":"59","issue":"2","source":"PubMed","abstract":"Proteasome inhibition represents a promising strategy of cancer pharmacotherapy, but resistant tumor cells often emerge. Here we show that the microRNA-101 (miR-101) targets the proteasome maturation protein POMP, leading to impaired proteasome assembly and activity, and resulting in accumulation of p53 and cyclin-dependent kinase inhibitors, cell cycle arrest, and apoptosis. miR-101-resistant POMP restores proper turnover of proteasome substrates and re-enables tumor cell growth. In ERα-positive breast cancers, miR-101 and POMP levels are inversely correlated, and high miR-101 expression or low POMP expression associates with prolonged survival. Mechanistically, miR-101 expression or POMP knockdown attenuated estrogen-driven transcription. Finally, suppressing POMP is sufficient to overcome tumor cell resistance to the proteasome inhibitor bortezomib. Taken together, proteasome activity can not only be manipulated through drugs, but is also subject to endogenous regulation through miR-101, which targets proteasome biogenesis to control overall protein turnover and tumor cell proliferation.","DOI":"10.1016/j.molcel.2015.05.036","ISSN":"1097-4164","note":"PMID: 26145175","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Zhang","given":"Xin"},{"family":"Schulz","given":"Ramona"},{"family":"Edmunds","given":"Shelley"},{"family":"Krüger","given":"Elke"},{"family":"Markert","given":"Elke"},{"family":"Gaedcke","given":"Jochen"},{"family":"Cormet-Boyaka","given":"Estelle"},{"family":"Ghadimi","given":"Michael"},{"family":"Beissbarth","given":"Tim"},{"family":"Levine","given":"Arnold J."},{"family":"Moll","given":"Ute M."},{"family":"Dobbelstein","given":"Matthias"}],"issued":{"date-parts":[["2015",7,16]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Remarkably, POMP inhibition overcomes tumor cell resistance to the proteasome inhibitor bortezomib[109]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2l4h4t7d8h","properties":{"formattedCitation":"{\\rtf \\super 115\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":172,"uris":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"uri":["http://zotero.org/users/4604651/items/RN7SQ3U3"],"itemData":{"id":172,"type":"article-journal","title":"MicroRNA-101 Suppresses Tumor Cell Proliferation by Acting as an Endogenous Proteasome Inhibitor via Targeting the Proteasome Assembly Factor POMP","container-title":"Molecular Cell","page":"243-257","volume":"59","issue":"2","source":"PubMed","abstract":"Proteasome inhibition represents a promising strategy of cancer pharmacotherapy, but resistant tumor cells often emerge. Here we show that the microRNA-101 (miR-101) targets the proteasome maturation protein POMP, leading to impaired proteasome assembly and activity, and resulting in accumulation of p53 and cyclin-dependent kinase inhibitors, cell cycle arrest, and apoptosis. miR-101-resistant POMP restores proper turnover of proteasome

substrates and re-enables tumor cell growth. In ERα-positive breast cancers, miR-101 and POMP levels are inversely correlated, and high miR-101 expression or low POMP expression associates with prolonged survival. Mechanistically, miR-101 expression or POMP knockdown attenuated estrogen-driven transcription. Finally, suppressing POMP is sufficient to overcome tumor cell resistance to the proteasome inhibitor bortezomib. Taken together, proteasome activity can not only be manipulated through drugs, but is also subject to endogenous regulation through miR-101, which targets proteasome biogenesis to control overall protein turnover and tumor cell proliferation.","DOI":"10.1016/j.molcel.2015.05.036","ISSN":"1097-4164","note":"PMID: 26145175","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Zhang","given":"Xin"},{"family":"Schulz","given":"Ramona"},{"family":"Edmunds","given":"Shelley"},{"family":"Krüger","given":"Elke"},{"family":"Markert","given":"Elke"},{"family":"Gaedcke","given":"Jochen"},{"family":"Cormet-Boyaka","given":"Estelle"},{"family":"Ghadimi","given":"Michael"},{"family":"Beissbarth","given":"Tim"},{"family":"Levine","given":"Arnold J."},{"family":"Moll","given":"Ute M."},{"family":"Dobbelstein","given":"Matthias"}],"issued":{"date-parts":[["2015",7,16]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. Moreover, it has been independently shown that POMP overexpression in drug-naïve cells confers resistance to bortezomib and is associated with increased levels of Nrf2 which gives rise to a positive feedback loop by binding to the POMP promoter[189]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a7itned86p","properties":{"formattedCitation":"{\\rtf \\super 190\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":103,"uris":["http://zotero.org/users/4604651/items/GT7DM6IN"],"uri":["http://zotero.org/users/4604651/items/GT7DM6IN"],"itemData":{"id":103,"type":"article-journal","title":"The Nuclear Factor (Erythroid-derived 2)-like 2 and Proteasome Maturation Protein Axis Mediates Bortezomib Resistance in Multiple Myeloma","container-title":"Journal of Biological Chemistry","page":"jbc.M115.664953","source":"www.jbc.org","abstract":"Resistance to the proteasome inhibitor bortezomib is an emerging clinical problem whose mechanisms have not been fully elucidated. We considered the possibility that this could be associated with enhanced proteasome activity in part through the action of Proteasome maturation protein (POMP). Bortezomib-resistant myeloma models were used to examine the correlation between POMP expression and bortezomib sensitivity. POMP expression was then modulated using genetic and pharmacologic approaches to determine the effects on proteasome inhibitor sensitivity in cell lines and in vivo models. Resistant cell lines were found to overexpress POMP, and while its suppression in cell lines enhanced bortezomib sensitivity, POMP overexpression in drug-naive cells conferred resistance. Overexpression of POMP was associated with increased levels of Nuclear factor (erythroid-derived 2)-like (NRF2), and NRF2 was found to bind to and activate the POMP promoter. Knockdown of NRF2 in bortezomib-resistant cells reduced POMP levels and proteasome activity, while its overexpression in drug-naive cells increased POMP and proteasome activity. The NRF2 inhibitor all-trans retinoic acid (ATRA) reduced cellular NRF2 levels, and increased the anti-proliferative and pro-apoptotic activities of bortezomib in resistant cells, while decreasing proteasome capacity. Finally, the combination of ATRA with bortezomib showed enhanced activity against primary patient samples, and in a murine model of bortezomib-resistant myeloma.Taken together, these studies validate a role for the NRF2/POMP axis in bortezomib resistance, and identify NRF2 and POMP as potentially attractive targets for chemosensitization to this proteasome inhibitor.","DOI":"10.1074/jbc.M115.664953","ISSN":"0021-9258, 1083-351X","note":"PMID: 26483548","journalAbbreviation":"J. Biol.

Chem.","language":"en","author":[{"family":"Li","given":"Bingzong"},{"family":"Fu","given":"Jinxiang"},{"family":"Chen","given":"Ping"},{"family":"Ge","given":"Xueping"},{"family":"Li","given":"Yali"},{"family":"Kuiatse","given":"Isere"},{"family":"Wang","given":"Hua"},{"family":"Whang","given":"Huihan"},{"family":"Zhang","given":"Xingding"},{"family":"Orlowski","given":"Robert Z."}],"issued":{"date-parts":[["2015",10,19]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. Another possible level of intervention has been identified with the selective peptide inhibitor of PAC3 dimerization[190]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1r3hfiahp0","properties":{"formattedCitation":"{\\rtf \\super 191\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":100,"uris":["http://zotero.org/users/4604651/items/CCGD7AV2"],"uri":["http://zotero.org/users/4604651/items/CCGD7AV2"],"itemData":{"id":100,"type":"article-journal","title":"Novel In Vitro Protein Fragment Complementation Assay Applicable to High-Throughput Screening in a 1536-Well Format","container-title":"Journal of Biomolecular Screening","page":"970-979","volume":"14","issue":"8","source":"SAGE Journals","abstract":"Protein-protein interactions (PPIs) play key roles in all cellular processes and hence are useful as potential targets for new drug development. To facilitate the screening of PPI inhibitors as anticancer drugs, the authors have developed a high-throughput screening (HTS) system using an in vitro protein fragment complementation assay (PCA) with monomeric Kusabira-Green fluorescent protein (mKG). The in vitro PCA system was established by the topological formation of a functional complex between 2 split inactive mKG fragments fused to target proteins, which fluoresces when 2 target proteins interact to allow complementation of the mKG fragments. Using this assay system, the authors screened inhibitors for TCF7/β-catenin, PAC1/PAC2, and PAC3 homodimer PPIs from 123,599 samples in their natural product library. Compound TB1 was identified as a specific inhibitor for PPI of PAC3 homodimer. TB1 strongly inhibited the PPI of PAC3 homodimer with an IC 50 value of 0.020 μM and did not inhibit PPI between TCF7/β-catenin and PAC1/PAC2 even at a concentration of 250 μM. The authors thus demonstrated that this in vitro PCA system applicable to HTS in a 1536-well format is capable of screening for PPI inhibitors from a huge natural product library. (Journal of Biomolecular Screening 2009:970-979)","DOI":"10.1177/1087057109341406","ISSN":"1087-0571","journalAbbreviation":"J Biomol Screen","language":"en","author":[{"family":"Hashimoto","given":"Junko"},{"family":"Watanabe","given":"Taku"},{"family":"Seki","given":"Tatsuya"},{"family":"Karasawa","given":"Satoshi"},{"family":"Izumikawa","given":"Miho"},{"family":"Seki","given":"Tomoe"},{"family":"Iemura","given":"Shun-Ichiro"},{"family":"Natsume","given":"Tohru"},{"family":"Nomura","given":"Nobuo"},{"family":"Goshima","given":"Naoki"},{"family":"Miyawaki","given":"Atsushi"},{"family":"Takagi","given":"Motoki"},{"family":"Shin-Ya","given":"Kazuo"}],"issued":{"date-parts":[["2009",9,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} } which has long-term cytotoxicity in human cervical carcinoma cells[191]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a16bcufohoc","properties":{"formattedCitation":"{\\rtf \\super 192\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":99,"uris":["http://zotero.org/users/4604651/items/5DPPFHQW"],"uri":["http://zotero.org/users/4604651/items/5DPPFHQW"],"itemData":{"id":99,"type":"article-journal","title":"JBIR-22, an inhibitor for protein-protein interaction of the homodimer of proteasome assembly factor 3","container-title":"Journal of Natural Products","page":"628-631","volume":"73","issue":"4","source":"PubMed","abstract":"Proteasome assembling chaperone (PAC) 3 acts as a homodimer and plays an important role in proteasome formation. We screened JBIR-22 (1) as an inhibitor for protein-protein interaction (PPI) of PAC3 homodimer

from our natural product library using a protein fragment complementation assay (PCA) with monomeric Kusabira-Green fluorescent protein (mKG) in vitro and found that 1 exhibited potent inhibitory activity against PAC3 homodimerization. Compound 1 showed long-term cytotoxicity against the human cervical carcinoma cell line, HeLa. This is the first report of a PPI inhibitor for proteasome assembly factors.","DOI":"10.1021/np900788e","ISSN":"1520-6025","note":"PMID: 20180542","journalAbbreviation":"J. Nat. Prod.","language":"eng","author":[{"family":"Izumikawa","given":"Miho"},{"family":"Hashimoto","given":"Junko"},{"family":"Hirokawa","given":"Takatsugu"},{"family":"Sugimoto","given":"Satoshi"},{"family":"Kato","given":"Taira"},{"family":"Takagi","given":"Motoki"},{"family":"Shin-Ya","given":"Kazuo"}],"issued":{"date-parts":[["2010",4,23]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}.

Thus, inhibiting proteasome assembly could be a promising anti-cancer strategy. Interfering with proteasome assembly could be a valuable therapeutic strategy to impede proteasome functions either alone or in conjunction with existing drugs inhibiting the catalytic activity of the proteasome such as bortezomib.

[H1] Conclusions and perspectives

The identification of proteasome assembly chaperones has revealed that proteasome assembly is a highly complex and tightly regulated process that is integrated with cellular metabolism via the stress and growth controller TORC1. The regulation of proteasome homeostasis is an emerging field of research and it is likely that more nodes of regulation of proteasome assembly and activity remain to be elucidated. It is interesting to note that ribosome biogenesis requires more than 200 factors. By analogy, one might wonder how many more proteasome assembly factors remain to be discovered. As the proteasome has a crucial role in regulating cell function that is relevant to diseases, understanding and modulating assembly mechanisms could open up valuable therapeutic intervention opportunities relevant to diverse human age-related diseases including cancer and neurodegeneration.

References

For references that are particularly worth reading (5-10 maximum), please provide a single bold sentence (placed under the relevant reference) that indicates the significance of the work.]

1. Schoenheimer, R. & Clarke, H. T. *The dynamic state of body constituents*. (Harvard university press, 1942).

2. Young, V. R., Steffee, W. P., Pencharz, P. B., Winterer, J. C. & Scrimshaw, N. S. Total human body protein synthesis in relation to protein requirements at various ages. *Nature* **253,** 192–194 (1975).

This paper shows that the bulk of amino acids required for protein synthesis is provided

by the recycling existing proteins.
3. Nakatogawa, H., Suzuki, K., Kamada, Y. & Ohsumi, Y. Dynamics and diversity in autophagy mechanisms: lessons from yeast. *Nat. Rev. Mol. Cell Biol.* **10,** 458–467 (2009).
4. Kaushik, S. & Cuervo, A. M. The coming of age of chaperone-mediated autophagy. Nat. Rev. Mol. Cell Biol. 19, 365–381 (2018).

5. Onodera, J. & Ohsumi, Y. Autophagy is required for maintenance of amino acid levels and protein synthesis under nitrogen starvation. *J. Biol. Chem.* **280,** 31582–31586 (2005).
This paper demonstrates the importance of autophagy, under nutrient starvation, for the maintenance of amino acid levels and protein synthesis.
6. Ohsumi, Y. Historical landmarks of autophagy research. *Cell Res.* **24,** 9–23 (2014).
7. Finley, D. Recognition and processing of ubiquitin-protein conjugates by the proteasome. *Annu. Rev. Biochem.* **78,** 477–513 (2009).
8. Varshavsky, A. Regulated protein degradation. *Trends Biochem. Sci.* **30,** 283–286 (2005).
9. Ciechanover, A. Intracellular protein degradation: From a vague idea thru the lysosome and the ubiquitin–proteasome system and onto human diseases and drug targeting. *Biochim. Biophys. Acta BBA - Proteins Proteomics* **1824,** 3–13 (2012).
10. Tanaka, K. The proteasome: Overview of structure and functions. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **85,** 12–36 (2009).
11. Hershko, A. & Ciechanover, A. The ubiquitin system. *Annu. Rev. Biochem.* **67,** 425–479 (1998).
12. Suraweera, A., Münch, C., Hanssum, A. & Bertolotti, A. Failure of Amino Acid Homeostasis Causes Cell Death following Proteasome Inhibition. *Mol. Cell* **48,** 242–253 (2012).
This paper demonstrates that a vital function of the proteasome, under normal conditions, is to recycle amino acid levels.
13. Komander, D. & Rape, M. The ubiquitin code. *Annu. Rev. Biochem.* **81,** 203–229 (2012).
14. Yu, H. & Matouschek, A. Recognition of Client Proteins by the Proteasome. *Annu. Rev. Biophys.* **46,** 149–173 (2017).
15. Saeki, Y. Ubiquitin recognition by the proteasome. *J. Biochem. (Tokyo)* **161,** 113–124 (2017).
16. Prakash, S., Tian, L., Ratliff, K. S., Lehotzky, R. E. & Matouschek, A. An unstructured initiation site is required for efficient proteasome-mediated degradation. *Nat. Struct. Mol. Biol.* **11,** 830–837 (2004).
This paper establishes the concept that an unstructured region is required to initiate protein degradation by the proteasome.
17. Inobe, T. & Matouschek, A. Paradigms of protein degradation by the proteasome. *Curr. Opin. Struct. Biol.* **24,** 156–164 (2014).
18. Huang, X. & Dixit, V. M. Drugging the undruggables: exploring the ubiquitin system for drug development. *Cell Res.* **26,** 484 (2016).
19. Schmidt, M. & Finley, D. Regulation of proteasome activity in health and disease. *Biochim. Biophys. Acta* **1843,** (2014).
20. Collins, G. A. & Goldberg, A. L. The Logic of the 26S Proteasome. *Cell* **169,** 792–806 (2017).
21. Murata, S., Yashiroda, H. & Tanaka, K. Molecular mechanisms of proteasome assembly. *Nat. Rev. Mol. Cell Biol.* **10,** 104–115 (2009).
22. Lander, G. C. *et al.* Complete subunit architecture of the proteasome regulatory particle. *Nature* **482,** 186–191 (2012).

