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Deciphering Subunit-Specific Functions within SWI/SNF Complexes

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In this issue of *Cell Reports*, Sen et al. and Dutta et al. reveal the modularity of the yeast SWI/SNF chromatin remodeling complex and show that loss of different subunits leads to distinct consequences for gene expression.

One of the major unanticipated outcomes of large-scale tumor genome sequencing projects has been the finding that subunits of the human SWI/SNF chromatin remodeling complex are mutated at high frequency across a broad range of cancers. Even more baffling, different subunits are observed to be mutated in tumors of different tissues (Kadoch and Crabtree, 2015). This highlights the importance of the functional consequences of inactivating specific subunits. Recent studies of both yeast (Sen et al. 2017 and Dutta et al. 2017 [this issue of *Cell Reports*]) and human complexes (Wang et al., 2017) shed light on how loss of different subunits has such differing effects on complex structure and function.

SWI/SNF complexes contain members of an extended family of ATPases that use energy generated from ATP hydrolysis to regulate DNA-protein contacts (Flaus et al., 2006). The yeast SWI/SNF complex was the first member of the family to be found to act at the level of chromatin. The catalytic ATPase, in this case Snf2, is associated with 12 subunits as a multiprotein complex that acts to alter histone-DNA contacts. SWI/SNF complexes are conserved across eukaryotes, and in humans, the ATPases BRG1 (SMARCA4) and BRM (SMARCA2) are associated with similar accessory subunits to form related multiprotein complexes. These enzymes have been shown to play a role in regulating access to DNA for processes such as transcription, replication, and repair. They have been found to bind many regulatory elements across genomes (Kadoch and Crabtree, 2015). As a result, it has been somewhat puzzling as to why ubiquitously functioning enzymes should have tissue-specific effects. An important step toward understanding how specific subunits function is to understand how they interact within these complexes. Two papers in this issue address this using complimentary approaches. Sen et al. (2017) take a direct, cross-linking approach to define interactions between SWI/SNF subunits, while Dutta et al. (2017) use co-purification from wild-type and mutant complexes in order to define modules of SWI/SNF. The cross-links mapped by Sen et al. (2017) reveal extensive contacts of the Snf5 subunit with the Snf2 ATPase subunit, the ARID domain-containing Swi1 subunit, the Swi3, Swp82, and Taf14 subunits. When the complex is purified from strains mutated for Snf5, Taf14 and Swp82 are not present. This is an approach that was pursued further by Dutta et al. (2017), who also find these subunits are lost when the Snf5 subunit is deleted; conversely, Swp82 and Taf14 are not required for retaining Snf5 within the complex. In humans, loss of the SNF5 (SMARCB1) subunit results in highly penetrant Rhabdoid tumors derived from tissues such as kidney and brain. Wang et al. (2017) investigate the consequences of removing or restoring the SNF5/SMARCB1 subunit in cell lines derived from relevant human tissue. In this case, absence of SNF5 results in a more substantial loss of complex integrity. Total protein levels for some subunits, including SMARCC1 and ARID1A, are reduced following loss of hSNF5. In addition, only a small proportion of the remaining subunits associates to form a large complex. The different effects of losing the SNF5 subunit in human and yeast may in part be explained by ubiquitin-mediated degradation of subunits not incorporated into complexes in human cells (Narayanan et al., 2015).

Having gained insight into how different subunits affect complex assembly, it is next important to establish how the altered complexes affect gene regulation. This is often confounded by partial redundancy between related enzymes, making individual effects subtle (Yen et al., 2012). Nonetheless, it remains important to establish how gene expression is reprogrammed as a result of subunit loss. Dutta et al. (2017) address this by monitoring changes in gene expression and binding of SWI/SNF complexes in mutants. Expression profiles indicate significant differences in the genes affected by mutation of different subunits, consistent with previous observations following mutation of selected subunits of *Drosophila* complexes (Moshkin et al., 2007). This is to some extent expected as subunits such as Taf14 have additional functions, in this case as a component of TFIID. Hierarchical clustering shows that there is similarity in the profile of genes affected by subgroups of subunits, such as the Snf6, Snf5, Snf12 module. Loss of this module affects Snf2 occupancy at only 206 genes but undermines the complex's catalytic activity (Sen et al., 2017). It is known that interactions with histone modifications and transcriptional activators contribute to targeting of SWI/SNF complexes, and it is shown that complexes are more likely to be retained at genes with high levels of histone H3 K9 acetylation. Only a subset of the genes that respond to loss of SWI/SNF subunits are bound by SWI/SNF. This suggests

that many of the changes to transcription observed are indirect. Genes upregulated following loss of the Snf5 and Swi3 subunits include the transcription factors MET28 and MET32. Increased Snf2 occupancy and transcription are observed at a cohort of genes regulated by these transcription factors. This provides a clear example of how indirect effects contribute to the reprogramming of the transcriptome following loss of specific subunits.

In human cells, loss of hSNF5 has been seen to silence the tumor suppressor, INK4 (Kia et al., 2008), which would be expected to have secondary effects on transcription. In this case, recent observations suggest that hSWI/SNF complexes act to directly to remove Polycomb repressive complexes on a time scale of minutes (Kadoch et al., 2017; Stanton et al., 2017). Loss of the human SNF5 subunit has the greatest effects on the engagement of SWI/SNF complexes with promoter distal enhancers (Wang et al., 2017). Changes in SWI/SNF occupancy at enhancers are observed to occur over several days or longer and are associated with changes in histone H3 K27 acetylation and histone H3 K4 monomethylation. Transcription of neighboring genes, many of which are involved in processes such as tissue-specific differentiation, were observed. Interestingly, effects at super-enhancers are minimal, possibly reflecting multiple modes of recruitment, perhaps involving histone acetylation as observed in yeast. Genes proximal to rhabdoid-specific super-enhancers, including SPRY, SAL4, and HMGA2, were found to be required for proliferation of rhabdoid tumor cell lines and to represent a vulnerability that may have potential for development of therapeutic approaches.

Through building understanding of structural and functional roles for individual subunits within SWI/SNF complexes, it is becoming clearer how they have specific effects on gene expression and tumor suppression.

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