

Lysosomal signaling in control of degradation pathways

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Autophagy mediates the (non-)selective bulk degradation of cytoplasm, protein aggregates, damaged organelles and certain pathogens. The endosomal membrane system uses multivesicular bodies (MVBs) to selectively deliver ubiquitinated membrane proteins together with extracellular components into lysosomes. Microautophagy (MA) and chaperone-mediated autophagy (CMA) additionally contribute to the selective delivery of cargo into lysosomes. The coordinated function of these lysosomal degradation pathways is essential to maintain cellular homeostasis. Their activity is controlled by mTOR (mammalian target of rapamycin) signaling and thus coupled to metabolic processes during cell growth. Here, we will discuss how TORC1 on lysosomes and TORC2 at the plasma membrane coordinate the different membrane biogenesis pathways with cargo selection, vesicle transport and fusion with lysosomes in response to intracellular and extracellular cues.

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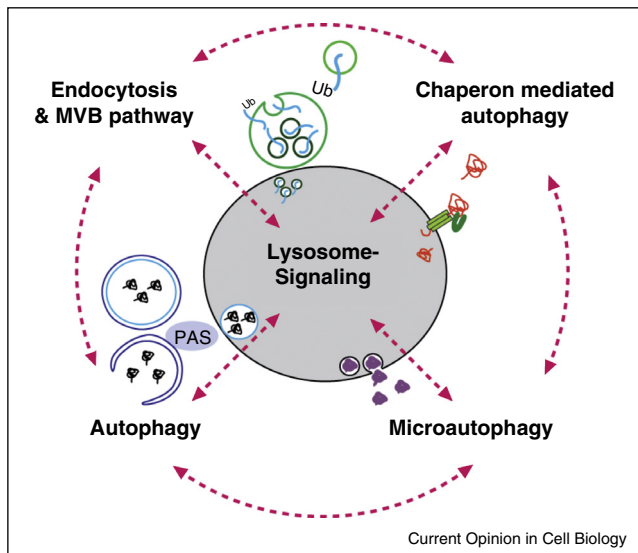
For a long time lysosomal degradation pathways have been considered as means to rid cells of waste products, simply required for the disposal and degradation of intracellular and extracellular macromolecules. Today, it has become clear that these catabolic pathways serve a much broader function than originally anticipated, including the regulation of cell signaling, metabolism and degradation of toxic protein aggregates and of damaged organelles as well as pathogen clearance. Their activity is tightly regulated and defects in each of these lysosomal degradation pathways can lead to metabolic disorders, cancer or neuro-degeneration [1,2]. The major goal of this review is to highlight our current understanding of how signaling from lysosomes triggers and coordinates different lysosomal degradation pathways and how they interact to maintain cellular homeostasis and organismal health (Figures 1 and 2).

Different vesicular and non-vesicular pathways target cargo to lysosomes for degradation (Figure 1). Autophagy delivers cytoplasmic material, damaged organelles, invading pathogens and protein aggregates into lysosomes [3]. Extracellular cargo and nutrients, together with components of the plasma membrane, integral membrane proteins and hydrolytic enzymes reach the lumen of lysosomes through the endosomal system via the multivesicular body (MVB) pathway [4]. Together, the MVB pathway and autophagy probably deliver the lion's share of cellular material to lysosomes. In addition, microautophagy (MA) and chaperone mediated autophagy (CMA) deliver cargo selectively into lysosomes [5]. The function of these lysosomal degradation pathways requires complex molecular machineries. The autophagy (ATG)-core machinery and the endosomal sorting complexes required for transport (ESCRT) couple (selective) cargo sorting to elaborate membrane biogenesis reactions to form transport intermediates [6,7]. (Endosomal) MA also relies on the ESCRT machinery for membrane remodeling [8]. Heterotypic membrane fusion of MVBs or autophagosomes with lysosomes (or with each other) finally delivers the cargo into the lumen of lysosomes. Cytoplasmic proteins degraded by CMA take a non-vesicular route into lysosomes and are directly imported across the limiting membrane of lysosomes. We are just beginning to understand how the individual pathways function. Yet, it is unclear how they are triggered and how these processes are coordinated with each other.

Signaling pathways central for cell growth and survival adjust the flux of cargo and regulate the biogenesis of lysosomal degradation pathways (Figure 2). The most prominent example is mTOR signaling, which integrates signaling from nutrients, growth factors, and energy availability [9]. mTOR exists in two distinct complexes, mTORC1 and mTORC2. They are found in various subcellular locations [10] and fulfill different tasks. Amongst others, mTORC1 signaling on late endosomes (LE)/lysosomes and mTORC2 at the PM and on lysosomes also seem to control cargo selection, membrane biogenesis and trafficking in different lysosomal degradation pathways.