This paper provides the structure of the proteasoe regulatory particle by cryo-electron microscopy.

23. Budenholzer, L., Cheng, C. L., Li, Y. & Hochstrasser, M. Proteasome Structure and Assembly. *J. Mol. Biol.* **429,** 3500–3524 (2017).
24. Pick, E. & Berman, T. S. Formation of alternative proteasomes: Same lady, different cap? *FEBS Lett.* **587,** 389–393 (2013).
25. Stadtmueller, B. M. & Hill, C. P. Proteasome Activators. *Mol. Cell* **41,** 8–19 (2011).
26. Goldberg, A. L. Functions of the proteasome: from protein degradation and immune surveillance to cancer therapy. *Biochem. Soc. Trans.* **35,** 12–17 (2007).
27. Cascio, P. PA28αβ: the enigmatic magic ring of the proteasome? *Biomolecules* **4,** 566–584 (2014).
28. Huber, E. M. & Groll, M. The Mammalian Proteasome Activator PA28 Forms an Asymmetric α4β3Complex. *Struct. Lond. Engl. 1993* **25,** 1473–1480.e3 (2017).
29. Coux, O., Tanaka, K. & Goldberg, A. L. Structure and functions of the 20S and 26S proteasomes. *Annu. Rev. Biochem.* **65,** 801–847 (1996).
30. Lupas, A., Zwickl, P., Wenzel, T., Seemüller, E. & Baumeister, W. Structure and Function of the 20S Proteasome and of Its Regulatory Complexes. *Cold Spring Harb. Symp. Quant. Biol.* **60,** 515–524 (1995).
31. Kunjappu, M. J. & Hochstrasser, M. Assembly of the 20S proteasome. *Biochim. Biophys. Acta* **1843,** 2–12 (2014).
32. Groll, M. *et al.* Structure of 20S proteasome from yeast at 2.4 A resolution. *Nature* **386,** 463–471 (1997).
33. Unno, M. *et al.* The structure of the mammalian 20S proteasome at 2.75 A resolution. *Struct. Lond. Engl. 1993* **10,** 609–618 (2002).
34. Arendt, C. S. & Hochstrasser, M. Identification of the yeast 20S proteasome catalytic centers and subunit interactions required for active-site formation. *Proc. Natl. Acad. Sci. U. S. A.* **94,** 7156–7161 (1997).
35. Griffin, T. A. *et al.* Immunoproteasome Assembly: Cooperative Incorporation of Interferon γ (IFN-γ)–inducible Subunits. *J. Exp. Med.* **187,** 97–104 (1998).
36. Heink, S., Ludwig, D., Kloetzel, P.-M. & Krüger, E. IFN-gamma-induced immune adaptation of the proteasome system is an accelerated and transient response. *Proc. Natl. Acad. Sci. U. S. A.* **102,** 9241–9246 (2005).
37. Florea, B. I. *et al.* Activity-based profiling reveals reactivity of the murine thymoproteasome-specific subunit beta5t. *Chem. Biol.* **17,** 795–801 (2010).
38. Ripen, A. M., Nitta, T., Murata, S., Tanaka, K. & Takahama, Y. Ontogeny of thymic cortical epithelial cells expressing the thymoproteasome subunit β5t. *Eur. J. Immunol.* **41,** 1278–1287 (2011).
39. Bhattacharyya, S., Yu, H., Mim, C. & Matouschek, A. Regulated protein turnover: snapshots of the proteasome in action. *Nat. Rev. Mol. Cell Biol.* **15,** 122–133 (2014).
40. Bedford, L., Paine, S., Sheppard, P. W., Mayer, R. J. & Roelofs, J. Assembly, Structure and Function of the 26S proteasome. *Trends Cell Biol.* **20,** 391–401 (2010).
41. Tomko, R. J. & Hochstrasser, M. Molecular architecture and assembly of the eukaryotic proteasome. *Annu. Rev. Biochem.* **82,** 415–445 (2013).
42. Glickman, M. H. *et al.* A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome and eIF3. *Cell* **94,** 615–623 (1998).
43. Dambacher, C. M., Worden, E. J., Jr, M. A. H., Martin, A. & Lander, G. C. Atomic structure of the 26S proteasome lid reveals the mechanism of deubiquitinase inhibition. *eLife* **5,** e13027 (2016).
44. Schweitzer, A. *et al.* Structure of the human 26S proteasome at a resolution of 3.9 Å.

Proc. Natl. Acad. Sci. **113,** 7816–7821 (2016).
45. da Fonseca, P. C. A., He, J. & Morris, E. P. Molecular model of the human 26S proteasome. *Mol. Cell* **46,** 54–66 (2012).
46. Witt, E. *et al.* Characterisation of the newly identified human Ump1 homologue POMP and analysis of LMP7(β5i) incorporation into 20 S proteasomes11Edited by R. Huber. *J. Mol. Biol.* **301,** 1–9 (2000).
47. Hirano, Y. *et al.* A heterodimeric complex that promotes the assembly of mammalian 20S proteasomes. *Nature* **437,** 1381–1385 (2005).
This paper identifies two chaperones involved in the maturation of mammalian 20S proteasomes.
48. Hirano, Y. *et al.* Cooperation of Multiple Chaperones Required for the Assembly of Mammalian 20S Proteasomes. *Mol. Cell* **24,** 977–984 (2006).
49. Le Tallec, B. *et al.* 20S proteasome assembly is orchestrated by two distinct pairs of chaperones in yeast and in mammals. *Mol. Cell* **27,** 660–674 (2007).
50. Wani, P. S., Rowland, M. A., Ondracek, A., Deeds, E. J. & Roelofs, J. Maturation of the proteasome core particle induces an affinity switch that controls regulatory particle association. *Nat. Commun.* **6,** 6384 (2015).
51. Stadtmueller, B. M. *et al.* Structure of a Proteasome Pba1-Pba2 Complex IMPLICATIONS FOR PROTEASOME ASSEMBLY, ACTIVATION, AND BIOLOGICAL FUNCTION. *J. Biol. Chem.* **287,** 37371–37382 (2012).
52. Kusmierczyk, A. R. & Hochstrasser, M. Some Assembly Required: Dedicated Chaperones in Eukaryotic Proteasome Biogenesis. *Biol. Chem.* **389,** 1143–1151 (2008).
53. Kusmierczyk, A. R., Kunjappu, M. J., Funakoshi, M. & Hochstrasser, M. A multimeric assembly factor controls the formation of alternative 20S proteasomes. *Nat. Struct. Mol. Biol.* **15,** 237–244 (2008).
54. Padmanabhan, A., Vuong, S. A.-T. & Hochstrasser, M. Assembly of an Evolutionarily Conserved Alternative Proteasome Isoform in Human Cells. *Cell Rep.* **14,** 2962–2974 (2016).
55. Hirano, Y. *et al.* Dissecting β-ring assembly pathway of the mammalian 20S proteasome. *EMBO J.* **27,** 2204–2213 (2008).
56. Li, X., Kusmierczyk, A. R., Wong, P., Emili, A. & Hochstrasser, M. β-Subunit appendages promote 20S proteasome assembly by overcoming an Ump1-dependent checkpoint. *EMBO J.* **26,** 2339–2349 (2007).
57. Li, X., Li, Y., Arendt, C. S. & Hochstrasser, M. Distinct Elements in the Proteasomal β5 Subunit Propeptide Required for Autocatalytic Processing and Proteasome Assembly. *J. Biol. Chem.* **291,** 1991–2003 (2016).
58. Ramos, P. C., Höckendorff, J., Johnson, E. S., Varshavsky, A. & Dohmen, R. J. Ump1p Is Required for Proper Maturation of the 20S Proteasome and Becomes Its Substrate upon Completion of the Assembly. *Cell* **92,** 489–499 (1998).
59. Kock, M. *et al.* Proteasome assembly from 15S precursors involves major conformational changes and recycling of the Pba1–Pba2 chaperone. *Nat. Commun.* **6,** 6123 (2015).
60. Tomko Jr., R. J. & Hochstrasser, M. Incorporation of the Rpn12 Subunit Couples Completion of Proteasome Regulatory Particle Lid Assembly to Lid-Base Joining. *Mol. Cell* **44,** 907–917 (2011).
61. Funakoshi, M., Tomko Jr., R. J., Kobayashi, H. & Hochstrasser, M. Multiple Assembly Chaperones Govern Biogenesis of the Proteasome Regulatory Particle Base. *Cell* **137,** 887–899 (2009).
This paper identifies assembly chaperones for the regulatory particles of the proteasome.

62. Kaneko, T. *et al.* Assembly Pathway of the Mammalian Proteasome Base Subcomplex Is Mediated by Multiple Specific Chaperones. *Cell* **137,** 914–925 (2009).
This paper identifies assembly chaperones for the regulatory particles of the proteasome.
63. Saeki, Y., Toh-E, A., Kudo, T., Kawamura, H. & Tanaka, K. Multiple proteasome-interacting proteins assist the assembly of the yeast 19S regulatory particle. *Cell* **137,** 900–913 (2009).
This paper identifies assembly chaperones for the regulatory particles of the proteasome.
64. Le Tallec, B., Barrault, M.-B., Guérois, R., Carré, T. & Peyroche, A. Hsm3/S5b Participates in the Assembly Pathway of the 19S Regulatory Particle of the Proteasome. *Mol. Cell* **33,** 389–399 (2009).
65. Hanssum, A. *et al.* An inducible chaperone adapts proteasome assembly to stress. *Mol. Cell* **55,** 566–577 (2014).
This paper shows that proteasome assembly is a regulated.
66. Roelofs, J. *et al.* Chaperone-mediated pathway of proteasome regulatory particle assembly. *Nature* **459,** 861–865 (2009).
This paper identifies assembly chaperones for the regulatory particles of the proteasome.
67. Park, S. *et al.* Reconfiguration of the proteasome during chaperone-mediated assembly. *Nature* **497,** 512–516 (2013).
68. Park, S. *et al.* Hexameric assembly of the proteasomal ATPases is templated through their C termini. *Nature* **459,** 866–870 (2009).
This paper identifies assembly chaperones for the regulatory particles of the proteasome.
69. Tomko, R. J., Funakoshi, M., Schneider, K., Wang, J. & Hochstrasser, M. Heterohexameric ring arrangement of the eukaryotic proteasomal ATPases: implications for proteasome structure and assembly. *Mol. Cell* **38,** 393–403 (2010).
70. Förster, F. *et al.* An atomic model AAA-ATPase/20S core particle sub-complex of the 26S proteasome. *Biochem. Biophys. Res. Commun.* **388,** 228–233 (2009).
71. Li, F. *et al.* Nucleotide-dependent switch in proteasome assembly mediated by the Nas6 chaperone. *Proc. Natl. Acad. Sci.* **114,** 1548–1553 (2017).
72. Satoh, T. *et al.* Structural Basis for Proteasome Formation Controlled by an Assembly Chaperone Nas2. *Structure* **22,** 731–743 (2014).
73. Barrault, M.-B. *et al.* Dual functions of the Hsm3 protein in chaperoning and scaffolding regulatory particle subunits during the proteasome assembly. *Proc. Natl. Acad. Sci.* **109,** E1001–E1010 (2012).
74. Tomko Jr., R. J. & Hochstrasser, M. The Intrinsically Disordered Sem1 Protein Functions as a Molecular Tether during Proteasome Lid Biogenesis. *Mol. Cell* **53,** 433–443 (2014).
75. Fukunaga, K., Kudo, T., Toh-e, A., Tanaka, K. & Saeki, Y. Dissection of the assembly pathway of the proteasome lid in Saccharomyces cerevisiae. *Biochem. Biophys. Res. Commun.* **396,** 1048–1053 (2010).
76. Estrin, E., Lopez-Blanco, J. R., Chacón, P. & Martin, A. Formation of an Intricate Helical Bundle Dictates the Assembly of the 26S Proteasome Lid. *Structure* **21,** 1624–1635 (2013).
77. Tomko, R. J. *et al.* A Single α Helix Drives Extensive Remodeling of the Proteasome Lid and Completion of Regulatory Particle Assembly. *Cell* **163,** 432–444 (2015).
78. Park, S., Tian, G., Roelofs, J. & Finley, D. Assembly manual for the proteasome regulatory particle: the first draft. *Biochem. Soc. Trans.* **38,** 6–13 (2010).

79. Sokolova, V., Li, F., Polovin, G. & Park, S. Proteasome Activation is Mediated via a Functional Switch of the Rpt6 C-terminal Tail Following Chaperone-dependent Assembly. *Sci. Rep.* **5,** srep14909 (2015).
80. Shi, Y. *et al.* Rpn1 provides adjacent receptor sites for substrate binding and deubiquitination by the proteasome. *Science* **351,** (2016).
81. van Nocker, S. *et al.* The multiubiquitin-chain-binding protein Mcb1 is a component of the 26S proteasome in Saccharomyces cerevisiae and plays a nonessential, substrate-specific role in protein turnover. *Mol. Cell. Biol.* **16,** 6020–6028 (1996).
82. Hamazaki, J., Hirayama, S. & Murata, S. Redundant Roles of Rpn10 and Rpn13 in Recognition of Ubiquitinated Proteins and Cellular Homeostasis. *PLOS Genet.* **11,** e1005401 (2015).
83. Hamazaki, J. *et al.* Rpn10-Mediated Degradation of Ubiquitinated Proteins Is Essential for Mouse Development. *Mol. Cell. Biol.* **27,** 6629–6638 (2007).
84. de Poot, S. A. H., Tian, G. & Finley, D. Meddling with Fate: The Proteasomal Deubiquitinating Enzymes. *J. Mol. Biol.* **429,** 3525–3545 (2017).
85. Lee, B.-H. *et al.* Enhancement of proteasome activity by a small-molecule inhibitor of USP14. *Nature* **467,** 179–184 (2010).
86. Hoyt, M. A. & Coffino, P. Ubiquitin-free routes into the proteasome. *Cell. Mol. Life Sci. CMLS* **61,** 1596–1600 (2004).
87. Ben-Nissan, G. & Sharon, M. Regulating the 20S proteasome ubiquitin-independent degradation pathway. *Biomolecules* **4,** 862–884 (2014).
88. Navon, A. & Ciechanover, A. The 26 S proteasome: from basic mechanisms to drug targeting. *J. Biol. Chem.* **284,** 33713–33718 (2009).
89. Mannhaupt, G., Schnall, R., Karpov, V., Vetter, I. & Feldmann, H. Rpn4p acts as a transcription factor by binding to PACE, a nonamer box found upstream of 26S proteasomal and other genes in yeast. *FEBS Lett.* **450,** 27–34 (1999).
90. Xie, Y. & Varshavsky, A. RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome: A negative feedback circuit. *Proc. Natl. Acad. Sci.* **98,** 3056–3061 (2001).
This paper identifies a transcription factor controlling expression of all proteasome subunits.
91. Ma, M. & Liu, Z. L. Comparative transcriptome profiling analyses during the lag phase uncover YAP1, PDR1, PDR3, RPN4, and HSF1 as key regulatory genes in genomic adaptation to the lignocellulose derived inhibitor HMF for Saccharomyces cerevisiae. *BMC Genomics* **11,** 660 (2010).
92. Meiners, S. *et al.* Inhibition of Proteasome Activity Induces Concerted Expression of Proteasome Genes and de Novo Formation of Mammalian Proteasomes. *J. Biol. Chem.* **278,** 21517–21525 (2003).
93. Kwak, M.-K., Wakabayashi, N., Greenlaw, J. L., Yamamoto, M. & Kensler, T. W. Antioxidants Enhance Mammalian Proteasome Expression through the Keap1-Nrf2 Signaling Pathway. *Mol. Cell. Biol.* **23,** 8786–8794 (2003).
94. Radhakrishnan, S. K. *et al.* Transcription factor Nrf1 mediates the proteasome recovery pathway after proteasome inhibition in mammalian cells. *Mol. Cell* **38,** 17–28 (2010).
95. Taguchi, K., Motohashi, H. & Yamamoto, M. Molecular mechanisms of the Keap1–Nrf2 pathway in stress response and cancer evolution. *Genes Cells Devoted Mol. Cell. Mech.* **16,** 123–140 (2011).
96. Kraft, D. C., Deocaris, C. C., Wadhwa, R. & Rattan, S. I. S. Preincubation with the proteasome inhibitor MG-132 enhances proteasome activity via the Nrf2 transcription factor in aging human skin fibroblasts. *Ann. N. Y. Acad. Sci.* **1067,** 420–424 (2006).

