RESEARCH HIGHLIGHT

mTOR gets greasy: lysosomal sensing of cholesterol

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The mechanistic Target of Rapamycin Complex 1 (mTORC1) regulates diverse metabolic processes in response to nutrient stimuli and environmental cues. In a recent issue of *Science*, Shin et al. report the identification of a lysosomal G protein-coupled receptor-like protein that binds to cholesterol and couples the availability of this critical macronutrient to mTORC1 activation.

The mechanistic Target of Rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase that is inhibited by rapamycin, a small molecule discovered in samples collected on Easter Island almost 50 years ago. Over the past two decades, it has become clear that mTOR, in particular, mTOR complex 1 (mTORC1), plays a central role in essential cellular processes and metabolism, functioning as a signaling node to integrate cellular nutrient and hormonal cues to appropriately coordinate anabolic and catabolic processes with the availability of nutrients.[1] Some of the best characterized substrates of mTORC1 include S6K1, 4E-BP1, and ULK1, through which mTORC1 regulates processes including protein translation, ribosome biogenesis, lipogenesis, nucleotide synthesis, and autophagy.

mTORC1 kinase activity is regulated through control of its interaction with the small GTPase Rheb at the lysosomal surface. The recruitment of mTORC1 to the lysosomal surface by the availability of specific nutrients, particularly amino acids, is described in detail elsewhere.[2] Briefly, mTORC1 is recruited to the lysosomal surface by heterodimeric complexes of the Rag family of small GTPases; when these Rag proteins are loaded with GTP or GDP in a specific configuration, they localize mTORC1 to the lysosomal surface. The nucleotide loading state of the Rag GTPases is controlled by GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs).

Of particular relevance, the GATOR1 complex functions as a GAP for RagA and RagB, while a second complex, GATOR2, acts to inhibit GATOR1 GAP activity via unknown mechanisms.[3] As shown in Fig. 1, specific nutrient sensors for amino acids including leucine and arginine and the methionine metabolite SAM act by binding to and inhibiting the activity of either GATOR2 (e.g., Sestrin1/2/3 and CASTOR1/2) or GATOR1 (SAMTOR). An unknown sensor of the glycolysis intermediate DHAP also signals to mTORC1 via GATOR1. The sensing of other amino acids involves a low-affinity lysosomal amino acid transporter, SLC38A9, which may signal to mTORC1 via the Ragulator, which has GEF activity toward RagA/RagB.

If mTORC1 activity indicates the availability of nutrients required to fuel anabolic processes and serve as building blocks for macromolecule synthesis, we might expect that mTORC1 would sense many critical nutrients. Cholesterol is an important component of cell membranes and precursor for steroid hormones that is preferentially acquired from the environment due to the large bioenergetic cost of its synthesis, and therefore should logically be sensed by mTORC1. Although SREBP pathway is regulated by mTORC1, a direct mechanism to communicate cholesterol levels to mTORC1 remained unclear until recently.

In 2017, the laboratory of Dr. Roberto Zoncu demonstrated that depleting cells of LDL-derived cholesterol downregulates mTORC1 activity and disrupts its localization, connecting cholesterol sensing to Rag activity.[4] Bioinformatic analysis of mTORC1 pathway components containing cholesterol-regulated motifs revealed a potential cholesterol-binding site on SLC38A9. Through elegant biochemical dissection, Castellano demonstrated that SLC38A9 is required to deliver the cholesterol signal to mTORC1 via the Rags. SLC38A9 is inhibited by the cholesterol transporter Niemann-Pick type C (NPC) 1, suggesting that intra-lysosomal levels of cholesterol are sensed by this process. Indeed, inhibition of mTORC1 downstream of cholesterol ameliorates the mitochondrial dysfunction of NPC neurons.[5]

