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Regulation of autophagy by lysosomal positioning

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The mammalian target of rapamycin (mTOR) is a well-conserved negative regulator of autophagy. Here we review our recent data describing how lysosomal positioning influences and coordinates mTOR activity, autophagosome biogenesis and autophagosome-lysosome fusion. In this way, lysosomal positioning regulates many diverse cellular responses to starvation and subsequent nutrient replenishment.

Key words: autophagy, lysosome, mTOR, intracellular pH, ARL8, kinesin

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Macroautophagy (hereafter autophagy) has emerged during recent years as an important cellular process involved in many aspects of normal cellular physiology, as well as being affected in a variety of pathological conditions. In order to adjust its activity to upstream stimuli, autophagy needs to be tightly controlled and carefully orchestrated. A number of mechanisms ensuring such control have been described in the scientific literature to date, most of those acting primarily at the stage of autophagosome synthesis. It is clear, however, that in order to maintain an efficient flux through the pathway, the 2 main events in the short life of an autophagosome, its formation and degradation, need to be coupled. This would mean that the upregulation of autophagosomal synthesis should ideally be accompanied by a matching increase in autophagosome-lysosome fusion. We have recently described one such potential mechanism based on the intracellular positioning of late endosomes/lysosomes.

Lysosomes are dynamic organelles and their localization within the cell has frequently been noted to respond to a variety of treatments. One of the best-known effectors of lysosomal positioning is intracellular pH, where acidification redistributes lysosomes from their predominantly perinuclear location toward the cell periphery. However, the question of the physiological functions for these changes in lysosomal positioning has rarely been addressed in the past. We have noticed that in addition to intracellular pH, lysosomes also respond to nutrients, such as amino acids and growth factors, by moving toward the plasma membrane, whereas starvation results in a tighter perinuclear localization. We hypothesized that these changes in lysosomal positioning could have an impact upon autophagic flux. First, as demonstrated by Sabatini and Guan's laboratories, TORC1 is recruited to the surface of lysosomes in response to amino acids by Rag GTPases, and this lysosomal association is required for activation of mTORC1 by the small GTPase Rheb. We reasoned that intracellular positioning of lysosomes, together with associated mTORC1, may contribute to mTORC1 activation by regulating its proximity to the upstream signals at the plasma membrane. As a consequence, positioning of lysosomal mTORC1 will also have an impact upon the induction of mTOR-dependent autophagy. Second, the availability of lysosomes at the perinuclear region, where autophagosomes are delivered by microtubule-dependent transport, in order to facilitate fusion with lysosomes, could control the rate of autophagosomal degradation. In this case, increased numbers of perinuclear lysosomes would provide more acceptor sites for autophagosomes to fuse with.

We used chemical (depolymerization of microtubules by nocodazole) as well as genetic (overexpression or knockdown