97. Koizumi, S. *et al.* The aspartyl protease DDI2 activates Nrf1 to compensate for proteasome dysfunction. *eLife* **5,** e18357 (2016).
98. Lehrbach, N. J. & Ruvkun, G. Proteasome dysfunction triggers activation of SKN-1A/Nrf1 by the aspartic protease DDI-1. *eLife* **5,** e17721 (2016).
99. Sykiotis, G. P. & Bohmann, D. Stress-activated cap'n'collar transcription factors in aging and human disease. *Sci. Signal.* **3,** re3 (2010).
100. Kwak, M.-K. *et al.* Modulation of gene expression by cancer chemopreventive dithiolethiones through the Keap1-Nrf2 pathway. Identification of novel gene clusters for cell survival. *J. Biol. Chem.* **278,** 8135–8145 (2003).
101. Kapeta, S., Chondrogianni, N. & Gonos, E. S. Nuclear erythroid factor 2-mediated proteasome activation delays senescence in human fibroblasts. *J. Biol. Chem.* **285,** 8171–8184 (2010).
102. Sha, Z. & Goldberg, A. L. Proteasome-Mediated Processing of Nrf1 Is Essential for Coordinate Induction of All Proteasome Subunits and p97. *Curr. Biol.* **24,** 1573–1583 (2014).
103. Gladman, N. P., Marshall, R. S., Lee, K.-H. & Vierstra, R. D. The Proteasome Stress Regulon Is Controlled by a Pair of NAC Transcription Factors in Arabidopsis. *Plant Cell* **28,** 1279–1296 (2016).
104. Yabuta, Y. *et al.* Identification of recognition sequence of ANAC078 protein by the cyclic amplification and selection of targets technique. *Plant Signal. Behav.* **5,** 695–697 (2010).
105. Nguyen, H. M. *et al.* An upstream regulator of the 26S proteasome modulates organ size in Arabidopsis thaliana. *Plant J.* **74,** 25–36 (2013).
106. Rousseau, A. & Bertolotti, A. An evolutionarily conserved pathway controls proteasome homeostasis. *Nature* **536,** 184–189 (2016).
This paper identifies a signaling pathway controlling proteasome assembly.
107. Gao, X. *et al.* Quantitative profiling of initiating ribosomes in vivo. *Nat. Methods* **12,** 147–153 (2015).
108. Shirozu, R., Yashiroda, H. & Murata, S. Identification of minimum Rpn4-responsive elements in genes related to proteasome functions. *FEBS Lett.* **589,** 933–940 (2015).
109. Zhang, X. *et al.* MicroRNA-101 Suppresses Tumor Cell Proliferation by Acting as an Endogenous Proteasome Inhibitor via Targeting the Proteasome Assembly Factor POMP. *Mol. Cell* **59,** 243–257 (2015).
110. Wrobel, L. *et al.* Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol. *Nature* **524,** 485–488 (2015).
111. Lee, W. *et al.* iRhom1 regulates proteasome activity via PAC1/2 under ER stress. *Sci. Rep.* **5,** 11559 (2015).
112. Freeman, M. The Rhomboid-Like Superfamily: Molecular Mechanisms and Biological Roles. *Annu. Rev. Cell Dev. Biol.* **30,** 235–254 (2014).
113. Zettl, M., Adrain, C., Strisovsky, K., Lastun, V. & Freeman, M. Rhomboid Family Pseudoproteases Use the ER Quality Control Machinery to Regulate Intercellular Signaling. *Cell* **145,** 79–91 (2011).
114. Bergbold, N. & Lemberg, M. K. Emerging role of rhomboid family proteins in mammalian biology and disease. *Biochim. Biophys. Acta* **1828,** 2840–2848 (2013).
115. Akahane, T., Sahara, K., Yashiroda, H., Tanaka, K. & Murata, S. Involvement of Bag6 and the TRC pathway in proteasome assembly. *Nat. Commun.* **4,** ncomms3234 (2013).
116. Smith, D. M. *et al.* Docking of the proteasomal ATPases' carboxyl termini in the 20S proteasome's alpha ring opens the gate for substrate entry. *Mol. Cell* **27,** 731–744 (2007).
117. Śledź, P. *et al.* Structure of the 26S proteasome with ATP-γS bound provides insights into the mechanism of nucleotide-dependent substrate translocation. *Proc. Natl. Acad. Sci. U. S. A.* **110,** 7264–7269 (2013).

118. Bajorek, M., Finley, D. & Glickman, M. H. Proteasome disassembly and downregulation is correlated with viability during stationary phase. *Curr. Biol. CB* **13,** 1140–1144 (2003).
119. Kleijnen, M. F. *et al.* Stability of the proteasome can be regulated allosterically through engagement of its proteolytic active sites. *Nat. Struct. Mol. Biol.* **14,** 1180–1188 (2007).
120. Wang, X., Yen, J., Kaiser, P. & Huang, L. Regulation of the 26S Proteasome Complex During Oxidative Stress. *Sci Signal* **3,** ra88-ra88 (2010).
121. Liu, C.-W. *et al.* ATP Binding and ATP Hydrolysis Play Distinct Roles in the Function of 26S Proteasome. *Mol. Cell* **24,** 39–50 (2006).
122. Livnat-Levanon, N. *et al.* Reversible 26S Proteasome Disassembly upon Mitochondrial Stress. *Cell Rep.* **7,** 1371–1380 (2014).
123. Imai, J., Maruya, M., Yashiroda, H., Yahara, I. & Tanaka, K. The molecular chaperone Hsp90 plays a role in the assembly and maintenance of the 26S proteasome. *EMBO J.* **22,** 3557–3567 (2003).
124. Yamano, T. *et al.* Hsp90-mediated Assembly of the 26 S Proteasome Is Involved in Major Histocompatibility Complex Class I Antigen Processing. *J. Biol. Chem.* **283,** 28060–28065 (2008).
125. Acquah, J.-R. Q., Haratake, K., Rakwal, R., Udono, H. & Chiba, T. Hsp90 and ECM29 Are Important to Maintain the Integrity of Mammalian 26S Proteasome. *Adv. Biol. Chem.* **05,** 255 (2015).
126. Schopf, F. H., Biebl, M. M. & Buchner, J. The HSP90 chaperone machinery. *Nat. Rev. Mol. Cell Biol.* **18,** 345–360 (2017).
127. Vilchez, D. *et al.* RPN-6 determines C. elegans longevity under proteotoxic stress conditions. *Nature* **489,** 263–268 (2012).
128. Vilchez, D. *et al.* Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. *Nature* **489,** 304–308 (2012).
129. Lehmann, A., Niewienda, A., Jechow, K., Janek, K. & Enenkel, C. Ecm29 Fulfils Quality Control Functions in Proteasome Assembly. *Mol. Cell* **38,** 879–888 (2010).
130. Park, S., Kim, W., Tian, G., Gygi, S. P. & Finley, D. Structural Defects in the Regulatory Particle-Core Particle Interface of the Proteasome Induce a Novel Proteasome Stress Response. *J. Biol. Chem.* **286,** 36652–36666 (2011).
131. De La Mota-Peynado, A. *et al.* The proteasome-associated protein Ecm29 inhibits proteasomal ATPase activity and in vivo protein degradation by the proteasome. *J. Biol. Chem.* **288,** 29467–29481 (2013).
132. Lee, S. Y.-C., Mota-Peynado, A. D. L. & Roelofs, J. Loss of Rpt5 Protein Interactions with the Core Particle and Nas2 Protein Causes the Formation of Faulty Proteasomes That Are Inhibited by Ecm29 Protein. *J. Biol. Chem.* **286,** 36641–36651 (2011).
133. Wang, X. *et al.* The proteasome-interacting Ecm29 protein disassembles the 26S proteasome in response to oxidative stress. *J. Biol. Chem.* **292,** 16310–16320 (2017).
134. Asher, G., Reuven, N. & Shaul, Y. 20S proteasomes and protein degradation 'by default'. *BioEssays News Rev. Mol. Cell. Dev. Biol.* **28,** 844–849 (2006).
135. Im, E. & Chung, K. C. Precise assembly and regulation of 26S proteasome and correlation between proteasome dysfunction and neurodegenerative diseases. *BMB Rep.* **49,** 459–473 (2016).
136. Livneh, I., Cohen-Kaplan, V., Cohen-Rosenzweig, C., Avni, N. & Ciechanover, A. The life cycle of the 26S proteasome: from birth, through regulation and function, and onto its death. *Cell Res.* **26,** 869 (2016).
137. Guo, X., Huang, X. & Chen, M. J. Reversible phosphorylation of the 26S proteasome. *Protein Cell* **8,** 255–272 (2017).

138. Satoh, K., Sasajima, H., Nyoumura, K., Yokosawa, H. & Sawada, H. Assembly of the 26S Proteasome Is Regulated by Phosphorylation of the p45/Rpt6 ATPase Subunit. *Biochemistry (Mosc.)* **40,** 314–319 (2001).
139. Pereira, M. E. & Wilk, S. Phosphorylation of the multicatalytic proteinase complex from bovine pituitaries by a copurifying cAMP-dependent protein kinase. *Arch. Biochem. Biophys.* **283,** 68–74 (1990).
140. Lin, J.-T. *et al.* Regulation of Feedback between Protein Kinase A and the Proteasome System Worsens Huntington's Disease. *Mol. Cell. Biol.* **33,** 1073–1084 (2013).
141. Asai, M. *et al.* PKA rapidly enhances proteasome assembly and activity in in vivo canine hearts. *J. Mol. Cell. Cardiol.* **46,** 452–462 (2009).
142. Myeku, N. *et al.* Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. *Nat. Med.* **22,** 46–53 (2016).
143. Myeku, N., Wang, H. & Figueiredo-Pereira, M. E. cAMP stimulates the ubiquitin/proteasome pathway in rat spinal cord neurons. *Neurosci. Lett.* **527,** 126–131 (2012).
144. Lokireddy, S., Kukushkin, N. V. & Goldberg, A. L. cAMP-induced phosphorylation of 26S proteasomes on Rpn6/PSMD11 enhances their activity and the degradation of misfolded proteins. *Proc. Natl. Acad. Sci.* **112,** E7176–E7185 (2015).
145. Guo, X. *et al.* UBLCP1 is a 26S proteasome phosphatase that regulates nuclear proteasome activity. *Proc. Natl. Acad. Sci. U. S. A.* **108,** 18649–18654 (2011).
146. Sun, S. *et al.* Phosphatase UBLCP1 controls proteasome assembly. *Open Biol.* **7,** (2017).
147. Cho-Park, P. F. & Steller, H. Proteasome regulation by ADP-ribosylation. *Cell* **153,** 614–627 (2013).
148. Li, X., Thompson, D., Kumar, B. & DeMartino, G. N. Molecular and cellular roles of PI31 (PSMF1) protein in regulation of proteasome function. *J. Biol. Chem.* **289,** 17392–17405 (2014).
149. Kikuchi, J. *et al.* Co- and post-translational modifications of the 26S proteasome in yeast. *Proteomics* **10,** 2769–2779 (2010).
150. Tanaka, K. & Matsuda, N. Proteostasis and neurodegeneration: the roles of proteasomal degradation and autophagy. *Biochim. Biophys. Acta* **1843,** 197–204 (2014).
151. Dikic, I. Proteasomal and Autophagic Degradation Systems. *Annu. Rev. Biochem.* **86,** 193–224 (2017).
152. Pilla, E., Schneider, K. & Bertolotti, A. Coping with Protein Quality Control Failure. *Annu. Rev. Cell Dev. Biol.* **33,** 439–465 (2017).
153. Marshall, R. S., Li, F., Gemperline, D. C., Book, A. J. & Vierstra, R. D. Autophagic Degradation of the 26S Proteasome Is Mediated by the Dual ATG8/Ubiquitin Receptor RPN10 in Arabidopsis. *Mol. Cell* **58,** 1053–1066 (2015).
154. Waite, K. A., De-La Mota-Peynado, A., Vontz, G. & Roelofs, J. Starvation Induces Proteasome Autophagy with Different Pathways for Core and Regulatory Particles. *J. Biol. Chem.* **291,** 3239–3253 (2016).
155. Marshall, R. S., McLoughlin, F. & Vierstra, R. D. Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone. *Cell Rep.* **16,** 1717–1732 (2016).
156. Cohen-Kaplan, V. *et al.* p62- and ubiquitin-dependent stress-induced autophagy of the mammalian 26S proteasome. *Proc. Natl. Acad. Sci.* **113,** E7490–E7499 (2016).
157. Saxton, R. A. & Sabatini, D. M. mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **168,** 960–976 (2017).
158. González, A. & Hall, M. N. Nutrient sensing and TOR signaling in yeast and

mammals. *EMBO J.* **36,** 397–408 (2017).
159. Kim, J., Kundu, M., Viollet, B. & Guan, K.-L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* **13,** 132–141 (2011).
160. Martina, J. A., Chen, Y., Gucek, M. & Puertollano, R. MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB. *Autophagy* **8,** 903–914 (2012).
161. Roczniak-Ferguson, A. *et al.* The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis. *Sci. Signal.* **5,** ra42 (2012).
162. Settembre, C. *et al.* A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. *EMBO J.* **31,** 1095–1108 (2012).
163. Kaur, J. & Debnath, J. Autophagy at the crossroads of catabolism and anabolism. *Nat. Rev. Mol. Cell Biol.* **16,** 461–472 (2015).
164. Luo, T. *et al.* PSMD10/gankyrin induces autophagy to promote tumor progression through cytoplasmic interaction with ATG7 and nuclear transactivation of ATG7 expression. *Autophagy* **12,** 1355–1371 (2016).
165. Zhang, Y. *et al.* Coordinated regulation of protein synthesis and degradation by mTORC1. *Nature* **513,** 440–443 (2014).
166. Zhao, J., Zhai, B., Gygi, S. P. & Goldberg, A. L. mTOR inhibition activates overall protein degradation by the ubiquitin proteasome system as well as by autophagy. *Proc. Natl. Acad. Sci.* **112,** 15790–15797 (2015).
167. Zhao, J. & Goldberg, A. L. Coordinate regulation of autophagy and the ubiquitin proteasome system by MTOR. *Autophagy* **12,** 1967–1970 (2016).
168. Vabulas, R. M. & Hartl, F. U. Protein synthesis upon acute nutrient restriction relies on proteasome function. *Science* **310,** 1960–1963 (2005).
This paper demonstrates the importance of the proteasome, under nutrient starvation, for the maintenance of amino acid levels and protein synthesis.
169. Fujiwara, T. *et al.* Proteasomes are essential for yeast proliferation. cDNA cloning and gene disruption of two major subunits. *J. Biol. Chem.* **265,** 16604–16613 (1990).
170. Gomes, A. V. Genetics of Proteasome Diseases. *Scientifica* (2013). doi:10.1155/2013/637629
171. Parzych, K. *et al.* Inadequate fine-tuning of protein synthesis and failure of amino acid homeostasis following inhibition of the ATPase VCP/p97. *Cell Death Dis.* **6,** e2031 (2015).
172. Chondrogianni, N., Sakellari, M., Lefaki, M., Papaevgeniou, N. & Gonos, E. S. Proteasome activation delays aging in vitro and in vivo. *Free Radic. Biol. Med.* **71,** 303–320 (2014).
173. Saez, I. & Vilchez, D. The Mechanistic Links Between Proteasome Activity, Aging and Age-related Diseases. *Curr. Genomics* **15,** 38–51 (2014).
174. N, C. *et al.* Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases. *Ageing Res. Rev.* **23,** 37–55 (2015).
175. Vilchez, D., Saez, I. & Dillin, A. The role of protein clearance mechanisms in organismal ageing and age-related diseases. *Nat. Commun.* **5,** ncomms6659 (2014).
176. Bertolotti, A. The Ubiquitin–Proteasome System in Neurodegenerative Diseases: More than the Usual Suspects. in *Protein Chaperones and Protection from Neurodegenerative Diseases* 179–210 (Wiley-Blackwell, 2011). doi:10.1002/9781118063903.ch5
177. Marshall, A. G. *et al.* Genetic Background Alters the Severity and Onset of Neuromuscular Disease Caused by the Loss of Ubiquitin-Specific Protease 14 (Usp14). *PLOS ONE* **8,** e84042 (2013).
178. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The