As SLC38A9 is primarily involved in arginine sensing, Zoncu and colleagues hypothesized the existence of a dedicated cholesterol sensor akin to amino acid sensors. Querying an exhaustive list of lysosomal resident proteins for transmembrane and annotated signaling domains, Shin and colleagues[6] identified a poorly annotated GPCR (G protein-coupled receptor), GPR155, whose depletion blocked mTORC1 localization to the lysosome in a Rag-dependent manner. GPR155, renamed lysosomal cholesterol sensing protein (LYCHOS), mediates cholesterol signaling to mTORC1 through its sequestration of GATOR1 away from RagA. Using a photo-crosslinkable cholesterol analog, Shin et al. localized the cholesterol-binding site to the N-terminal permease domain, and identified four cysteine residues in a C-terminal cytoplasmic loop required for cholesterol-dependent interaction with GATOR1. Importantly, LYCHOS appears to function independently of SLC38A9, offering another mechanism by which cholesterol impinges on the nutrient sensing arm of mTORC1.

There are many open questions regarding these intriguing discoveries. First, there appear to be at least two distinct cholesterol signaling mechanisms upstream of mTORC1 signaling; the relative roles of these sensors in different cell types and in vivo remains unknown, although LYCHOS expression is decreased in mouse tissues following fasting. Cholesterol is also sensed by the SREBP pathway downstream of mTORC1, while Sestrin1, which functions as a leucine sensor that regulates mTORC1 activity via

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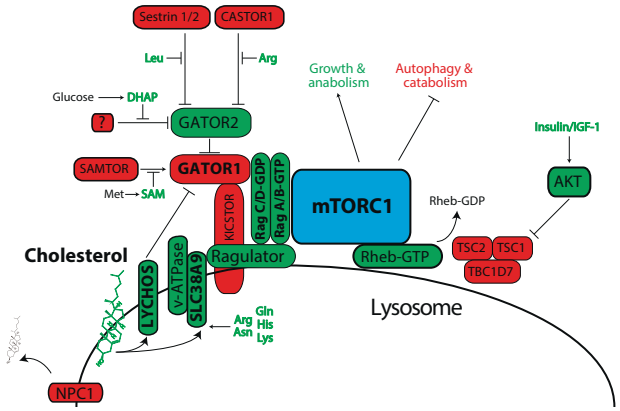

Fig. 1 The regulation of mTORC1 activity. mTORC1 is recruited to the lysosomal surface by heterodimers of the Rag family of small GTPases; the nucleotide-binding state of the Rags is controlled by protein complexes including the Ragulator, a GEF for RagA and RagB; and GATOR1, a GAP for RagA and RagB. Cholesterol binds to SLC38A9 and regulates the Ragulator-Rag GTPase complex.[4] Shin and colleagues have shown that cholesterol is sensed by the GPCR LYCHOS; when cholesterol is high, LYCHOS activates mTORC1 activity by sequestering GATOR1.[6] This figure is adapted from.[10]

GATOR2, also functions as cholesterol regulator, apparently via an mTORC1-independent function.[7] Notably, blood levels of cholesterol are highly variable between individuals as a result of both diet and genetics. While it remains unclear if mTORC1 senses extracellular cholesterol, the findings by Zoncu and colleagues suggest that this may contribute to differences in baseline mTORC1 activity between individuals. If so, it suggests that mTOR inhibitors such as rapamycin may have greater impact in individuals consuming high cholesterol diets.[8]

Finally, interfering with LYCHOS function may offer a new way to selectively inhibit mTORC1 activity. It is now well appreciated that many of the side effects of rapamycin and its analogs are the result of off-target inhibition of a second mTOR complex, mTORC2. A number of laboratories and companies have begun to develop mTORC1-selective compounds with the aim of developing new ways to intervene in diseases of aging and even to extend lifespan (reviewed in[9]). The discovery of LYCHOS may permit leveraging the significant pharmacological arsenal targeting GPCRs be deployed towards the selective inhibition of mTORC1.

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ADDITIONAL INFORMATION

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