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1 **Glucose starvation blocks translation at multiple levels**

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13 **Deficiency of glucose, even under sufficient amino acid supply, turns off**
14 **translation, and promotes catabolic processes to aid cell survival. A recent report**
15 **by Yoon et al. (2019) shows that glucose is required for the full activity of the**
16 **leucyl-tRNA synthetase LARS1, and maintains mTORC1 function via LARS1 to**
17 **enhance translation. Glucose starvation abolishes both effects via**
18 **phosphorylation of LARS1 by the AMPK-ULK1 signaling pathway. This study**
19 **supports the idea that glucose starvation inhibits translation at multiple levels.**

20
21 Translation is an energy-consuming process that consumes at least two molecules
22 of ATP and two of GTP to add each new amino acid to the growing polypeptide chain.

23 Cells employ multiple regulatory mechanisms to ensure that this energy-consuming
24 anabolic process can only take place when ample nutrients and growth factors are
25 available. Availability of glucose, the major energy source for most cells, is known to
26 be a prerequisite for translation. It has long been known that AMP-activated protein
27 kinase (AMPK), a cellular sensor of energy and nutrients, is activated upon glucose
28 starvation, in turn switching off the mammalian target of rapamycin complex 1
29 (mTORC1) pathway, which is critical for both the initiation and elongation steps of
30 translation (Johanns et al., 2017). AMPK inhibits mTORC1 by dual mechanisms: i)
31 phosphorylation of tuberous sclerosis 2 (TSC2) (Inoki et al., 2003), leading to
32 inhibition of RHEB (Ras homolog enriched in brain), a lysosome-localized small
33 GTPase that facilitates mTORC1 activation only in the GTP-bound status; ii)
34 phosphorylation of RAPTOR (regulatory-associated protein of mTOR), a component
35 of the mTORC1 complex (Gwinn et al., 2008). As well as these effects via mTORC1,
36 AMPK also phosphorylates and activates eukaryotic elongation factor-2 (eEF2)
37 kinase, which then triggers phosphorylation and inactivation of eEF2 itself to directly
38 block the elongation step of translation (Johanns et al., 2017).

39 The recent report by Yoon et al. (2019) adds a new tier to the regulation of
40 translation by AMPK in response to glucose availability. They first reported a new
41 mechanism in which leucyl-tRNA synthetase 1 (LARS1), which catalyzes the
42 ATP-dependent ligation of L-leucine to its cognate tRNA, can accelerate the
43 inhibition of mTORC1 in low glucose in an AMPK-dependent manner. LARS1 has
44 been previously identified as a leucine sensor that binds to RAGD, a

45 lysosome-localized Rag GTPase essential for the stimulation of mTORC1 by amino
46 acids, thus promoting conversion of RAGD from the GTP- to the GDP-bound state
47 (Han et al., 2012). RAGD:GDP subsequently promotes mTORC1 translocation to the
48 lysosomal surface to allow its activation by leucine. Intriguingly, the affinity of
49 LARS1 towards RagD, as well as its ability to activate mTORC1, was reduced in low
50 glucose even in the presence of leucine, indicating that glucose may exert a dominant
51 regulation of LARS1. Through RNAi screening, they identified AMPK and its
52 substrate ULK1 (Unc-51 like autophagy activating kinase), as being involved in the
53 suppression of the LARS-RagD pathway in low glucose. Mechanistically, ULK1,
54 which is phosphorylated and activated by AMPK in low glucose (Egan et al., 2011;
55 Kim et al., 2011), phosphorylates S391 and S720 on LARS1, reducing its affinity
56 towards RagD. Yoon et al. (2019) also showed that phosphorylation of LARS1 by
57 ULK1 reduces the binding of both ATP and leucine to LARS1, leading to an
58 inhibition of leucine loading onto tRNA and thus limiting protein elongation. This
59 finding introduces the additional concept that glucose starvation directly disrupts an
60 early step in translation, i.e., aminoacylation of tRNA. As a result, increased free
61 intracellular leucine (originating both from enhanced autophagy after AMPK
62 activation/mTORC1 inhibition and reduced translation), can then be used as an
63 alternative carbon source for the catabolic production of ATP (via the TCA cycle) in
64 low glucose. Consistent with this, removal of leucine from glucose-free medium
65 reduced ATP concentrations in rhabdomyosarcoma cells. This study reveals a finely
66 tuned network that connects AMPK to LARS1, as well as mTORC1, to determine the

67 catabolic or anabolic fate of leucine when availability of glucose is limiting.