Hallmarks of Aging. *Cell* **153,** 1194–1217 (2013).
179. Finkel, T., Serrano, M. & Blasco, M. A. The common biology of cancer and ageing. *Nature* **448,** 767–774 (2007).
180. Manasanch, E. E. & Orlowski, R. Z. Proteasome inhibitors in cancer therapy. *Nat. Rev. Clin. Oncol.* **14,** 417–433 (2017).
181. Grigoreva, T. A., Tribulovich, V. G., Garabadzhiu, A. V., Melino, G. & Barlev, N. A. The 26S proteasome is a multifaceted target for anti-cancer therapies. *Oncotarget* **6,** 24733–24749 (2015).
182. Acosta-Alvear, D. *et al.* Paradoxical resistance of multiple myeloma to proteasome inhibitors by decreased levels of 19S proteasomal subunits. *eLife* **4,** e08153 (2015).
183. Langlands, F. E. *et al.* PSMD9 expression predicts radiotherapy response in breast cancer. *Mol. Cancer* **13,** 73 (2014).
184. Hopper, J. L., Begum, N., Smith, L. & Hughes, T. A. The role of PSMD9 in human disease: future clinical and therapeutic implications. *Mol. 2015 Vol 2 Pages 476-484* (2015). doi:10.3934/molsci.2015.4.476
185. Dawson, S., Higashitsuji, H., Wilkinson, A. J., Fujita, J. & Mayer, R. J. Gankyrin: a new oncoprotein and regulator of pRb and p53. *Trends Cell Biol.* **16,** 229–233 (2006).
186. Higashitsuji, H. *et al.* The oncoprotein gankyrin binds to MDM2/HDM2, enhancing ubiquitylation and degradation of p53. *Cancer Cell* **8,** 75–87 (2005).
187. Walerych, D. *et al.* Proteasome machinery is instrumental in a common gain-of-function program of the p53 missense mutants in cancer. *Nat. Cell Biol.* **18,** 897–909 (2016).
188. Varambally, S. *et al.* Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science* **322,** 1695–1699 (2008).
189. Li, B. *et al.* The Nuclear Factor (Erythroid-derived 2)-like 2 and Proteasome Maturation Protein Axis Mediates Bortezomib Resistance in Multiple Myeloma. *J. Biol. Chem.* jbc.M115.664953 (2015). doi:10.1074/jbc.M115.664953
190. Hashimoto, J. *et al.* Novel In Vitro Protein Fragment Complementation Assay Applicable to High-Throughput Screening in a 1536-Well Format. *J. Biomol. Screen.* **14,** 970–979 (2009).
191. Izumikawa, M. *et al.* JBIR-22, an inhibitor for protein-protein interaction of the homodimer of proteasome assembly factor 3. *J. Nat. Prod.* **73,** 628–631 (2010).
192. Glynne, R. *et al.* A proteasome-related gene between the two ABC transporter loci in the class II region of the human MHC. *Nature* **353,** 357 (1991).
193. Kelly, A. *et al.* Second proteasome-related gene in the human MHC class II region. *Nature* **353,** 667 (1991).
194. Hisamatsu, H. *et al.* Newly identified pair of proteasomal subunits regulated reciprocally by interferon gamma. *J. Exp. Med.* **183,** 1807–1816 (1996).
195. Nandi, D., Jiang, H. & Monaco, J. J. Identification of MECL-1 (LMP-10) as the third IFN-gamma-inducible proteasome subunit. *J. Immunol. Baltim. Md 1950* **156,** 2361–2364 (1996).
196. Ortiz-Navarrete, V. *et al.* Subunit of the '20S' proteasome (multicatalytic proteinase) encoded by the major histocompatibility complex. *Nature* **353,** 662–664 (1991).
197. Groettrup, M. *et al.* A third interferon-γ-induced subunit exchange in the 20S proteasome. *Eur. J. Immunol.* **26,** 863–869 (1996).
198. Eskandari, S. K., Seelen, M. a. J., Lin, G. & Azzi, J. R. The immunoproteasome: An old player with a novel and emerging role in alloimmunity. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* **17,** 3033–3039 (2017).
199. Kaur, G. & Batra, S. Emerging role of immunoproteasomes in pathophysiology. *Immunol. Cell Biol.* **94,** 812–820 (2016).
200. Kimura, H., Caturegli, P., Takahashi, M. & Suzuki, K. New Insights into the Function

of the Immunoproteasome in Immune and Nonimmune Cells. *J. Immunol. Res.* **2015,** 541984 (2015).
201. Murata, S. *et al.* Regulation of CD8+ T cell development by thymus-specific proteasomes. *Science* **316,** 1349–1353 (2007).
202. Tomaru, U. & Kasahara, M. Thymoproteasome: role in thymic selection and clinical significance as a diagnostic marker for thymic epithelial tumors. *Arch. Immunol. Ther. Exp. (Warsz.)* **61,** 357–365 (2013).
203. Kniepert, A. & Groettrup, M. The unique functions of tissue-specific proteasomes. *Trends Biochem. Sci.* **39,** 17–24 (2014).
204. Qian, M.-X. *et al.* Acetylation-Mediated Proteasomal Degradation of Core Histones during DNA Repair and Spermatogenesis. *Cell* **153,** 1012–1024 (2013).
205. Uechi, H., Hamazaki, J. & Murata, S. Characterization of the Testis-specific Proteasome Subunit α4s in Mammals. *J. Biol. Chem.* **289,** 12365–12374 (2014).
206. Reinke, A. *et al.* TOR complex 1 includes a novel component, Tco89p (YPL180w), and cooperates with Ssd1p to maintain cellular integrity in Saccharomyces cerevisiae. *J. Biol. Chem.* **279,** 14752–14762 (2004).
207. Loewith, R. *et al.* Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. *Mol. Cell* **10,** 457–468 (2002).
This paper identifies TORC1, the complex sensitive to rapamycin.
208. Kim, D.-H. *et al.* GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. *Mol. Cell* **11,** 895–904 (2003).
209. Kim, D.-H. *et al.* mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell* **110,** 163–175 (2002).
This paper sheds light on the nutrient sensing complex signaling to TORC1.
210. Hara, K. *et al.* Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell* **110,** 177–189 (2002).
This paper sheds light on the nutrient sensing proteins upstream of TORC1.
211. Wang, L., Harris, T. E., Roth, R. A. & Lawrence, J. C. PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding. *J. Biol. Chem.* **282,** 20036–20044 (2007).
212. Sancak, Y. *et al.* PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. *Mol. Cell* **25,** 903–915 (2007).
213. Vander Haar, E., Lee, S.-I., Bandhakavi, S., Griffin, T. J. & Kim, D.-H. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. *Nat. Cell Biol.* **9,** 316–323 (2007).
214. Chantranupong, L. *et al.* The Sestrins Interact with GATOR2 to Negatively Regulate the Amino-Acid-Sensing Pathway Upstream of mTORC1. *Cell Rep.* **9,** 1–8 (2014).
215. Parmigiani, A. *et al.* Sestrins Inhibit mTORC1 Kinase Activation through the GATOR Complex. *Cell Rep.* **9,** 1281–1291 (2014).
216. Chantranupong, L. *et al.* The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway. *Cell* **165,** 153–164 (2016).
217. Saxton, R. A., Chantranupong, L., Knockenhauer, K. E., Schwartz, T. U. & Sabatini, D. M. Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature* **536,** 229–233 (2016).
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Acknowledgments

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Author contributions

A. R. and A. B. researched data for the article, wrote and revised the article.

Competing interests statement

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Reviewer information

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Display items

Box 1 | **Tissues specific proteasomes**

One key role of the proteasome in the immune system is to generate antigenic peptides for presentation on major histocompatibility complex (MHC) class I molecules. This process is mainly mediated by a specialised-type of proteasome known as immunoproteasome. The proteolytic subunits of the immunoproteasome differ from those of the constitutive proteasome (see the figure, parts a-b). β1, β2 and β5 are replaced by β1i (also known as low molecular weight protein 2 (LMP2) and PSMB9), β2i (also known as multicatalytic endopeptidase complex-like 1 (MECL-1), LMP10 and PSMB10) and β5i (also known as LMP7 and PSMB8), respectively[192–197]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"afncu7eiic","properties":{"formattedCitation":"{\\rtf \\super 193\\uc0\\u8211{}198\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":312,"uris":["http://zotero.org/users/4604651/items/YX2C5QH5"],"uri":["http://zotero.org/users/4604651/items/YX2C5QH5"],"itemData":{"id":312,"type":"article-journal","title":"A proteasome-related gene between the two ABC transporter loci in the class II region of the human MHC","container-title":"Nature","page":"357","volume":"353","issue":"6342","source":"www.nature.com","abstract":"A proteasome-related gene between the two ABC transporter loci in the class II region of the human MHC","DOI":"10.1038/353357a0","ISSN":"1476-

4687","language":"En","author":[{"family":"Glynne","given":"Richard"},{"family":"Powis","given":"Stephen H."},{"family":"Beck","given":"Stephan"},{"family":"Kelly","given":"Adrian"},{"family":"Kerr","given":"Lesley-Anne"},{"family":"Trowsdale","given":"John"}],"issued":{"date-parts":[["1991",9]]}},{"id":309,"uris":["http://zotero.org/users/4604651/items/KGDBWLY6"],"uri":["http://zotero.org/users/4604651/items/KGDBWLY6"],"itemData":{"id":309,"type":"article-journal","title":"Second proteasome-related gene in the human MHC class II region","container-title":"Nature","page":"667","volume":"353","issue":"6345","source":"www.nature.com","abstract":"Second proteasome-related gene in the human MHC class II region","DOI":"10.1038/353667a0","ISSN":"1476-4687","language":"En","author":[{"family":"Kelly","given":"Adrian"},{"family":"Powis","given":"Stephen H."},{"family":"Glynne","given":"Richard"},{"family":"Radley","given":"Elizabeth"},{"family":"Beck","given":"Stephan"},{"family":"Trowsdale","given":"John"}],"issued":{"date-parts":[["1991",10]]}},{"id":315,"uris":["http://zotero.org/users/4604651/items/Z3XZKAPP"],"uri":["http://zotero.org/users/4604651/items/Z3XZKAPP"],"itemData":{"id":315,"type":"article-journal","title":"Newly identified pair of proteasomal subunits regulated reciprocally by interferon gamma","container-title":"The Journal of Experimental Medicine","page":"1807-1816","volume":"183","issue":"4","source":"PubMed","abstract":"Interferon (IFN) gamma induces replacements of the proteasomal subunits X and Y by LMP7 and LMP2, respectively, resulting in an alteration of the proteolytic specificity. We found a third pair of proteasome subunits expressed reciprocally in response to IFN-gamma. Molecular cloning of a cDNA encoding one subunit designated as Z, downregulated by IFN-gamma, showed that it is a novel proteasomal subunit with high homology to MECL1, which is markedly induced by IFN-gamma. Thus, IFN-gamma induces subunit replacements of not only X and Y by LMP7 and LMP2, respectively, but also of Z by MECL1, producing proteasomes responsible for immunological processing of endogenous antigens. When processed from their precursors, three pairs of the 10 homologous, but distinct, beta-type subunits of eukaryotic proteasomes, that is, X/LMP7, Y/LMP2, and Z/MECL1, have an NH2-terminal threonine residue, assumed to be part of a catalytic center. These findings suggest that the altered molecular organization of the proteasome induced by IFN-gamma may be responsible for acquisition of its functional change.","ISSN":"0022-1007","note":"PMID: 8666937\nPMCID: PMC2192534","journalAbbreviation":"J. Exp. Med.","language":"eng","author":[{"family":"Hisamatsu","given":"H."},{"family":"Shimbara","given":"N."},{"family":"Saito","given":"Y."},{"family":"Kristensen","given":"P."},{"family":"Hendil","given":"K. B."},{"family":"Fujiwara","given":"T."},{"family":"Takahashi","given":"E."},{"family":"Tanahashi","given":"N."},{"family":"Tamura","given":"T."},{"family":"Ichihara","given":"A."},{"family":"Tanaka","given":"K."}],"issued":{"date-parts":[["1996",4,1]]}},{"id":317,"uris":["http://zotero.org/users/4604651/items/8AAPKFJE"],"uri":["http://zotero.org/users/4604651/items/8AAPKFJE"],"itemData":{"id":317,"type":"article-journal","title":"Identification of MECL-1 (LMP-10) as the third IFN-gamma-inducible proteasome subunit","container-title":"Journal of Immunology (Baltimore, Md.: 1950)","page":"2361-2364","volume":"156","issue":"7","source":"PubMed","abstract":"We show that six proteasome-associated proteins are induced by IFN-gamma, corresponding to three proteasome beta-type subunits and their precursors: the MHC-linked subunits (LMP-2 and LMP-7) and LMP-10. Concurrently, incorporation of LMP-9, LMP-17, and LMP-19 into proteasomes is reduced. LMP-10 appears to be the product of a previously cloned proteasome subunit gene, MECL-1. MECL-1 transcription is increased in the presence of IFN-gamma, whereas the

