LARS1 Guides Leucine Catabolism Under Nutrient Deprivation

Preview for Preview for “Yoon, I., Nam, M., et al. (2020). Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1. Science 367, 205-210.”

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Introduction

Nutrient sensing is essential to the growth and survival of individual organisms, and to the evolution of species as a whole. In order to utilize the resources in the most efficient way, the biological system has developed very sophisticated networks to recognize, deliver, distribute and conserve fuel substrates including glucose and amino acids. These processes are highly regulated and coordinated so that the organism can better survive when nutrient becomes scarce or even in the harshest starving condition. In energy metabolism, glucose is the most important source of energy in all organisms. Glucose deprivation induces metabolic oxidative stress and cellular toxicity, an SOS signal for the cell to direct all possible resources to shut down energy consuming cellular processes such as protein synthesis and to turn on backup mechanisms to generate ATP including amino acid catabolism. The AMP activated protein kinase (AMPK) is most established energy sensor, which can be activated by low glucose to inhibit the mammalian target of rapamycin (mTOR) and thus block protein synthesis[1]. It is well known that low glucose induces proteolysis to supply amino acids for ATP production. However, the energy sensor and the executing mechanism that relays low glucose to amino acid metabolism remain relatively unexplored. By showing that leucyl-tRNA synthetase 1 (LARS1) promotes the mTOR activity in a nutrient rich condition but not in a nutrient deprived condition, Yoon *et al.*[2] uncovered a hitherto unknown link between energy sensing and amino acid catabolism.

Results

Yoon et al. reported that LARS1 plays a role in the interactions between glucose sensing and

leucine metabolism. First of all, the authors found that glucose was required for the function of LARS1 as leucine sensor. In addition, glucose can induce the interaction between LARS1 and RagD, which is a subunit of mTORC1, leading to the activation of mTOC1 signaling pathway. To further illustrate the potential role of glucose in regulating leucine sensing ability of LARS1, the authors investigated post-translational modification of LARS1 and demonstrated that glucose starvation increased LARS1 phosphorylation. From siRNA-based screening, they showed that ULK1 decreased LARS1 phosphorylation. Co-IP, FRET, and *in vitro* pulled down and phosphorylation assays confirmed that LARS1 was associated with ULK1 and underwent glucose starvation-dependent phosphorylation at S391 and S720 by ULK1.

The authors then demonstrated the effects of ULK1-mediated LARS1 phosphorylation on regulating metabolic activities. Notably, the phosphorylation of LARS1 by ULK1 blocked the binding of leucine and ATP, thereby decreasing leucylation of LARS1. Additionally, they showed that inhibiting leucylation of LARS1 suppressed mTORC1 signaling and protein synthesis. Leucine can be catabolized to generate acetyl-coA to TCA cycle in the absence of glucose. The authors then determined the fraction of ^{13}C-labelled citrate and malate which were leucine-derived carbons by LC-MS and found that LARS1 phosphorylation increased leucine catabolism upon glucose starvation. Finally, they observed the increased ATP concentration in cells expressing LARS1 phosphomimetic mutant under glucose deprivation, suggesting LARS1 phosphorylation also helps to maintain adequate ATP production. Collectively, these results indicated that LARS1 controls of glucose-dependent leucine metabolism and coordinates leucine usage for protein synthesis and energy production.

Future direction

Just like most great publication, this paper raised more questions than it has solved. One of the mysteries is how LARS1 changes its cellular localization during glucose deprivation. It would be amazing if the authors can show that the interaction level change between LARS1 and RagD is responsible for the change in localization. Furthermore, ULK1 has been shown to be inhibited by mTORC1 via S757 phosphorylation[1]. Combining this with the finding in the paper, it seems

that the negative regulation is mutual between ULK1 and mTORC1, with LARS1 and RagD as intermediate regulators in the ULK1 regulation of mTORC1. It would be fascinating if the authors can show that overexpression of constitutively activated ULK1 S757A mutant suppresses both mTORC1 and LARS1 to verify the negative feedback loop. Last but not least, we would like to know whether LARS1 expression level alteration affects lifespan and healthspan. Utilize RNA inactivation of *lars-1* to test lifespan and healthspan in *C. elegans* would be optimal since knock out of *lars-1*, or knock out of its ortholog in other species is likely to be lethal.

References

1. Kim, J., Kundu, M., Viollet, B., and Guan, K.L. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol *13*, 132-141.
2. Yoon, I., Nam, M., Kim, H.K., Moon, H.S., Kim, S., Jang, J., Song, J.A., Jeong, S.J., Kim, S.B., Cho, S., et al. (2020). Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1. Science *367*, 205-210.