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COMMENTARY

A spatially and functionally distinct pool of TORC1 defines signaling endosomes in yeast

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ABSTRACT

The evolutionarily conserved target of rapamycin complex 1 (TORC1) regulates cell growth in a homeostatic manner by tuning anabolic and catabolic processes in response to nutritional and hormonal cues. Interestingly, rather than being localized at the plasma membrane as perhaps expected for an integrator of extracellular signals, TORC1 mainly localizes at vacuolar (in yeast) and lysosomal (in more complex eukaryotes) membranes where it seems optimally placed to sense both the nutrient status within the cytoplasm and the vacuolar/lysosomal compartment. How TORC1 controls downstream targets that are distant from the vacuole/lysosome, is currently poorly understood. In this context, we recently identified and characterized 2 spatially and functionally distinct pools of TORC1 in the budding yeast *Saccharomyces cerevisiae*: one at the vacuole that promotes protein synthesis, and another one at endosomes that inhibits protein degradation. Thus, our findings highlight the presence of spatially separated pools of TORC1 that are commissioned with functionally specific tasks within cells. In addition, they pinpoint the existence of signaling endosomes in yeast, which raises numerous new questions that are warranted to direct future research in this area.

KEYWORDS

Amino acid signaling; EGO complex; ESCRT; macroautophagy; microautophagy; target of rapamycin complex 1

Summary

Eukaryotic cells tightly adjust their protein metabolism in a homeostatic manner in response to the availability of nutrients and hormones. A central regulator of the underlying physiological processes is the target of rapamycin complex 1 (TORC1), which oppositely controls protein anabolism and catabolism in response to the presence or absence of various nutritional cues among which amino acids are specifically important. Hitherto, studies in yeast and in more complex eukaryotes have been largely focused on the regulatory role that TORC1 executes at vacuolar and lysosomal membranes, respectively. In yeast, TORC1, like the EGO complex (EGOC) and Pib2 that both inform TORC1 with respect to the quantity and/or quality of the available amino acids, also localizes to punctate structures of previously unknown identity. In a recent study [1], we distinguished these structures as perivacuolar endosomes and, using a newly developed reporter system, demonstrated that the endosomal TORC1 activity is spatially and functionally distinct from the one localized at vacuolar membranes. Supporting the idea that TORC1 and its regulators form separate pools at both locations, our genetic and cell biological experiments allowed us to demonstrate that Meh1/Ego1, the membrane-anchoring subunit of the EGOC, can travel from the trans-Golgi network (where it is palmitoylated by Akr1) to either endosomes or vacuoles using the GGA (Golgi-localized, γ ear-containing, ARF-binding protein) or AP-3 (adaptor protein 3) pathways, respectively. Moreover, we uncovered that some tasks are rather specifically assigned to either of the 2 pools of TORC1: endosomal TORC1 inhibits (through phosphorylation of Atg13) macroautophagic and (through phosphorylation of the ESCRT-0 subunit Vps27) microautophagic protein degradation; vacuolar TORC1, in contrast, mainly promotes protein synthesis through phosphorylation and activation of the protein kinase Sch9. Thus, the distinct pools of TORC1 fulfill complementary roles to coordinately regulate protein homeostasis.

The existence of distinct TORC1 assemblies may represent a more general concept according to which TORC1 targets its effectors within different subcellular neighborhoods to fine-tune growth both spatially and conceivably also temporally. In the context of our studies in yeast, this raises a number of important questions that warrant future research in this area. For instance, a comprehensive search for local (endosomal versus vacuolar) TORC1 effectors may, in addition to corroborating our current model, provide insight into whether and how TORC1 impinges on protein trafficking events that are critically controlled at the level of endosomes or vacuoles. Moreover, isolation (e.g. following cell fractionation) and characterization of the different TORC1 assemblies may clarify whether endosomal and vacuolar TORC1 complexes exhibit structural differences that explain their different localizations. Such presumed disparities may also be functionally relevant, because they could have an impact on the way the respective TORC1 complexes communicate with their known (and perhaps currently elusive) upstream regulators to perceive locally different inputs. Finally, although perivacuolar endosomes appear to be quite long-lived compartments of stable composition, they do deliver intralumenal vesicles/material likely by 'kiss-and-run' events to the

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proximal vacuole. It will therefore be interesting to determine whether these temporal fusion events affect the subcellular distribution of TORC1 assemblies (and possibly also of their downstream effectors) to tune the balance between protein synthesis and degradation.

Curiously, TORC1 and EGOC seem to decorate only about half of the Vps27-positive endosomes. This suggests an intriguing model according to which cells simultaneously harbor TORC1- and EGOC-positive signaling and respective non-signaling endosomes. If so, how are these divergent endosomes established and maintained, and to what extent do they differ in their capacities to perform cellular processes such as protein sorting? Of immediate interest, in this context, is whether the TORC1-dependent control of ESCRT-0 via Vps27 may also define its role in protein sorting through the multivesicular body (MVB) pathway that destines endocytosed plasma membrane proteins for vacuolar/lysosomal degradation. Depending on the diffusibility of Vps27 between subcellular compartments, it seems even possible that the fluxes through the ESCRT-dependent MVB pathway may differ between TORC1-positive and -negative endosomes. Taken together, the discovery of spatially separated pools of TORC1 is likely to spur future research that is poised to refine our general understanding of how TORC1 signaling is intertwined with cellular trafficking events to homeostatically control growth.

Disclosure statement

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Reference

[1] Hatakeyama R, Péli-Gulli MP, Hu Z, et al. Spatially distinct pools of TORC1 balance protein homeostasis. Mol Cell. 2019 Jan 17;73:325–338.e8. PubMed PMID: 30527664.