transcription of two other proteasome genes, Lmp-15 and Lmp-3, is not affected. The three IFN-gamma-inducible subunits and their constitutively expressed counterparts contain most or all of the catalytic sites of the proteasome. Independent assortment of LMP-2, LMP-7, and LMP-10 into different proteasome complexes may thus generate up to 36 unique proteasome subsets. This may increase the repertoire of potentially antigenic peptides for presentation by MHC class I.","ISSN":"0022-1767","note":"PMID: 8786291","journalAbbreviation":"J. Immunol.","language":"eng","author":[{"family":"Nandi","given":"D."},{"family":"Jiang","given":"H."},{"family":"Monaco","given":"J. J."}],"issued":{"date-parts":[["1996",4,1]]}}},{"id":307,"uris":["http://zotero.org/users/4604651/items/GNLI23DC"],"uri":["http://zotero.org/users/4604651/items/GNLI23DC"],"itemData":{"id":307,"type":"article-journal","title":"Subunit of the '20S' proteasome (multicatalytic proteinase) encoded by the major histocompatibility complex","container-title":"Nature","page":"662-664","volume":"353","issue":"6345","source":"PubMed","abstract":"Cytotoxic T lymphocytes recognize fragments (peptides) of protein antigens presented by major histocompatibility complex (MHC) class I molecules. In general, the peptides are derived from cytosolic proteins and are then transported to the endoplasmic reticulum where they assemble with the MHC class I heavy chains and beta 2-microglobulin to form stable and functional class I molecules. The proteases involved in the generation of these peptides are unknown. One candidate is the proteasome, a nonlysosomal proteinase complex abundantly present in the cytosol. Proteasomes have several proteolytically active sites and are complexes of high relative molecular mass (Mr about 600K), consisting of about 20-30 subunits with Mrs between 15 and 30K. Here we show that at least one of these subunits is encoded by the mouse MHC in the region between the K locus and the MHC class II region, and inducible by interferon-gamma. This raises the intriguing possibility that the MHC encodes not only the MHC class I molecules themselves but also proteases involved in the formation of MHC-binding peptides.","DOI":"10.1038/353662a0","ISSN":"0028-0836","note":"PMID: 1922384","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Ortiz-Navarrete","given":"V."},{"family":"Seelig","given":"A."},{"family":"Gernold","given":"M."},{"family":"Frentzel","given":"S."},{"family":"Kloetzel","given":"P. M."},{"family":"Hämmerling","given":"G. J."}],"issued":{"date-parts":[["1991",10,17]]}},"locator":"-"},{"id":326,"uris":["http://zotero.org/users/4604651/items/3WK4BJHQ"],"uri":["http://zotero.org/users/4604651/items/3WK4BJHQ"],"itemData":{"id":326,"type":"article-journal","title":"A third interferon-γ-induced subunit exchange in the 20S proteasome","container-title":"European Journal of Immunology","page":"863-869","volume":"26","issue":"4","source":"Wiley Online Library","abstract":"The 20S proteasome is a protease complex of functional importance for antigen processing. Two of the 14 proteasome subunits, δ and MB1, can be replaced by the major histocompatibility complex (MHC)-encoded and interferon-γ (IFN–γ)-inducible subunits LMP2 and LMP7, respectively. LMP2 and LMP7 alter the cleavage site specificity of the 20S proteasome and are required for the efficient generation of T cell epitopes from a number of viral proteins and for optimal MHC class I cell surface expression. We compared the 20S proteasome subunit pattern from IFN-γ-induced and non-induced mouse fibroblasts on two-dimensional gels and identified a third subunit exchange by microsequencing: the non-MHC-encoded subunit MECL-1 is induced by IFN-γ and replaces a so-far barely characterized β subunit designated ‘MC14’. In analogy to LMP2 and LMP7, MECL-1 may be functional in MHC class I-restricted antigen presentation.","DOI":"10.1002/eji.1830260421","ISSN":"1521-4141","journalAbbreviation":"Eur. J. Immunol.","language":"en","author":[{"family":"Groettrup","given":"Marcus"},{"family":"Kraft","given":"Regine"},{"family":"Kostka","given":"Susanne"},{"family":"Standera","given":"Sybille"},{"family":"Stohwasser","given":"Ralf"},{"family":"Kloetzel","given":"Peter-

M."}],"issued":{"date-parts":[["1996",4,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}

}. These immunosubunits are constitutively expressed in different immune tissues including the thymus and the spleen, but they are also induced in a broader range of cell types following exposition to proinflammatory cytokines such as interferon-γ[198,199]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2dnfuvbpjl","properties":{"formattedCitation":"{\\rtf \\super 199,200\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":328,"uris":["http://zotero.org/users/4604651/items/45NG8YTN"],"uri":["http://zotero.org/users/4604651/items/45NG8YTN"],"itemData":{"id":328,"type":"article-journal","title":"The immunoproteasome: An old player with a novel and emerging role in alloimmunity","container-title":"American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons","page":"3033-3039","volume":"17","issue":"12","source":"PubMed","abstract":"Modern treatment strategies for the maintenance of allograft acceptance frequently target ubiquitously-expressed pathways, leading to significant side-effects and poor long-term allograft outcomes. Constitutive proteasome inhibitors, which have recently been introduced for the treatment of antibody-mediated rejection, target the ubiquitously-expressed proteasome. To limit off-target effects and serious mechanism-based toxicity, however, these inhibitors are administered intermittently and suboptimally. Immunoproteasomes, which are an inducible subset of proteasomes enriched in immune cells, replace constitutive proteasomes after cell exposure to proinflammatory cytokines such as interferon-γ. While immunoproteasomes were first described as processors of antigen for presentation by major histocompatibility complex molecules, recent findings point to its broader biological roles. These vary from activating different subsets of the immune system, by controlling transcriptional activators and downstream cytokines, to affecting their differentiation and survival. These emerging roles of the immunoproteasome in activated immune cells have made it a rational candidate for the targeted treatment of immune-mediated diseases. Preclinical studies have established its role in maintaining allograft acceptance without significant short- or long-term toxicity. This review provides a brief background of the immunoproteasome and outlines its role in immunological pathways and its potential in alloimmunity.","DOI":"10.1111/ajt.14435","ISSN":"1600-6143","note":"PMID: 28719024","shortTitle":"The immunoproteasome","journalAbbreviation":"Am. J. Transplant.","language":"eng","author":[{"family":"Eskandari","given":"S. K."},{"family":"Seelen","given":"M. a. J."},{"family":"Lin","given":"G."},{"family":"Azzi","given":"J. R."}],"issued":{"date-parts":[["2017",12]]}}},{"id":330,"uris":["http://zotero.org/users/4604651/items/T5GXYZUE"],"uri":["http://zotero.org/users/4604651/items/T5GXYZUE"],"itemData":{"id":330,"type":"article-journal","title":"Emerging role of immunoproteasomes in pathophysiology","container-title":"Immunology and Cell Biology","page":"812-820","volume":"94","issue":"9","source":"PubMed","abstract":"The immunoproteasome is a proteasome variant that is found only in jawed vertebrates. It is responsible for degrading intracellular proteins to generate a major source of peptides with substantial major histocompatibility complex I binding affinity. The immunoproteasome also has roles in T-cell survival, differentiation and proliferation in various pathological conditions. In humans, any alteration in the expression, assembly or function of the immunoproteasome can lead to cancer, autoimmune disorders or inflammatory diseases. Although the roles of the immunoproteasome in cancer and neurodegenerative disorders have been extensively studied, its significance in other disease conditions has only recently become known. Therefore, there is

renewed interest in the development of drugs, vaccines and biomarkers that target the immunoproteasome. The current review highlights the involvement of this complex in disease pathology in addition to the advances made in immunoproteasome research.","DOI":"10.1038/icb.2016.50","ISSN":"1440-1711","note":"PMID: 27192937","journalAbbreviation":"Immunol. Cell Biol.","language":"eng","author":[{"family":"Kaur","given":"Gagandeep"},{"family":"Batra","given":"Sanjay"}],"issued":{"date-parts":[["2016"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The immunoproteasome exhibits elevated chymotrypsin-like and trypsin-like activities which produces antigenic peptides harbouring hydrophobic residues that better binds MHC class I molecules. Recent studies have expanded the role of immunoproteasome in B and T cell differentiation, response to infection and dendritic cell activation[199,200]. It has also been associated with various human diseases including cancer and immune and inflammatory disorders[198–200]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2kidesq7ih","properties":{"formattedCitation":"{\\rtf \\super

199\\uc0\\u8211{}201\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":328,"uris":["http://zotero.org/users/4604651/items/45NG8YTN"],"uri":["http://zotero.org/users/4604651/items/45NG8YTN"],"itemData":{"id":328,"type":"article-journal","title":"The immunoproteasome: An old player with a novel and emerging role in alloimmunity","container-title":"American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons","page":"3033-3039","volume":"17","issue":"12","source":"PubMed","abstract":"Modern treatment strategies for the maintenance of allograft acceptance frequently target ubiquitously-expressed pathways, leading to significant side-effects and poor long-term allograft outcomes. Constitutive proteasome inhibitors, which have recently been introduced for the treatment of antibody-mediated rejection, target the ubiquitously-expressed proteasome. To limit off-target effects and serious mechanism-based toxicity, however, these inhibitors are administered intermittently and suboptimally. Immunoproteasomes, which are an inducible subset of proteasomes enriched in immune cells, replace constitutive proteasomes after cell exposure to proinflammatory cytokines such as interferon-γ. While immunoproteasomes were first described as processors of antigen for presentation by major histocompatibility complex molecules, recent findings point to its broader biological roles. These vary from activating different subsets of the immune system, by controlling transcriptional activators and downstream cytokines, to affecting their differentiation and survival. These emerging roles of the immunoproteasome in activated immune cells have made it a rational candidate for the targeted treatment of immune-mediated diseases. Preclinical studies have established its role in maintaining allograft acceptance without significant short- or long-term toxicity. This review provides a brief background of the immunoproteasome and outlines its role in immunological pathways and its potential in alloimmunity.","DOI":"10.1111/ajt.14435","ISSN":"1600-6143","note":"PMID: 28719024","shortTitle":"The immunoproteasome","journalAbbreviation":"Am. J. Transplant.","language":"eng","author":[{"family":"Eskandari","given":"S. K."},{"family":"Seelen","given":"M. a. J."},{"family":"Lin","given":"G."},{"family":"Azzi","given":"J. R."}],"issued":{"date-parts":[["2017",12]]}}},{"id":330,"uris":["http://zotero.org/users/4604651/items/T5GXYZUE"],"uri":["http://zotero.org/users/4604651/items/T5GXYZUE"],"itemData":{"id":330,"type":"article-journal","title":"Emerging role of immunoproteasomes in pathophysiology","container-title":"Immunology and Cell Biology","page":"812-

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Another type of specialised proteasome identified in cortical thymic epithelial cells (cTECs) is the thymoproteasome (see the figure, part c). This specialised proteasome contains the two immunosubunits, β1i and β2i, as well as a thymic-specific β-subunit referred to as β5t[201]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"arvdad9ivo","properties":{"formattedCitation":"{\\rtf \\super 202\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":340,"uris":["http://zotero.org/users/4604651/items/YGAF6G7M"],"uri":["http://zotero.org/users/4604651/items/YGAF6G7M"],"itemData":{"id":340,"type":"article-journal","title":"Regulation of CD8+ T cell

development by thymus-specific proteasomes","container-title":"Science (New York, N.Y.)","page":"1349-1353","volume":"316","issue":"5829","source":"PubMed","abstract":"Proteasomes are responsible for generating peptides presented by the class I major histocompatibility complex (MHC) molecules of the immune system. Here, we report the identification of a previously unrecognized catalytic subunit called beta5t. beta5t is expressed exclusively in cortical thymic epithelial cells, which are responsible for the positive selection of developing thymocytes. Although the chymotrypsin-like activity of proteasomes is considered to be important for the production of peptides with high affinities for MHC class I clefts, incorporation of beta5t into proteasomes in place of beta5 or beta5i selectively reduces this activity. We also found that beta5t-deficient mice displayed defective development of CD8(+) T cells in the thymus. Our results suggest a key role for beta5t in generating the MHC class I-restricted CD8(+) T cell repertoire during thymic selection.","DOI":"10.1126/science.1141915","ISSN":"1095-9203","note":"PMID: 17540904","journalAbbreviation":"Science","language":"eng","author":[{"family":"Murata","given":"Shigeo"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Kishimoto","given":"Toshihiko"},{"family":"Niwa","given":"Shin-Ichiro"},{"family":"Hayashi","given":"Hidemi"},{"family":"Takahama","given":"Yousuke"},{"family":"Tanaka","given":"Keiji"}],"issued":{"date-parts":[["2007",6,1]]},"locator":"8"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The expression of the subunit β5t is controlled by Foxn1, a transcription factor regulating thymus development[38]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2pedgqha99","properties":{"formattedCitation":"{\\rtf \\super 38\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":342,"uris":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"uri":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"itemData":{"id":342,"type":"article-journal","title":"Ontogeny of thymic cortical epithelial cells expressing the thymoproteasome subunit β5t","container-title":"European Journal of Immunology","page":"1278-1287","volume":"41","issue":"5","source":"PubMed","abstract":"Proteasomes are responsible for generating peptides presented by class I MHC molecules of the immune system. β5t, a recently identified proteasome component, is specifically expressed in thymic cortical epithelial cells (cTECs) and plays a pivotal role in generating an immunocompetent repertoire of class I MHC-restricted CD8(+) T cells. Here, we report that β5t is detectable in the thymus as early as E12.5 mouse embryos. We also found that β5t expression in cTECs was detectable in mice deficient for RelB or Rag2, indicating that β5t in cTECs is expressed in the absence of thymic medulla formation or thymocyte development beyond the CD4(-) CD8(-) stage. β5t expression in the embryonic thymus was not detectable in Foxn1-deficient nude mice, although its expression was not reduced in mice deficient for both CCR7 and CCR9, in which fetal thymus colonization by leukocytes is defective. These results indicate that β5t expression in cTECs is dependent on Foxn1 but independent of thymocyte crosstalk or thymic medulla formation.","DOI":"10.1002/eji.201041375","ISSN":"1521-4141","note":"PMID: 21469133","journalAbbreviation":"Eur. J. Immunol.","language":"eng","author":[{"family":"Ripen","given":"Adiratna Mat"},{"family":"Nitta","given":"Takeshi"},{"family":"Murata","given":"Shigeo"},{"family":"Tanaka","given":"Keiji"},{"family":"Takahama","given":"Yousuke"}],"issued":{"date-parts":[["2011",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The thymoproteasome is essential for positive selection of developing T cells, a process selecting T cells capable of interacting with MHC[38,202,203]{ ADDIN

