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Glutaminolysis feeds mTORC1

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Abbreviations: 2-HG, 2-hydroxyglutarate; αKG, α-ketoglutarate; GDH, glutamate dehydrogenase; GLS, glutaminase; IDH, isocitrate dehydrogenase; mTOR, mammalian target of rapamycin; TCA, tricarboxylic acid

Glutamine is an important amino acid from a metabolic point of view. As an amino acid and a precursor for other amino acids, it sustains protein synthesis. It is also required for production of nucleotides (pyrimidines) and α-ketoglutarate (αKG). αKG is produced via double deamination of glutamine, a process termed glutaminolysis. Glutamine is first de-aminated by glutaminase (GLS) to produce glutamate. Glutamate is then converted to αKG by glutamate dehydrogenase (GDH). The production of αKG from glutamine is critical to replenish the tricarboxylic acid (TCA) cycle and thus to sustain ATP levels. The metabolic importance of glutamine is also reflected in the fact that cancer cells are often glutamine addicted. Intriguingly, the catabolism of glutamine by cancer cells exceeds the cellular requirement for glutamine in the production of amino acids, nucleotides and energy. What else is glutamine used for that could explain the glutamine addiction of cancer cells? Recent findings by Durán et al. demonstrate that glutaminolysis activates mammalian target of rapamycin (mTOR), hence inhibiting autophagy and promoting cell growth.[1] This suggests that glutamine metabolism is additionally required as part of a signaling process to upregulate cell growth and proliferation.

TOR is a conserved serine/threonine kinase that regulates cell growth, metabolism and aging.[2,3] It forms two structurally and functionally distinct complexes termed TORC1 and TORC2 (mTORC1 and mTORC2 in mammals). While mTORC1 is activated by nutrients (amino acids), growth factors and cellular energy, mTORC2 is activated by growth factors alone. Of note, among the amino acids, leucine is the most effective activator of mTORC1.[4] While the mechanism by which leucine activates mTORC1 has been investigated for many years, the study by Durán et al.[1] suggests leucine activates mTORC1 through its role as an activator of glutaminolysis. Leucine is an allosteric activator of GDH. By directly binding to GDH, leucine stimulates de-amination of glutamate to form αKG. αKG, in turn, activates mTORC1 via activation of prolyl hydroxylases,[5] a family of αKG-dependent dioxygenases. Importantly, this provides a mechanism by which mTORC1 senses leucine. The activation of GDH by leucine is also known to play a role in insulin secretion in pancreatic β cells. Thus, the findings of Durán et al.[1] also suggest that mTORC1 may mediate leucine-dependent stimulation of insulin secretion.

Activation of mTORC1 by glutaminolysis provides an explanation for why glutamine metabolism in tumor cells exceeds the need for glutamine as a biosynthetic precursor. mTORC1 activation is necessary for protein synthesis, nutrient uptake and cell growth. Indeed, mTORC1 is upregulated in a broad variety of cancers.[6] Durán et al.[1] suggest that upregulation of glutaminolysis in cancer cells ensures mTORC1 activation to sustain cell growth. This model also suggests that glutamine-addicted cancer cells might be particularly sensitive to rapamycin.

Neomorphic mutations in the enzyme isocitrate dehydrogenase 1 (IDH1), which are found in gliomas and acute myelogenous leukemia, are associated with glutamine addiction.[7] The oncogenic versions of IDH1 convert αKG to the oncometabolite 2-hydroxyglutarate (2-HG). The mechanism by which 2-HG promotes tumorigenesis is currently under intensive investigation. A recent study using cultured human astrocytes suggests that 2-HG may be a particularly effective activator of prolyl hydroxylases.[8] Hyperactivation of prolyl hydroxylases by 2-HG may, in turn, lead to hyperactivation of mTORC1. However, in vivo studies using knock-in mice suggest that 2-HG prevents activation of prolyl hydroxylases,[9] and a role of mTORC1 in 2-HG-mediated tumorigenesis remains to be investigated.

Future strategies targeting both glutamine metabolism and mTOR signaling might show synergistic effects against cell growth and proliferation in glutamine-addicted cancer cells. Further work will help to elucidate the therapeutic repercussion of the recently discovered link between glutamine metabolism and mTORC1. Certainly, the findings of Durán et al.[1] are an example of crosstalk between metabolism and cell signaling, and may provide new approaches for the design of targeted therapies against cancer.

Glutaminolysis, via activation of mTORC1, also inhibits autophagy and increases cell size. The inhibition of autophagy by glutaminolysis prevents the needless production of excess energy derived from recycling cellular components. Conversely, a lack of glutaminolysis inhibits mTORC1, hence activating autophagy. In this case, autophagy is an alternative means of obtaining nutrients and energy when the TCA cycle is not sustained by glutaminolysis. αKG production through glutaminolysis is the major anaplerotic reaction maintaining the TCA cycle. Thus, controlling mTORC1 and autophagy via glutaminolysis ensures that

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the cell coordinates energetic demand and nutrient availability.

In agreement with Durán et al.,[1] van der Vos et al.[10] recently reported that an increase in glutamine synthetase (which catalyzes the reaction opposite to that of GLS, producing glutamine from glutamate) inhibits mTORC1 and activates autophagy. Thus, mTORC1 appears to sense the flux between glutamine and αKG in both directions. When flux is toward αKG production, mTORC1 is activated to inhibit autophagy. Conversely, mTORC1 is inactivated when flux is toward glutamine production, enabling autophagy to provide nutrients and energy. However, flux toward glutamine synthesis may have physiological relevance only in certain conditions. Most mammalian tissues express low levels of glutamine synthetase, with liver being a notable exception.

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