68 Highly relevant to these findings are earlier reports (Zhang et al., 2017; Zhang et
69 al., 2014) showing that glucose starvation simultaneously switches on AMPK and
70 switches off mTORC1 on the lysosomal surface. In low glucose, decreased levels of
71 the glycolytic intermediate fructose-1,6-bisphosphate (FBP) are sensed by the
72 glycolytic enzyme aldolase, which cleaves FBP into phosphotrioses. Aldolase that is
73 not occupied by FBP inhibits the vacuolar-type H⁺-ATPase (v-ATPase) on the
74 lysosomal surface, leading to a change in its interaction with the pentameric Ragulator
75 complex. Under these circumstances AXIN (either AXIN1 or AXIN2), in complex
76 with LKB1, docks onto the v-ATPase-Ragulator complex, triggering phosphorylation
77 and activation of the lysosomal pool of AMPK by LKB1. The translocation of AXIN
78 to lysosomal surfaces also facilitates release of mTORC1 from the lysosome, thereby
79 at the same time inhibiting mTORC1. Consistent with this, when AXIN1 is depleted
80 in MEFs (in which AXIN2 is not expressed), mTORC1 inhibition becomes much
81 slower after glucose removal. AXIN1 exerts this effect by facilitating the GAP
82 activity of the Ragulator complex towards the RagC GTPase. Therefore, we would
83 argue that high glucose does not activate mTORC1, rather it prevents inhibition of
84 mTORC1 via its dissociation from the lysosome. It is important to stress that glucose
85 starvation can still render mTORC1 inactive even in AMPK-null cells, albeit at a
86 slower rate (Zhang et al., 2014). In support for a critical effect of AXIN on the GAP
87 activity of Ragulator, a “constitutively active” RAG, i.e., the GTP-constitutive
88 binding mutant of RAGA or RAGB, completely blocks the inhibition of mTORC1 in

89 low glucose, despite intact AMPK activation (Efeyan et al., 2013; Zhang et al., 2014).
90 Therefore, the AXIN-dependent and AMPK-independent mechanisms can operate in
91 parallel to control the activity of mTORC1 (Figure 1). It would be interesting in future
92 to compare the dynamics of translational inhibition following knockout of the various
93 components of the AXIN-AMPK-ULK1 pathway. In summary, it is remarkable that
94 glucose, as the most abundant cellular nutrient, exerts so many regulatory roles to
95 control translation.

96

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132 and anabolism. *Cell Metab.* 20, 526-540.

134 **Figure legend**

135 **Figure 1. Glucose starvation inhibits translation at multiple levels to maintain**
136 **energy balance.**

137 Upon glucose starvation, AXIN in complex with LKB1 translocates to the lysosomal
138 surface, activating the lysosomal pool of AMPK, which in turn inhibits mTORC1 by
139 phosphorylating TSC2 and RAPTOR. Importantly, the translocation of AXIN itself to
140 the lysosomal surface results in inhibition of mTORC1 by facilitating dissociation of
141 mTORC1 from the lysosome, even in the absence of AMPK. The recent report (Yoon
142 et al., 2019) shows that glucose deprivation blocks translation at an early step of
143 aminacylation. They found that LARS1 is phosphorylated by the AMPK-ULK1
144 pathway under glucose starvation, promoting conversion of RAGD from the GDP- to
145 the GTP-bound state to inhibit mTORC1, but also impairing the binding capability of
146 both ATP and leucine to LARS1 to block the leucylation of tRNA(Leu). As a result,
147 intracellular levels of free leucine increase due to lesser usage for translation or to
148 increased autophagy. Leucine can thus be used instead as an alternative carbon source
149 for the catabolic production of ATP (right-hand side), while the energy-consuming
150 process of translation is blocked at multiple levels.

Figure 1