ZOTERO_ITEM CSL_CITATION {"citationID":"a1htr73n2ko","properties":{"formattedCitation":"{\\rtf \\super 38,203,204\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":342,"uris":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"uri":["http://zotero.org/users/4604651/items/VGZ7QGRF"],"itemData":{"id":342,"type":"article-journal","title":"Ontogeny of thymic cortical epithelial cells expressing the thymoproteasome subunit β5t","container-title":"European Journal of Immunology","page":"1278-1287","volume":"41","issue":"5","source":"PubMed","abstract":"Proteasomes are responsible for generating peptides presented by class I MHC molecules of the immune system. β5t, a recently identified proteasome component, is specifically expressed in thymic cortical epithelial cells (cTECs) and plays a pivotal role in generating an immunocompetent repertoire of class I MHC-restricted CD8(+) T cells. Here, we report that β5t is detectable in the thymus as early as E12.5 mouse embryos. We also found that β5t expression in cTECs was detectable in mice deficient for RelB or Rag2, indicating that β5t in cTECs is expressed in the absence of thymic medulla formation or thymocyte development beyond the CD4(-) CD8(-) stage. β5t expression in the embryonic thymus was not detectable in Foxn1-deficient nude mice, although its expression was not reduced in mice deficient for both CCR7 and CCR9, in which fetal thymus colonization by leukocytes is defective. These results indicate that β5t expression in cTECs is dependent on Foxn1 but independent of thymocyte crosstalk or thymic medulla formation.","DOI":"10.1002/eji.201041375","ISSN":"1521-4141","note":"PMID: 21469133","journalAbbreviation":"Eur. J. Immunol.","language":"eng","author":[{"family":"Ripen","given":"Adiratna Mat"},{"family":"Nitta","given":"Takeshi"},{"family":"Murata","given":"Shigeo"},{"family":"Tanaka","given":"Keiji"},{"family":"Takahama","given":"Yousuke"}],"issued":{"date-parts":[["2011",5]]}}},{"id":338,"uris":["http://zotero.org/users/4604651/items/CZLEMYJA"],"uri":["http://zotero.org/users/4604651/items/CZLEMYJA"],"itemData":{"id":338,"type":"article-journal","title":"Thymoproteasome: role in thymic selection and clinical significance as a diagnostic marker for thymic epithelial tumors","container-title":"Archivum Immunologiae Et Therapiae Experimentalis","page":"357-365","volume":"61","issue":"5","source":"PubMed","abstract":"The thymoproteasome is a specialized type of proteasomes expressed exclusively in the thymic cortex. It has a unique catalytic subunit β5t with unusual enzymatic activity. The thymoproteasome exhibits lower chymotrypsin-like activity than other forms of proteasomes such as constitutive proteasomes and immunoproteasomes. Its cleavage specificity appears uniquely suited for the production of peptides that mediate positive selection of CD8+ T cells. Similar to major histocompatibility complex molecules and T/B-cell receptors, the thymoproteasome occurs only in jawed vertebrates, suggesting that it evolved concomitant with the cardinal elements of adaptive immunity. β5t can be used as a marker in the differential diagnosis of thymic tumors. It is expressed in most type B and some type AB thymomas, but not in type A thymoma, thymic carcinoma, or tumors of non-thymic epithelial origin.","DOI":"10.1007/s00005-013-0234-1","ISSN":"1661-4917","note":"PMID: 23645302","shortTitle":"Thymoproteasome","journalAbbreviation":"Arch. Immunol. Ther. Exp. (Warsz.)","language":"eng","author":[{"family":"Tomaru","given":"Utano"},{"family":"Kasahara","given":"Masanori"}],"issued":{"date-parts":[["2013",10]]}}},{"id":300,"uris":["http://zotero.org/users/4604651/items/Y4AIV796"],"uri":["http://zotero.org/users/4604651/items/Y4AIV796"],"itemData":{"id":300,"type":"article-journal","title":"The unique functions of tissue-specific proteasomes","container-title":"Trends in Biochemical Sciences","page":"17-24","volume":"39","issue":"1","source":"ScienceDirect","abstract":"The 26S proteasome is the main protease in eukaryotes. Proteolysis occurs within the cylindrical 20S proteasome that is constitutively expressed in most tissues. However, three tissue-specific versions of the 20S proteasome have been discovered to date. The immunoproteasome is optimized to process

antigens and it directs the differentiation of T helper (Th) cells. The thymoproteasome is selectively expressed in cortical epithelial cells of the thymus where it plays an essential role in the positive selection of T lymphocytes. Finally, the spermatoproteasome is found in the testes where it is required during spermatogenesis. Here, we outline how tissue-specific proteasomes adapt to functional needs in their respective tissues and how their selective inhibition may be used to interfere with autoimmune diseases and cancer.","DOI":"10.1016/j.tibs.2013.10.004","ISSN":"0968-0004","journalAbbreviation":"Trends in Biochemical Sciences","author":[{"family":"Kniepert","given":"Andrea"},{"family":"Groettrup","given":"Marcus"}],"issued":{"date-parts":[["2014",1,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. The β5t subunit has substrate preference for peptide harbouring hydrophilic side chains generating a different pool of peptides than that of the β5 and β5i subunits[37]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2abde9m775","properties":{"formattedCitation":"{\\rtf \\super 37\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":334,"uris":["http://zotero.org/users/4604651/items/9BDKI3DV"],"uri":["http://zotero.org/users/4604651/items/9BDKI3DV"],"itemData":{"id":334,"type":"article-journal","title":"Activity-based profiling reveals reactivity of the murine thymoproteasome-specific subunit beta5t","container-title":"Chemistry & Biology","page":"795-801","volume":"17","issue":"8","source":"PubMed","abstract":"Epithelial cells of the thymus cortex express a unique proteasome particle involved in positive T cell selection. This thymoproteasome contains the recently discovered beta5t subunit that has an uncharted activity, if any. We synthesized fluorescent epoxomicin probes that were used in a chemical proteomics approach, entailing activity-based profiling, affinity purification, and LC-MS identification, to demonstrate that the beta5t subunit is catalytically active in the murine thymus. A panel of established proteasome inhibitors showed that the broad-spectrum inhibitor epoxomicin blocks the beta5t activity and that the subunit-specific antagonists bortezomib and NC005 do not inhibit beta5t. We show that beta5t has a substrate preference distinct from beta5/beta5i that might explain how the thymoproteasome generates the MHC class I peptide repertoire needed for positive T cell selection.","DOI":"10.1016/j.chembiol.2010.05.027","ISSN":"1879-1301","note":"PMID: 20797608\nPMCID: PMC3039300","journalAbbreviation":"Chem. Biol.","language":"eng","author":[{"family":"Florea","given":"Bogdan I."},{"family":"Verdoes","given":"Martijn"},{"family":"Li","given":"Nan"},{"family":"Linden","given":"Wouter A.","non-dropping-particle":"van der"},{"family":"Geurink","given":"Paul P."},{"family":"Elst","given":"Hans","non-dropping-particle":"van den"},{"family":"Hofmann","given":"Tanja"},{"family":"Ru","given":"Arnoud","non-dropping-particle":"de"},{"family":"Veelen","given":"Peter A.","non-dropping-particle":"van"},{"family":"Tanaka","given":"Keiji"},{"family":"Sasaki","given":"Katsuhiro"},{"family":"Murata","given":"Shigeo"},{"family":"Dulk","given":"Hans","non-dropping-particle":"den"},{"family":"Brouwer","given":"Jaap"},{"family":"Ossendorp","given":"Ferry A."},{"family":"Kisselev","given":"Alexei F."},{"family":"Overkleeft","given":"Herman S."}],"issued":{"date-parts":[["2010",8,27]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. How this specific pool of peptides is needed for positive T cell selection remains to be established. The testis-specific proteasome (see the figure, part d) contains the α4s subunit instead of the constitutive α4 subunit. It has been proposed that this α4s subunit might preferentially interact

with specific complexes such as PA200[204,205]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a46chu860p","properties":{"formattedCitation":"{\\rtf \\super 205,206\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":496,"uris":["http://zotero.org/users/4604651/items/ZNBQHLB6"],"uri":["http://zotero.org/users/4604651/items/ZNBQHLB6"],"itemData":{"id":496,"type":"article-journal","title":"Acetylation-Mediated Proteasomal Degradation of Core Histones during DNA Repair and Spermatogenesis","container-title":"Cell","page":"1012-1024","volume":"153","issue":"5","source":"www.cell.com","DOI":"10.1016/j.cell.2013.04.032","ISSN":"0092-8674, 1097-4172","journalAbbreviation":"Cell","language":"English","author":[{"family":"Qian","given":"Min-Xian"},{"family":"Pang","given":"Ye"},{"family":"Liu","given":"Cui Hua"},{"family":"Haratake","given":"Kousuke"},{"family":"Du","given":"Bo-Yu"},{"family":"Ji","given":"Dan-Yang"},{"family":"Wang","given":"Guang-Fei"},{"family":"Zhu","given":"Qian-Qian"},{"family":"Song","given":"Wei"},{"family":"Yu","given":"Yadong"},{"family":"Zhang","given":"Xiao-Xu"},{"family":"Huang","given":"Hai-Tao"},{"family":"Miao","given":"Shiying"},{"family":"Chen","given":"Lian-Bin"},{"family":"Zhang","given":"Zi-Hui"},{"family":"Liang","given":"Ya-Nan"},{"family":"Liu","given":"Shan"},{"family":"Cha","given":"Hwangho"},{"family":"Yang","given":"Dong"},{"family":"Zhai","given":"Yonggong"},{"family":"Komatsu","given":"Takuo"},{"family":"Tsuruta","given":"Fuminori"},{"family":"Li","given":"Haitao"},{"family":"Cao","given":"Cheng"},{"family":"Li","given":"Wei"},{"family":"Li","given":"Guo-Hong"},{"family":"Cheng","given":"Yifan"},{"family":"Chiba","given":"Tomoki"},{"family":"Wang","given":"Linfang"},{"family":"Goldberg","given":"Alfred L."},{"family":"Shen","given":"Yan"},{"family":"Qiu","given":"Xiao-Bo"}],"issued":{"date-parts":[["2013",5,23]]}}},{"id":499,"uris":["http://zotero.org/users/4604651/items/LP7C53VV"],"uri":["http://zotero.org/users/4604651/items/LP7C53VV"],"itemData":{"id":499,"type":"article-journal","title":"Characterization of the Testis-specific Proteasome Subunit α4s in Mammals","container-title":"The Journal of Biological Chemistry","page":"12365-12374","volume":"289","issue":"18","source":"PubMed Central","abstract":"Background: Two subtypes of proteasome core particles (CPs) with tissue-specific β subunits have been identified in mammals., Results: Mammals have an additional proteasome α subunit, α4s, which forms the male germ-specific CP., Conclusion: The α4s-containing CP is a new subtype

of CP with unique properties distinct from the constitutive CP., Significance: Our results provide a clue for understanding the role of the proteasome in mammalian testes., The 26 S proteasome is responsible for regulated proteolysis in eukaryotic cells. It is composed of one 20 S core particle (CP) flanked by one or two 19 S regulatory particles. The CP is composed of seven different α-type subunits (α1-α7) and seven different β-type subunits, three of which are catalytic. Vertebrates encode four additional catalytic β subunits that are expressed predominantly in immune tissues and produce distinct subtypes of CPs particularly well suited for the acquired immune system. In contrast, the diversity of α subunits remains poorly understood. Recently, another α subunit, referred to as α4s, was reported. However, little is known about α4s. Here we provide a detailed characterization of α4s and the α4s-containing CP. α4s is exclusively expressed in germ cells that enter the meiotic prophase and is incorporated into the CP in place of α4. A comparison of structural models revealed that the differences in the primary sequences between α4 and α4s are located on the outer surface of the CP, suggesting that α4s interacts with specific molecules via these unique regions. α4s-containing CPs account for the majority of the CPs in mouse sperm. The catalytic β subunits in the α4s-containing CP are β1, β2, and β5, and immunosubunits are not included in the α4s-containing CP. α4s-containing CPs have a set of peptidase activities almost identical to those of α4-containing CPs. Our results provide a basis for understanding the role of α4s and male germ cell-specific proteasomes in mammals.","DOI":"10.1074/jbc.M114.558866","ISSN":"0021-9258","note":"PMID: 24668818\nPMCID: PMC4007433","journalAbbreviation":"J Biol Chem","author":[{"family":"Uechi","given":"Hiroyuki"},{"family":"Hamazaki","given":"Jun"},{"family":"Murata","given":"Shigeo"}],"issued":{"date-parts":[["2014",5,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**.

Box 2 | **TORC1 complex in yeast and mammals.**

The *Saccharomyces cerevisiae* TOR complex 1 (TORC1) is composed of three essential components, TOR1 or TOR2, Kog1 and Lst8 (lethal with Sec13 protein 8), and one non-essential protein, Tco89[159,206,207]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"asrnb8gblv","properties":{"formattedCitation":"{\\rtf \\super 159,207,208\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":277,"uris":["http://zotero.org/users/4604651/items/DR5MAWTP"],"uri":["http://zotero.org/users/4604651/items/DR5MAWTP"],"itemData":{"id":277,"type":"article-journal","title":"TOR complex 1 includes a novel component, Tco89p (YPL180w), and cooperates with Ssd1p to maintain cellular integrity in Saccharomyces cerevisiae","container-

title":"The Journal of Biological Chemistry","page":"14752-14762","volume":"279","issue":"15","source":"PubMed","abstract":"The Tor1p and Tor2p kinases, targets of the therapeutically important antibiotic rapamycin, function as components of two distinct protein complexes in yeast, termed TOR complex 1 (TORC1) and TORC2. TORC1 is responsible for a wide range of rapamycin-sensitive cellular activities and contains, in addition to Tor1p or Tor2p, two highly conserved proteins, Lst8p and Kog1p. By identifying proteins that co-purify with Tor1p, Tor2p, Lst8p, and Kog1p, we have characterized a comprehensive set of protein-protein interactions that define further the composition of TORC1 as well as TORC2. In particular, we have identified Tco89p (YPL180w) and Bit61p (YJL058c) as novel components of TORC1 and TORC2, respectively. Deletion of TOR1 or TCO89 results in two specific and distinct phenotypes, (i) rapamycin-hypersensitivity and (ii) decreased cellular integrity, both of which correlate with the presence of SSD1-d, an allele of SSD1 previously associated with defects in cellular integrity. Furthermore, we link Ssd1p to Tap42p, a component of the TOR pathway that is believed to act uniquely downstream of TORC1. Together, these results define a novel connection between TORC1 and Ssd1p-mediated maintenance of cellular integrity.","DOI":"10.1074/jbc.M313062200","ISSN":"0021-9258","note":"PMID: 14736892","journalAbbreviation":"J. Biol. Chem.","language":"eng","author":[{"family":"Reinke","given":"Aaron"},{"family":"Anderson","given":"Scott"},{"family":"McCaffery","given":"J. Michael"},{"family":"Yates","given":"John"},{"family":"Aronova","given":"Sofia"},{"family":"Chu","given":"Stephanie"},{"family":"Fairclough","given":"Stephen"},{"family":"Iverson","given":"Cory"},{"family":"Wedaman","given":"Karen P."},{"family":"Powers","given":"Ted"}],"issued":{"date-parts":[["2004",4,9]]}},{"id":280,"uris":["http://zotero.org/users/4604651/items/AQD57TD5"],"uri":["http://zotero.org/users/4604651/items/AQD57TD5"],"itemData":{"id":280,"type":"article-journal","title":"Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control","container-title":"Molecular Cell","page":"457-468","volume":"10","issue":"3","source":"PubMed","abstract":"The target of rapamycin (TOR) proteins in Saccharomyces cerevisiae, TOR1 and TOR2, redundantly regulate growth in a rapamycin-sensitive manner. TOR2 additionally regulates polarization of the actin cytoskeleton in a rapamycin-insensitive manner. We describe two functionally distinct TOR complexes. TOR Complex 1 (TORC1) contains TOR1 or TOR2, KOG1 (YHR186c), and LST8. TORC2 contains TOR2, AVO1 (YOL078w), AVO2 (YMR068w), AVO3 (YER093c), and LST8. FKBP-rapamycin binds TORC1, and TORC1 disruption mimics rapamycin treatment, suggesting that TORC1 mediates the rapamycin-sensitive, TOR-shared pathway. FKBP-rapamycin fails to bind TORC2, and TORC2 disruption causes an actin defect, suggesting that TORC2 mediates the rapamycin-insensitive, TOR2-unique pathway. Thus, the distinct TOR complexes account for the diversity, specificity, and selective rapamycin inhibition of TOR signaling. TORC1 and possibly TORC2 are conserved from yeast to man.","ISSN":"1097-2765","note":"PMID: 12408816","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Loewith","given":"Robbie"},{"family":"Jacinto","given":"Estela"},{"family":"Wullschleger","given":"Stephan"},{"family":"Lorberg","given":"Anja"},{"family":"Crespo","given":"José L."},{"family":"Bonenfant","given":"Débora"},{"family":"Oppliger","given":"Wolfgang"},{"family":"Jenoe","given":"Paul"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2002",9]]}},{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-