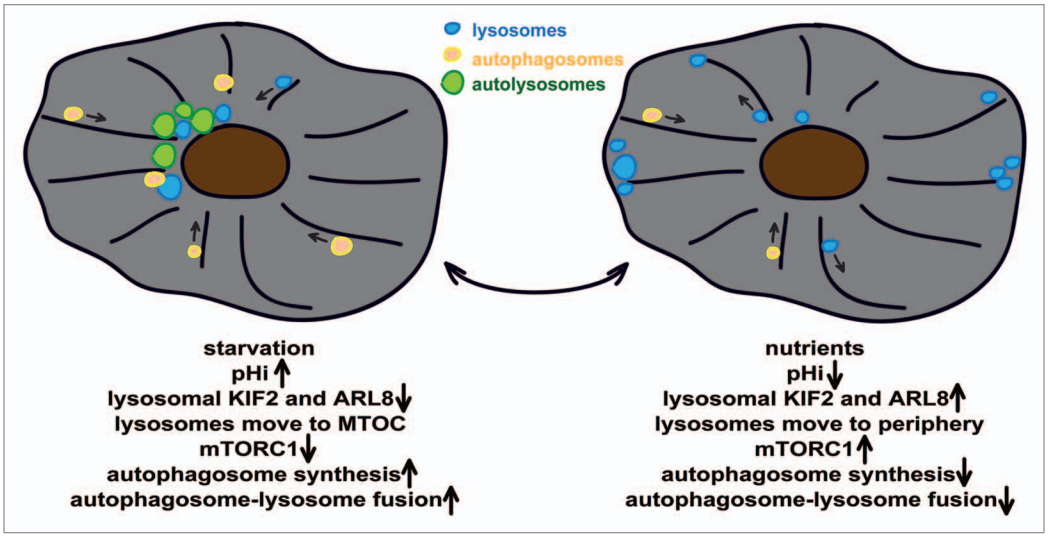

Figure 1. Diagram illustrating the proposed mechanism by which lysosomal positioning coordinates mTOR signaling and autophagy. Nutrients increase mTORC1 activity and inhibit autophagy, which is facilitated by increased peripheral lysosomal localization. In starved cells, lysosomes move to the microtubule organizing center (MTOC) promoting autophagosome synthesis and autophagosome-lysosome fusion. Nutrients are likely to impose their effect on lysosomal localization by pHi-dependent recruitment of anterograde transport machinery.

of kinesins KIF1Bβ and KIF2A as well as of small GTPases ARL8A and ARL8B involved in microtubule plus-end directed transport of lysosomes) approaches to control intracellular localization of lysosomes. We found that increased peripheral positioning of lysosomes correlates with increased mTOR activity. Additionally, we could also show that the appropriate mTORC1 response to nutrient replenishment after starvation can be enhanced or mitigated by an increase or a reduction, respectively, of the peripheral lysosomal pool. Using a similar experimental approach, we also obtained data to support the second part of our initial hypothesis. Indeed, preventing lysosomal scattering by kinesin or ARL8 knockdown not only increases autophagosome synthesis, as would be expected following reduced mTORC1 activity, but also results in increased autophagosome-lysosome fusion. By contrast, forcing lysosomes to the periphery is sufficient to prevent efficient degradation of autophagosomes, causing their accumulation and resulting in an overall reduction of the flux through the autophagosome-lysosome pathway.

We also addressed the question of a mechanism mediating nutrient-dependent trafficking of lysosomes. We found that fed and starved cells differ in their intracellular pH (pHi) and this difference is sufficient to affect kinesin and ARL8 recruitment to lysosomes, which may explain the observed changes in lysosomal localization and mTORC1 activity. One of the unresolved questions that remains following this study is how nutrient availability regulates pHi. A number of possible mechanisms could be envisaged, such as those involving proton transporters on the plasma membrane or even on the lysosome itself. The latter possibility, if demonstrated, would add an interesting twist to the story by changing the role of lysosomes from a mere passenger to an active driver of pHi changes in response to nutrients, thus mediating their own relocation within the cell.

Our results provide a rationale for the dynamic intracellular distribution of lysosomes. Indeed, lysosomal positioning emerges as a strong candidate for the role of a unifying factor coordinating autophagic flux at both ends of autophagosomal lifespan. We could speculate that this coordination is not only important for normal cellular physiology but may also be relevant to disease. As an example, the hypoxic environment of many tumors results in an overall reduction of extracellular pH. Although the relationship between extracellular and intracellular pH in tumors is complex and they do not always correlate, changes in pHi are likely to be involved in lysosomal scattering shown to occur in some tumor cells and found to be relevant to their invasiveness. Pathological changes in mTORC1 activity and in autophagy are other well-described characteristics of cancer cells. Our model provides a possible mechanism linking these seemingly unrelated phenomena, as well as suggesting possible ways of intervention. For instance, it would be expected that by interfering with the function of proteins involved in anterograde movement of lysosomes, it would be possible to simultaneously correct several processes deregulated in cancer cells. We have also shown that knockdown of KIF2B or ARL8 proteins enhances degradation of clinically relevant autophagy substrates. Since GTPases like ARL8 are likely to be druggable, they represent possible targets for future drug interventions.

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