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# SESTRINs regulate mTORC1 via RRAGs: The riddle of GATOR

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(mTORC1) kinase. mTORC1 integrates numerous signals from nutrients, growth

factors, and stress to control metabolism, autophagy, and cell growth. mTORC1 activity inversely correlates with the lifespan of most eukaryotes and mTORC1 contributes to several different pathologies including cancer, diabetes, and neurodegenerative diseases.<sup>2</sup> mTORC1 is activated by 2 groups of small guanine triphosphatases (GTPases): Ras homolog enriched in brain (RHEB) and members of the Ras-related GTP-binding protein (RRAG) family, working as RRAG-A/B and RRAG-C/D heterodimers. RHEB activity is inhibited by the tuberous sclerosis protein complex (TSC). TSC in turn is controlled by several stress insults via activation of 5'-AMP-activated protein kinase (AMPK), and we have shown previously that SESTRINs inhibit mTORC1 via the AMPK-TSC axis.<sup>3</sup> Amino acids and glucose control mTORC1 via RRAGs, which stimulate translocation of mTORC1 to the lysosomes where it can be activated by RHEB. RRAG-A/B is activated by its GTPase exchange factor (GEF) called ragulator and is inhibited by the protein complex GATOR1 (GTPase activating protein [GAP] activity toward RRAG complex 1) working as a GAP. GATOR1 in turn is suppressed by the GATOR2 protein complex within the GATOR supercomplex.<sup>4</sup>

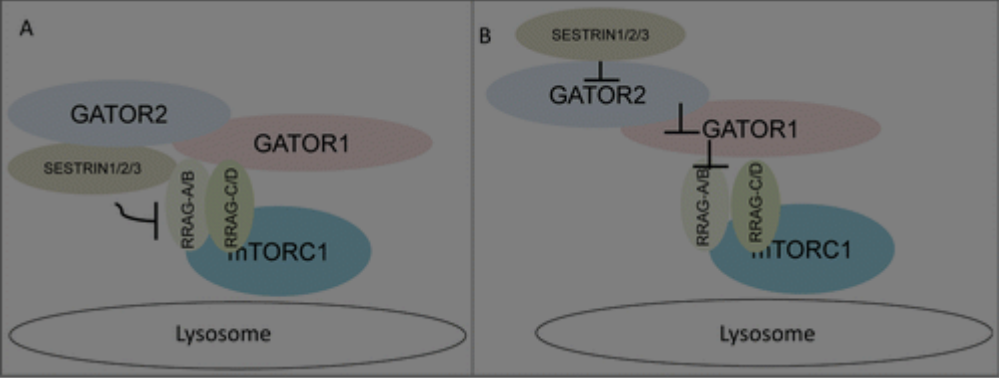
Three groups recently reported a novel mechanism of mTORC1 inhibition by SESTRINs via suppression of RRAG-dependent mTORC1 lysosomal translocation.<sup>5-7</sup> SESTRINs are critical for mTORC1 inhibition by amino acid withdrawal in mammalian cells.

Surprisingly, SESTRINs do not affect RRAG-A/B GDP/GTP loading, suggesting that they

are not important for mTORC1 activation. Using mass spectrometry, our group and Sabatini's group found that, in addition to our data, there is a high degree of similarity between the GATOR1 and GATOR2 complexes, suggesting that they may share a common mechanism of action. Li's group also found that SESTRINs inhibit mTORC1 activity by acting as a GAP for RRAG-A/B guanine nucleotide exchange factor (GEF) activity toward RHEB, a Ras-related GTPase







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To reconcile the discrepancy in localization studies we propose that the interaction between SESTRINs and GATOR-RRAGs complexes is a dynamic process and under certain conditions SESTRINs can be associated with lysosomes, although most of the proteins associated with GATOR are still located in the cytoplasm in close proximity to lysosomes. Our findings are consistent with recently published data from Avruch's laboratory<sup>8</sup> showing a predominantly cytoplasmic localization of RRAGs based on protein fractionation studies. In the future it would be important to analyze the localization of endogenous SESTRINs and RRAGs, and the role of SESTRINs in the control of RRAG localization in the cell under normal and stress conditions.

Interestingly, yeast mTORC1 is regulated by amino acids via a mechanism mediated by Gtr1 and Gtr2, orthologs of mammalian RRAG-A/B and RRAG-C/D, and the SEA complex (SEAC), suggesting that they are not obligate heterodimers. D. melanogaster has a similar aging pathway where function of SESTRINs might be controlled by mTORC1 switching.

Disclo

No potential conflicts of interest were disclosed.

## Funding

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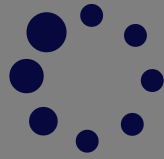
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