title":"The EMBO journal","page":"397-408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The TOR1/2 subunits harbour the kinase catalytic activity whereas the other components regulate the assembly and stability of TORC1 as well as its subcellular localisation and substrate recruitment[158,159]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a10dcg71egl","properties":{"formattedCitation":"{\\rtf \\super 158,159\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}}},{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-title":"The EMBO journal","page":"397-408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. The mammalian complex, mTORC1, comprises three orthologues of the essential subunits of the yeast TORC1 complex, mTOR (mammalian TOR) (TOR1/2 in yeast), Raptor (Regulatory protein associated with mTOR) (Kog1 in yeast) and mLST8 (mammalian Lst8) (Lst8 in yeast) [208–210]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a27mhth0n59","properties":{"formattedCitation":"{\\rtf \\super 209\\uc0\\u8211{}211\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":290,"uris":["http://zotero.org/users/4604651/items/GFQ4E6KM"],"uri":["http://zotero.org/users/4604651/items/GFQ4E6KM"],"itemData":{"id":290,"type":"article-journal","title":"GbetaL, a

positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR","container-title":"Molecular Cell","page":"895-904","volume":"11","issue":"4","source":"PubMed","abstract":"mTOR and raptor are components of a signaling pathway that regulates mammalian cell growth in response to nutrients and growth factors. Here, we identify a member of this pathway, a protein named GbetaL that binds to the kinase domain of mTOR and stabilizes the interaction of raptor with mTOR. Like mTOR and raptor, GbetaL participates in nutrient- and growth factor-mediated signaling to S6K1, a downstream effector of mTOR, and in the control of cell size. The binding of GbetaL to mTOR strongly stimulates the kinase activity of mTOR toward S6K1 and 4E-BP1, an effect reversed by the stable interaction of raptor with mTOR. Interestingly, nutrients and rapamycin regulate the association between mTOR and raptor only in complexes that also contain GbetaL. Thus, we propose that the opposing effects on mTOR activity of the GbetaL- and raptor-mediated interactions regulate the mTOR pathway.","ISSN":"1097-2765","note":"PMID: 12718876","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Kim","given":"Do-Hyung"},{"family":"Sarbassov","given":"D. D."},{"family":"Ali","given":"Siraj M."},{"family":"Latek","given":"Robert R."},{"family":"Guntur","given":"Kalyani V. P."},{"family":"Erdjument-Bromage","given":"Hediye"},{"family":"Tempst","given":"Paul"},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2003",4]]}}},{"id":288,"uris":["http://zotero.org/users/4604651/items/FRYNVCWM"],"uri":["http://zotero.org/users/4604651/items/FRYNVCWM"],"itemData":{"id":288,"type":"article-journal","title":"mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery","container-title":"Cell","page":"163-175","volume":"110","issue":"2","source":"PubMed","abstract":"mTOR/RAFT1/FRAP is the target of the immunosuppressive drug rapamycin and the central component of a nutrient- and hormone-sensitive signaling pathway that regulates cell growth. We report that mTOR forms a stoichiometric complex with raptor, an evolutionarily conserved protein with at least two roles in the mTOR pathway. Raptor has a positive role in nutrient-stimulated signaling to the downstream effector S6K1, maintenance of cell size, and mTOR protein expression. The association of raptor with mTOR also negatively regulates the mTOR kinase activity. Conditions that repress the pathway, such as nutrient deprivation and mitochondrial uncoupling, stabilize the mTOR-raptor association and inhibit mTOR kinase activity. We propose that raptor is a missing component of the mTOR pathway that through its association with mTOR regulates cell size in response to nutrient levels.","ISSN":"0092-8674","note":"PMID: 12150925","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Kim","given":"Do-Hyung"},{"family":"Sarbassov","given":"D. D."},{"family":"Ali","given":"Siraj M."},{"family":"King","given":"Jessie E."},{"family":"Latek","given":"Robert R."},{"family":"Erdjument-Bromage","given":"Hediye"},{"family":"Tempst","given":"Paul"},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2002",7,26]]}}},{"id":286,"uris":["http://zotero.org/users/4604651/items/2N8HX5E6"],"uri":["http://zotero.org/users/4604651/items/2N8HX5E6"],"itemData":{"id":286,"type":"article-journal","title":"Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action","container-title":"Cell","page":"177-189","volume":"110","issue":"2","source":"PubMed","abstract":"mTOR controls cell growth, in part by regulating p70 S6 kinase alpha (p70alpha) and eukaryotic initiation factor 4E binding protein 1 (4EBP1). Raptor is a 150 kDa mTOR binding protein that also binds 4EBP1 and p70alpha. The binding of raptor to mTOR is necessary for the mTOR-catalyzed phosphorylation of 4EBP1 in vitro, and it strongly enhances the mTOR kinase activity toward p70alpha. Rapamycin or amino acid withdrawal

increases, whereas insulin strongly inhibits, the recovery of 4EBP1 and raptor on 7-methyl-GTP Sepharose. Partial inhibition of raptor expression by RNA interference (RNAi) reduces mTOR-catalyzed 4EBP1 phosphorylation in vitro. RNAi of C. elegans raptor yields an array of phenotypes that closely resemble those produced by inactivation of Ce-TOR. Thus, raptor is an essential scaffold for the mTOR-catalyzed phosphorylation of 4EBP1 and mediates TOR action in vivo.","ISSN":"0092-8674","note":"PMID: 12150926","journalAbbreviation":"Cell","language":"eng","author":[{"family":"Hara","given":"Kenta"},{"family":"Maruki","given":"Yoshiko"},{"family":"Long","given":"Xiaomeng"},{"family":"Yoshino","given":"Ken-ichi"},{"family":"Oshiro","given":"Noriko"},{"family":"Hidayat","given":"Sujuti"},{"family":"Tokunaga","given":"Chiharu"},{"family":"Avruch","given":"Joseph"},{"family":"Yonezawa","given":"Kazuyoshi"}],"issued":{"date-parts":[["2002",7,26]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} , and two additional inhibitory subunits, PRAS40 (Proline-rich Akt substrate of 40 kDa) and Deptor (DEP domain containing mTOR interacting protein) [211–213] (see the figure){ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aimt011tkp","properties":{"formattedCitation":"{\\rtf \\super 212\\uc0\\u8211{}214\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":298,"uris":["http://zotero.org/users/4604651/items/9CZ8IQKU"],"uri":["http://zotero.org/users/4604651/items/9CZ8IQKU"],"itemData":{"id":298,"type":"article-journal","title":"PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding","container-title":"The Journal of Biological Chemistry","page":"20036-20044","volume":"282","issue":"27","source":"PubMed","abstract":"Mammalian target of rapamycin (mTOR) functions in two distinct signaling complexes, mTORC1 and mTORC2. In response to insulin and nutrients, mTORC1, consisting of mTOR, raptor (regulatory-associated protein of mTOR), and mLST8, is activated and phosphorylates eukaryotic initiation factor 4E-binding protein (4EBP) and p70 S6 kinase to promote protein synthesis and cell size. Previously we found that activation of mTOR kinase in response to insulin was associated with increased 4EBP1 binding to raptor. Here we identify prolinerich Akt substrate 40 (PRAS40) as a binding partner for mTORC1. A putative TOR signaling motif, FVMDE, is identified in PRAS40 and shown to be required for interaction with raptor. Insulin stimulation markedly decreases the level of PRAS40 bound by mTORC1. Recombinant PRAS40 inhibits mTORC1 kinase activity in vivo and in vitro, and this inhibition depends on PRAS40 association with raptor. Furthermore, decreasing PRAS40 expression by short hairpin RNA enhances 4E-BP1 binding to raptor, and recombinant PRAS40 competes with 4E-BP1 binding to raptor. We, therefore, propose that PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding.","DOI":"10.1074/jbc.M702376200","ISSN":"0021-9258","note":"PMID: 17510057","journalAbbreviation":"J. Biol.

Chem.","language":"eng","author":[{"family":"Wang","given":"Lifu"},{"family":"Harris","given":"Thurl E."},{"family":"Roth","given":"Richard A."},{"family":"Lawrence","given":"John C."}],"issued":{"date-parts":[["2007",7,6]]}}},{"id":296,"uris":["http://zotero.org/users/4604651/items/4E2GATKY"],"uri":["http://zotero.org/users/4604651/items/4E2GATKY"],"itemData":{"id":296,"type":"article-journal","title":"PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase","container-title":"Molecular Cell","page":"903-915","volume":"25","issue":"6","source":"PubMed","abstract":"The heterotrimeric mTORC1 protein kinase nucleates a signaling network that promotes cell growth in response to insulin and becomes constitutively active in cells missing the TSC1 or TSC2 tumor suppressors. Insulin stimulates the phosphorylation of S6K1, an mTORC1 substrate, but it is not known how mTORC1 kinase activity is regulated. We identify PRAS40 as a raptor-interacting protein that binds to mTORC1 in insulin-deprived cells and whose in vitro interaction with mTORC1 is disrupted by high salt concentrations. PRAS40 inhibits cell growth, S6K1 phosphorylation, and rheb-induced activation of the mTORC1 pathway, and in vitro it prevents the great increase in mTORC1 kinase activity induced by rheb1-GTP. Insulin stimulates Akt/PKB-mediated phosphorylation of PRAS40, which prevents its inhibition of mTORC1 in cells and in vitro. We propose that the relative strengths of the rheb- and PRAS40-mediated inputs to mTORC1 set overall pathway activity and that insulin activates mTORC1 through the coordinated regulation of both.","DOI":"10.1016/j.molcel.2007.03.003","ISSN":"1097-2765","note":"PMID: 17386266","journalAbbreviation":"Mol. Cell","language":"eng","author":[{"family":"Sancak","given":"Yasemin"},{"family":"Thoreen","given":"Carson C."},{"family":"Peterson","given":"Timothy R."},{"family":"Lindquist","given":"Robert A."},{"family":"Kang","given":"Seong A."},{"family":"Spooner","given":"Eric"},{"family":"Carr","given":"Steven A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2007",3,23]]}},"locator":"4"},{"id":294,"uris":["http://zotero.org/users/4604651/items/3FFWCQHR"],"uri":["http://zotero.org/users/4604651/items/3FFWCQHR"],"itemData":{"id":294,"type":"article-journal","title":"Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40","container-title":"Nature Cell Biology","page":"316-323","volume":"9","issue":"3","source":"PubMed","abstract":"Insulin stimulates protein synthesis and cell growth by activation of the protein kinases Akt (also known as protein kinase B, PKB) and mammalian target of rapamycin (mTOR). It was reported that Akt activates mTOR by phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2). However,

in recent studies the physiological requirement of Akt phosphorylation of TSC2 for mTOR activation has been questioned. Here, we identify PRAS40 (proline-rich Akt/PKB substrate 40 kDa) as a novel mTOR binding partner that mediates Akt signals to mTOR. PRAS40 binds the mTOR kinase domain and its interaction with mTOR is induced under conditions that inhibit mTOR signalling, such as nutrient or serum deprivation or mitochondrial metabolic inhibition. Binding of PRAS40 inhibits mTOR activity and suppresses constitutive activation of mTOR in cells lacking TSC2. PRAS40 silencing inactivates insulin-receptor substrate-1 (IRS-1) and Akt, and uncouples the response of mTOR to Akt signals. Furthermore, PRAS40 phosphorylation by Akt and association with 14-3-3, a cytosolic anchor protein, are crucial for insulin to stimulate mTOR. These findings identify PRAS40 as an important regulator of insulin sensitivity of the Akt-mTOR pathway and a potential target for the treatment of cancers, insulin resistance and hamartoma syndromes.","DOI":"10.1038/ncb1547","ISSN":"1465-7392","note":"PMID: 17277771","journalAbbreviation":"Nat. Cell Biol.","language":"eng","author":[{"family":"Vander Haar","given":"Emilie"},{"family":"Lee","given":"Seong-Il"},{"family":"Bandhakavi","given":"Sricharan"},{"family":"Griffin","given":"Timothy J."},{"family":"Kim","given":"Do-Hyung"}],"issued":{"date-parts":[["2007",3]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**.

TORC1 is a stress- and nutrient-responsive complex that adapts cell metabolism to the cell requirements, and one essential trigger of its activation is amino acid availability. TORC1 does not sense directly amino acid availability but through sensors. For example, sensors for arginine and leucine have been recently identified and referred to as Cellular Arginine Sensor for mTORC1 (CASTOR1) and Sestrin2, respectively[214–217]**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2383qt5bc3","properties":{"formattedCitation":"{\\rtf \\super 215\\uc0\\u8211{}218\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":353,"uris":["http://zotero.org/users/4604651/items/5QVAUL7X"],"uri":["http://zotero.org/users/4604651/items/5QVAUL7X"],"itemData":{"id":353,"type":"article-journal","title":"The Sestrins Interact with GATOR2 to Negatively Regulate the Amino-Acid-Sensing Pathway Upstream of mTORC1","container-title":"Cell Reports","page":"1-8","volume":"9","issue":"1","source":"www.cell.com","DOI":"10.1016/j.celrep.2014.09.014","ISSN":"2211-1247","note":"PMID: 25263562","journalAbbreviation":"Cell Reports","language":"English","author":[{"family":"Chantranupong","given":"Lynne"},{"family":"Wolfson","given":"Rachel L."},{"family":"Orozco","given":"Jose M."},{"family":"Saxton","given":"Robert A."},{"family":"Scaria","given":"Sonia M."},{"family":"Bar-Peled","given":"Liron"},{"family":"Spooner","given":"Eric"},{"family":"Isasa","given":"Marta"},{"family":"Gygi","given":"Steven

