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CELL SIGNALLING

Sensing nutrient availability

> …the missing link between nutrients and the activation of the mTOR pathway.

The mammalian target of rapamycin (mTOR) protein complexes regulate cell growth in response to nutrients. However, the first step of this pathway (how nutrients regulate activation of mTOR complexes) has remained unknown. Two recent reports now show that Rag GTPases functionally interact with mTOR complex-1 (mTORC1) and are necessary for the activation of the mTORC1 pathway by amino acids.

Mammalian Rag proteins (RagA–RagD; Gtr1 and Gtr2 in budding yeast) are Ras-related small GTPases. In yeast and human cells, the Gtr and Rag proteins function as heterodimers that consist of one Gtr1-like (RagA or RagB) and one Gtr2-like (RagC and RagD) component. In yeast, Gtr proteins regulate processes (such as microautophagy) that are modulated by amino-acid levels and the TOR pathway.

BANANASTOCK

The Sabatini laboratory had previously shown that RagC copurifies with raptor, the defining component of mTORC1, which prompted the authors to further investigate the link between Rag proteins and the mTORC1 pathway. However, Guan and colleagues identified Rag proteins through RNA interference screen in *Drosophila melanogaster* S2 cells for GTPases that, when silenced, prevent amino-acid-induced phosphorylation of the mTORC1 target S6K.

Knockdown of Rag gene expression suppressed the stimulatory effect of amino acids on TORC1 in S2 cells and mammalian cells. A heterodimer that contains a RagB mutant that is constitutively bound to guanosine triphosphate interacted strongly with mTORC1, and its expression in mammalian cells rendered the mTORC1 pathway resistant to amino-acid deprivation. By contrast, expression of a guanine diphosphate-bound RagB mutant prevented stimulation of mTORC1 by amino acids.

Amino-acid import was not significantly affected by Rag expression. So, how do Rag heterodimers regulate mTORC1 signalling, if not by promoting the availability of nutrients? Sabatini and colleagues showed that mTOR was localized in tiny puncta throughout the cytoplasm in amino-acid starved cells, whereas amino-acid treatment promoted the localization of mTOR to a RAB7-positive compartment that also contains its activator, Rheb. The amino-acid-induced change in mTOR localization required expression of the Rag proteins and of raptor. Sabatini and colleagues proposed that amino acids control the activity of the mTORC1 pathway by regulating, through Rag proteins, the movement of mTORC1 to the same intracellular compartment that contains Rheb, thereby promoting its activation.

The physiological role of Rag in the nutrient response is supported by *in vivo* studies in *D. melanogaster*. Guan and colleagues showed that overexpression of a constitutively active RagA mutant increased cell size in fat body and wings, especially in starved flies, whereas expression of a dominant-negative RagA mutant decreased cell size. Furthermore, expression of constitutively active *RagA* suppressed starvation-induced autophagy, whereas heterozygous disruption of *RagC* suppressed lethality (owing to hyperactive TOR signalling) of tuberous sclerosis-1 mutant flies. These findings indicate that Rag GTPases regulate cell growth, autophagy and animal viability under starvation conditions.

These studies establish a novel function for Rag GTPases in mTORC1 activation in response to amino-acid signals and provide the missing link between nutrients and the activation of the mTOR pathway.

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ORIGINAL RESEARCH PAPERS Sancak, Y. *et al.* The Rag GTPases bind Raptor and mediate amino acid signaling to mTORC1. *Science* **320**, 1496–1501 (2008) | Kim, E. *et al.* Regulation of mTORC1 by Rag GTPases in nutrient response. *Nature Cell Biol.* 6 July 2008 (doi: 10.1038/ncb1753)