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mTORC1 Controls Synthesis of Its Activator GTP

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http://dx.doi.org/10.1016/j.celrep.2017.06.032

In this issue of *Cell Reports*, Emmanuel et al. (2017) report that mTORC1 activity is regulated by purine availability. This increases the number of mTORC1 regulators to include metabolites whose synthesis mTORC1 controls.

mTORC1 is a major signaling hub that integrates inputs from varying nutrient, energy, and growth factor levels to regulate cell growth. Broadly, mTORC1 activates anabolic processes required for cell growth, including protein, nucleotide, and lipid synthesis. Conversely, mTORC1 inactivity lifts restraints on catabolic processes, such as autophagy, that enable the cell to sustain itself when resources are scarce.

Given the central role of mTORC1 activity in growth and metabolism, it is not surprising that it is tightly regulated. Stimuli are funneled into mTORC1 via the GTPase Rheb, the immediate upstream activator of mTORC1. Only GTP-bound Rheb activates mTORC1, and it is modulation of the Rheb GTP/GDP-loading status that ultimately determines mTORC1 activity.

Nucleotide biosynthesis (both pyrimidine and purine) is among the anabolic pathways activated by mTORC1 (Robitaille et al., 2013; Ben-Sahra et al., 2013; 2016). Besides its well-known role as a DNA building block, GTP also mediates protein synthesis and cytoskeletal dynamics and is a second messenger in signaling cascades. Depletion of the intra-cellular pool of GTP has an anti-proliferative effect and may be an anti-cancer strategy.

In this issue of *Cell Reports*, Emmanuel et al. report that GTP availability can control mTORC1 activity by determining the GTP-loading status of Rheb. Pharmacological inhibition of purine biosynthesis had an inhibitory effect on mTORC1, while inhibition of pyrimidine biosynthesis had no impact on mTORC1 activity. mTORC1 inhibition upon GTP depletion coincided with reduced proliferation. Exogenous adenine or guanine suppressed the effect of de novo purine biosynthesis inhibition on mTORC1 activity. However, only guanine could rescue mTORC1 activity upon inhibition of IMPDH1/2 (the guanine-specific step after the branchpoint for adenine and guanine synthesis), suggesting that it is guanine availability that is responsible for the observed effects on mTORC1 activity.

The authors found that GTP depletion reduced GTP loading of Rheb without affecting the activity or GTP loading of other GTPases such as Ras and Rac1 (and presumably Rag, see below), indicating that Rheb is particularly responsive to intra-cellular GTP concentration. mTORC1 activity is also regulated by another set of G proteins, the Rags, that activate mTORC1 in response to amino acids. Ectopic expression of a constitutively active form of the RagB/C heterodimer (which corresponds to $RagB^{GTP}$/$RagC^{GDP}$) rendered mTORC1 resistant to amino acid deprivation but was unable to prevent mTORC1 inhibition by purine synthesis inhibitors. However, constitutively active Rheb was able to rescue mTORC1 activity upon purine depletion, suggesting that the effect of GTP depletion on mTORC1 activation is primarily or solely via Rheb.

These results add a new dimension to the relationship between mTORC1 and purine synthesis, in particular for GTP. It places GTP both upstream and downstream of mTORC1. In proliferating cells, mTORC1 stimulates de novo purine biosynthesis, and adequate intra-cellular GTP levels are required to sustain mTORC1 activity. What is the physiological significance of this new relationship? It may simply be a positive feedback mechanism to amplify mTORC1 activity. Conversely, could the purpose be that low GTP levels play a role in inhibiting mTORC1 signaling, and if so, under what conditions would mTORC1 be negatively regulated by low GTP levels? A physiological situation in which GTP levels are insufficient to activate mTORC1 would presumably arise only after prolonged periods of nutrient unavailability (and thus reduced mTORC1-mediated GTP synthesis) when mTORC1 is already inactive. Indeed, Emmanuel et al. studied the effect of GTP depletion after extended inhibition of purine synthesis (overnight to 24 hr). mTORC1 typically responds to positive signals within seconds to minutes, thus allowing cells to mount a real-time response to fluctuating extra- and intracellular conditions. For example, rapid mTORC1 activation upon sudden availability of nutrients (following feeding or acquisition of a food source) calls for quick mobilization of metabolic pathways to assimilate the newly available resources. In contrast, turning off mTORC1 (such as upon limiting GTP or nutrient levels) would occur only after resource exhaustion and dissipation of an activating signal. This could be accomplished by dissociation of activating complexes or, as seen in the present case, limitation of GTP required for Rheb-dependent mTORC1 activation. Thus, there may be negative regulation of mTORC1 that operates over a gradual timescale (by comparison with rapid activation).

A key finding of this study is that a metabolite whose synthesis depends on mTORC1 is able to regulate mTORC1. This is similar to the case of the metabolic intermediate α-ketoglutarate. mTORC1 stimulates glutaminolysis and glutamine anaplerosis of the tricarboxylic acid cycle (Csibi, et al., 2013). This is achieved by increasing the activity of the glutaminolytic enzyme glutamate dehydrogenase (GDH) via mTORC1-mediated transcriptional repression of

its upstream inhibitor SIRT4. GDH produces α-ketoglutarate, which in turn activates mTORC1 by promoting mTORC1 translocation to the lysosome (Durán, et al., 2012). Is mTORC1 regulation by downstream products a general phenomenon? Future studies will establish if it is indeed a common feature of mTORC1 signaling and its physiological implications.

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