P."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2014",10,9]]}},{"id":356,"uris":["http://zotero.org/users/4604651/items/JKAA5WAS"],"uri":["http://zotero.org/users/4604651/items/JKAA5WAS"],"itemData":{"id":356,"type":"article-journal","title":"Sestrins Inhibit mTORC1 Kinase Activation through the GATOR Complex","container-title":"Cell Reports","page":"1281-1291","volume":"9","issue":"4","source":"www.cell.com","DOI":"10.1016/j.celrep.2014.10.019","ISSN":"2211-1247","note":"PMID: 25457612","journalAbbreviation":"Cell Reports","language":"English","author":[{"family":"Parmigiani","given":"Anita"},{"family":"Nourbakhsh","given":"Aida"},{"family":"Ding","given":"Boxiao"},{"family":"Wang","given":"Wei"},{"family":"Kim","given":"Young Chul"},{"family":"Akopiants","given":"Konstantin"},{"family":"Guan","given":"Kun-Liang"},{"family":"Karin","given":"Michael"},{"family":"Budanov","given":"Andrei V."}],"issued":{"date-parts":[["2014",11,20]]}},{"id":358,"uris":["http://zotero.org/users/4604651/items/22QNY3NB"],"uri":["http://zotero.org/users/4604651/items/22QNY3NB"],"itemData":{"id":358,"type":"article-journal","title":"The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway","container-title":"Cell","page":"153-164","volume":"165","issue":"1","source":"www.cell.com","DOI":"10.1016/j.cell.2016.02.035","ISSN":"0092-8674, 1097-4172","note":"PMID: 26972053","journalAbbreviation":"Cell","language":"English","author":[{"family":"Chantranupong","given":"Lynne"},{"family":"Scaria","given":"Sonia M."},{"family":"Saxton","given":"Robert A."},{"family":"Gygi","given":"Melanie P."},{"family":"Shen","given":"Kuang"},{"family":"Wyant","given":"Gregory A."},{"family":"Wang","given":"Tim"},{"family":"Harper","given":"J. Wade"},{"family":"Gygi","given":"Steven P."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2016",3,24]]}},{"id":360,"uris":["http://zotero.org/users/4604651/items/XBTS8RKL"],"uri":["http://zotero.org/users/4604651/items/XBTS8RKL"],"itemData":{"id":360,"type":"article-journal","title":"Mechanism of arginine sensing by CASTOR1 upstream of mTORC1","container-title":"Nature","page":"229-233","volume":"536","issue":"7615","source":"PubMed","abstract":"The mechanistic Target of Rapamycin Complex 1 (mTORC1) is a major regulator of eukaryotic growth that coordinates anabolic and catabolic cellular processes with inputs such as growth factors and nutrients, including amino acids. In mammals arginine is particularly important, promoting diverse physiological effects such as immune cell activation, insulin secretion, and muscle growth, largely mediated through activation of mTORC1 (refs 4, 5, 6, 7). Arginine activates mTORC1 upstream of the Rag family of GTPases, through either the lysosomal amino acid transporter SLC38A9 or the GATOR2-interacting Cellular Arginine Sensor for mTORC1 (CASTOR1). However, the mechanism by which the mTORC1 pathway detects and transmits this arginine signal has been elusive. Here, we present the 1.8 Å crystal structure of arginine-bound CASTOR1. Homodimeric CASTOR1 binds arginine at the interface of two Aspartate kinase, Chorismate mutase, TyrA (ACT) domains, enabling allosteric control of the adjacent GATOR2-binding site to trigger dissociation from GATOR2 and downstream activation of mTORC1. Our data reveal that CASTOR1 shares substantial structural homology with the lysine-binding regulatory domain of prokaryotic aspartate kinases, suggesting that the mTORC1 pathway exploited an ancient, amino-acid-dependent allosteric mechanism to acquire arginine sensitivity. Together, these results establish a structural basis for arginine sensing by the mTORC1 pathway and provide insights into the

evolution of a mammalian nutrient sensor.","DOI":"10.1038/nature19079","ISSN":"1476-4687","note":"PMID: 27487210\nPMCID: PMC4988899","journalAbbreviation":"Nature","language":"eng","author":[{"family":"Saxton","given":"Robert A."},{"family":"Chantranupong","given":"Lynne"},{"family":"Knockenhauer","given":"Kevin E."},{"family":"Schwartz","given":"Thomas U."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2016"]],"season":"11"}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. It is possible that more sensors will be discovered. Under nutrient-rich conditions, mTORC1 activation favours growth in part by promoting the synthesis of new cellular components including proteins. Well-characterized mTORC1 targets controlling translation in mammals are the ribosomal protein S6 kinase 1 (S6K1) and the eukaryotic translation initiation factor 4E (eIF4E) binding proteins (4E-BPs) [158,159]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aghu97r532","properties":{"formattedCitation":"{\\rtf \\super 158,159\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}}},{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-title":"The EMBO journal","page":"397-408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. mTORC1 also promotes anabolism by repressing the two degradative machineries, the autophagy-lysosome system and the ubiquitin-proteasome system (UPS). Under various stress conditions such as nutrient scarcity, mTORC1 is inhibited which decreases global protein synthesis while de-repressing degradative machineries[106,158,159,167]{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2fe7fauo7","properties":{"formattedCitation":"{\\rtf \\super 106,158,159,167\\nosupersub{}}","plainCitation":""},"citationItems":[{"id":141,"uris":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"uri":["http://zotero.org/users/4604651/items/LXEE4ZQW"],"itemData":{"id":141,"type":"article-journal","title":"Nutrient sensing and TOR signaling in yeast and mammals","container-title":"The EMBO journal","page":"397-

408","volume":"36","issue":"4","source":"PubMed","abstract":"Coordinating cell growth with nutrient availability is critical for cell survival. The evolutionarily conserved TOR (target of rapamycin) controls cell growth in response to nutrients, in particular amino acids. As a central controller of cell growth, mTOR (mammalian TOR) is implicated in several disorders, including cancer, obesity, and diabetes. Here, we review how nutrient availability is sensed and transduced to TOR in budding yeast and mammals. A better understanding of how nutrient availability is transduced to TOR may allow novel strategies in the treatment for mTOR-related diseases.","DOI":"10.15252/embj.201696010","ISSN":"1460-2075","note":"PMID: 28096180","journalAbbreviation":"EMBO J.","language":"eng","author":[{"family":"González","given":"Asier"},{"family":"Hall","given":"Michael N."}],"issued":{"date-parts":[["2017",2,15]]}},{"id":133,"uris":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"uri":["http://zotero.org/users/4604651/items/ZMJV3IYL"],"itemData":{"id":133,"type":"article-journal","title":"mTOR Signaling in Growth, Metabolism, and Disease","container-title":"Cell","page":"960-976","volume":"168","issue":"6","source":"www.cell.com","DOI":"10.1016/j.cell.2017.02.004","ISSN":"0092-8674, 1097-4172","note":"PMID: 28283069","journalAbbreviation":"Cell","language":"English","author":[{"family":"Saxton","given":"Robert A."},{"family":"Sabatini","given":"David M."}],"issued":{"date-parts":[["2017",3,9]]}},{"id":177,"uris":["http://zotero.org/users/4604651/items/UNIJTXJL"],"uri":["http://zotero.org/users/4604651/items/UNIJTXJL"],"itemData":{"id":177,"type":"article-journal","title":"An evolutionarily conserved pathway controls proteasome homeostasis","container-title":"Nature","page":"184-189","volume":"536","issue":"7615","source":"www.nature.com","abstract":"The proteasome is essential for the selective degradation of most cellular proteins, but how cells maintain adequate amounts of proteasome is unclear. Here we show that there is an evolutionarily conserved signalling pathway controlling proteasome homeostasis. Central to this pathway is TORC1, the inhibition of which induced all known yeast 19S regulatory particle assembly-chaperones (RACs), as well as proteasome subunits. Downstream of TORC1 inhibition, the yeast mitogen-activated protein kinase, Mpk1, acts to increase the supply of RACs and proteasome subunits under challenging conditions in order to maintain proteasomal degradation and cell viability. This adaptive pathway was evolutionarily conserved, with mTOR and ERK5 controlling the levels of the four mammalian RACs and proteasome abundance. Thus, the central growth and stress controllers, TORC1 and Mpk1/ERK5, endow cells with a rapid and vital adaptive response to adjust proteasome abundance in response to the rising needs of cells. Enhancing this pathway may be a useful therapeutic approach for diseases resulting from impaired proteasomal degradation.","DOI":"10.1038/nature18943","ISSN":"0028-0836","journalAbbreviation":"Nature","language":"en","author":[{"family":"Rousseau","given":"Adrien"},{"family":"Bertolotti","given":"Anne"}],"issued":{"date-parts":[["2016",8,11]]}},{"id":118,"uris":["http://zotero.org/users/4604651/items/42SRD4WN"],"uri":["http://zotero.org/users/4604651/items/42SRD4WN"],"itemData":{"id":118,"type":"article-journal","title":"mTOR inhibition activates overall protein degradation by the ubiquitin proteasome system as well as by autophagy","container-title":"Proceedings of the National Academy of Sciences","page":"15790-15797","volume":"112","issue":"52","source":"www.pnas.org","abstract":"Growth factors and nutrients enhance protein synthesis and suppress overall protein degradation by activating the protein kinase mammalian target of rapamycin (mTOR). Conversely, nutrient or serum deprivation inhibits mTOR and stimulates protein breakdown by inducing autophagy, which provides the starved cells with amino acids for protein synthesis and energy production. However, it is unclear whether proteolysis by the ubiquitin proteasome system (UPS), which catalyzes

most protein degradation in mammalian cells, also increases when mTOR activity decreases. Here we show that inhibiting mTOR with rapamycin or Torin1 rapidly increases the degradation of long-lived cell proteins, but not short-lived ones, by stimulating proteolysis by proteasomes, in addition to autophagy. This enhanced proteasomal degradation required protein ubiquitination, and within 30 min after mTOR inhibition, the cellular content of K48-linked ubiquitinated proteins increased without any change in proteasome content or activity. This rapid increase in UPS-mediated proteolysis continued for many hours and resulted primarily from inhibition of mTORC1 (not mTORC2), but did not require new protein synthesis or key mTOR targets: S6Ks, 4E-BPs, or Ulks. These findings do not support the recent report that mTORC1 inhibition reduces proteolysis by suppressing proteasome expression [Zhang Y, et al. (2014) Nature 513(7518):440–443]. Several growth-related proteins were identified that were ubiquitinated and degraded more rapidly after mTOR inhibition, including HMG-CoA synthase, whose enhanced degradation probably limits cholesterol biosynthesis upon insulin deficiency. Thus, mTOR inhibition coordinately activates the UPS and autophagy, which provide essential amino acids and, together with the enhanced ubiquitination of anabolic proteins, help slow growth.","DOI":"10.1073/pnas.1521919112","ISSN":"0027-8424, 1091-6490","note":"PMID: 26669439","journalAbbreviation":"PNAS","language":"en","author":[{"family":"Zhao","given":"Jinghui"},{"family":"Zhai","given":"Bo"},{"family":"Gygi","given":"Steven P."},{"family":"Goldberg","given":"Alfred Lewis"}],"issued":{"date-parts":[["2015",12,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} }. This well-orchestrated response is essential to maintain an adequate and functional proteome in cells.

Figure 1 | **The Ubiquitin-Proteasome System (UPS).** Ubiquitination consists of the covalent binding of ubiquitin (Ub) to lysine residues exposed at the surface of targeted substrates. Ub is first activated by the ubiquitin-activating enzyme (E1) in presence of ATP, prior to be bound to E1. The ubiquitin is then transferred from E1 to the ubiquitin-conjugating enzyme (E2). A ubiquitin ligase (E3) recruits the ubiquitin-bound E2 enzyme and a substrate to transfer the ubiquitin from E2 to the substrate. The formation of lysine 48-linked polyubiquitin chains, the main signal for proteasomal degradation, is mediated by successive cycle of ubiquitin conjugation. Monoubiquitination may be sufficient for proteasome targeting. When targeted to the proteasome, substrates are degraded into short peptides which are further broken down to amino acids by aminopeptidases (APPs). The mono- and polyubiquitin molecules are usually removed from the substrate by the proteasome by deubiquitylating enzymes (DUBs) prior to substrate degradation. Released free ubiquitin molecules are recycled for another round of ubiquitination.

Figure 2 | **Models of 20S core particle (CP) assembly.** The assembly of the CP is initiated by the assembly of the α–ring, which serves as a platform for the assembly of the β–ring. CP assembly is assisted by five assembly chaperones referred to as proteasome biogenesis-

associated 1 (Pba1)-Pba4 and underpinning maturation of proteasome 1 (Ump1). These assembly chaperones prevent aberrant dimerization of α–rings as well as premature association with the RP. They also control that α- and β-subunits are properly incorporated. Two half-proteasomes (15S) associate to form a nascent CP, which is remodelled by the successive removal of N-terminal propeptides from β1, β2, β5, β6 and β7 subunits. Ump1 is then degraded by the newly formed CP while the Pba1-Pba2 complex is recycled.

Figure 3 | **Models of 19S regulatory particle (RP) assembly.** The assembly of the RP base and the RP lid occurs independently to each other. The base is composed of 10 subunits, six regulatory particle triple-A (Rpt) proteins and four regulatory particle non-ATPase (Rpn) proteins and the lid is composed of nine Rpn proteins. The assembly of the base is assisted by five RP assembly chaperones (RACs), that ensure that the base subunits are properly assembled together. The lid is suggested to self-assemble thought the formation of a helical bundle consisting of the C-terminal helices of lid subunits. After completion of the base and the lid, these two subassemblies associate to form a mature RP.

Figure 4 | **Transcriptional regulation of proteasome subunits.** (a) Transcriptional regulation of proteasome subunits in yeast. Rpn4 is a transcription factor with an extremely short half-life ($t_{1/2}$~2 min). It is constantly degraded by the proteasome through both ubiquitin-dependent and -independent pathways under normal growth conditions. Ubiquitin-dependent degradation of Rpn4 is mediated by a complex formed by the ubiquitin-conjugating enzyme Rad6 and the ubiquitin ligase Ubr2. Upon proteasome inhibition or overload, Rpn4 is stabilised and translocates to the nucleus, where it binds to a nonamer box (5'-GGTGGCAAA-3') referred to as proteasome-associated control element (PACE) which is present in the promoters of most proteasomal subunit genes. This increases expression of proteasome subunits. (b) Transcriptional regulation of proteasome subunits in mammals. Nrf1 controls proteasome subunit expression in mammals. Nrf1 is constantly retrotranslocated to the cytosol, where it is rapidly ubiquitinated and degraded by the UPS with a half-life of only ~12 minutes. When proteasome is inhibited or overloaded, the stabilization of Nrf1 after retrotranslocation allows Nrf1 to be cleaved by the aspartyl protease DDI2. The resulting active form of Nrf1 translocates to the nucleus where it binds antioxidant response elements (AREs) and activates the transcription of its target genes, including those encoding the proteasome subunits. This response is referred to as "the proteasome bounce-back response".

Figure 5 | **Regulation of proteasome assembly.** The transcription of proteasome-related genes is coordinated by the transcription factors Rpn4 in yeast and Nrf1/2 in mammals. Under challenging conditions, inhibition of the stress and growth controller TORC1 signals to Mpk1 to increase assembly of the RP. CP assembly is also a regulated process with the TRC pathway and iRhom1 promoting CP assembly whilst miR-101, targeting POMP mRNA, interferes with CP assembly. The association of the RP at one or both ends of the CP will form the singly- and doubly-capped proteasome, respectively. RP-CP association is mediated by the insertion of the C-terminal HbYX (Hb: hydrophobic; Y: tyrosine or phenylalanine; X: any amino acid) motifs of Rpt proteins into the pockets formed by two adjacent α–subunits. Various proteins have been proposed to play a role in the regulation of RP-CP association both in yeast (Ecm29 and Hsp90) and in mammals (Hsp90 and Rpn6).

Figure 6 | **TORC1 integrates protein and amino acid homeostasis.** Under non-limiting nutrient conditions, TORC1 complex is activated to promote anabolic processes such as the synthesis of nucleotides, lipids and proteins. This elevated production of the building blocks of cellular components is associated to the repression of catabolic processes to favour cell growth. Diverse stresses including nutrient scarcity inhibit TORC1 to decrease cellular anabolism and increase catabolic processes including the autophagy and the UPS. Elevated protein catabolism allows the degradation of unwanted proteins into free amino acids which will support the synthesis of new stress proteins. This metabolic reprogramming of the cells is essential to maintain cell viability.

Glossary terms

Microautophagy: A form of autophagy that entraps cytosolic components in small vesicles formed by invagination of the lysosomal membrane either in bulk or selectively.

Chaperone-mediated autophagy: A form of selective autophagy involving the transfer of cytosolic components directly across the lysosomal membrane.

Tunicamycin:

Tunicamycin blocks N-linked glycosylation, a post translational modification required for the folding of many proteins in the endoplasmic reticulum (ER). Consequently, Tunicamycin causes accumulation of misfolded proteins in the ER, a treatment used to induce ER stress.

Rhomboid-like family of proteases: A family of pseudoproteases (proteolytically inactive) which bind membrane proteins to regulate their fate.

Integrated stress response:

The integrated stress response refers to signalling pathway which is controlled by 4 kinases, GNC2, PKR, PERK and HRI that phosphorylate eIF2α in response to diverse cellular stresses.

p97:

p97 is a AAA ATPase involved in a variety of cellular processes through its ability to pull proteins out of membranes or protein complexes for proteasome degradation.

ToC

Regulation of proteasome assembly and activity in health and disease

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[40 words max]

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