Activation of mTORC1 on the surface of MVBs/lysosomes by Rheb-GTP is a complex multi-step process and additionally requires the RagA-D family of GTPases. They form obligatory dimers (e.g. RagA/C) and in their GTP bound form they recruit mTORC1 to MVBs/lysosomes. Rag-GTP loading is mediated by their guanine exchange factor (GEF), the LE/lysosomal adaptor and

Figure 1



Regulation of lysosomal degradation pathways. Autophagy, endocytosis and the MVB pathway, chaperone mediated autophagy (CMA) and microautophagy (MA) are depicted. Regulation by lysosomal signaling (see also Figure 2) and potential cross-talks are indicated.

MAPK and mTOR activator complex (LAMTOR) also known as Ragulator [11–13].

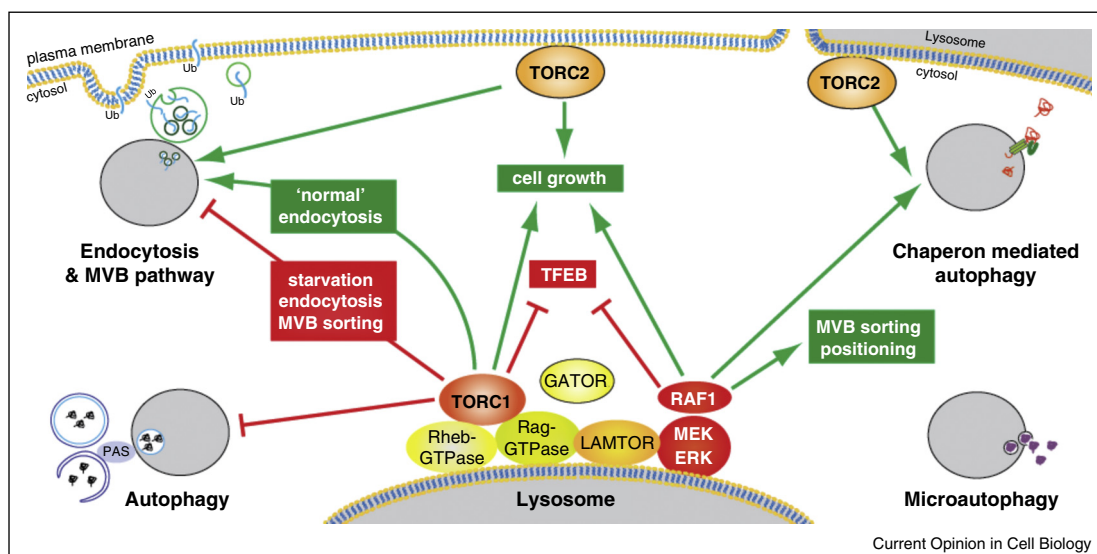
LAMTOR is a pentameric complex that is anchored by one of its subunits to LE/lysosomes [13,14]. The GEF activity of LAMTOR toward the Rag-GTPases and hence mTORC1 activation on lysosomes is regulated

by the interaction with a lysosomal nutrient transporter (SLC38A9) and the v-ATPase [15,16^{••},17^{••}]. In addition, LAMTOR functions as a scaffold complex for ERK signaling in response to growth factors [11,14,18,19]. LAMTOR mediated mTORC1 and ERK signaling control the nuclear translocation of the transcription factor, TFEB [20,21,22]. mTORC1 signaling appears to play the predominate role in regulating the nuclear translocation of TFEB in response to nutrient deprivation or lysosomal stress/dysfunction. The role of ERK signaling in TFEB regulation is less clear. Just as important as the activation of TOR signaling is its inactivation [23[•]]. The Rag-GTPases are inactivated by multisubunit complexes named SEA/GATOR that function as GTPase activating proteins (GAPs) [24^{••},25,26[•],27].

In line with the central role of mTOR and MAPK signaling in cell growth, LAMTOR and GATOR are required for tissue homeostasis *in vivo* and embryonic development [14,19,24^{••},28[•]]. Maybe more surprisingly, LAMTOR also controls several aspects of LE biogenesis. Its function is required for growth factor receptor degradation, lysosomal positioning through transport along microtubules and for the formation of recycling tubes on late LE/lysosomes [19,29,30[•]]. In addition, both LAMTOR and GATOR regulate autophagy. Despite their essential cellular functions and their role in tissue homeostasis, little is known about how LAMTOR and GATOR function, how they are regulated and how they mechanistically contribute to mTORC1 activation on lysosomes.

Much less is known about the mechanism resulting in TORC2 signaling at the PM, but TORC2 can be

Figure 2



Schematic presentation of lysosomal signaling complexes and their roles in lysosomal degradation pathways.

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