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Editorial Open Access

Preparing the Membrane for Autophagosome Biogenesis

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Editorial

Autophagy is a fundamental strategy eukaryotic cells employ for bulk turnover of cytoplasmic components to maintain cellular homeostasis. At the organismal level, autophagy is involved in a variety of physiological processes such as development, metabolism and immunity. Dysfunctional autophagy has been implicated in numerous human disorders including cancer, neurodegeneration, aging, infection and metabolic disease [1-3].

A key step of autophagy is the formation of a cup-shaped membrane precursor, called the phagophore, that engulfs part of the cytoplasm by membrane expansion to seal into a double membrane vesicle, termed the autophagosome. Fusion of the autophagosome with the lysosome leads to the degradation of the cytoplasmic components followed by release of the hydrolyzed products for material recycling [4-7].

To build an autophagosome, a hierarchical cascade of the autophagy related(ATG) proteins is required to assemble a cradle, termed the phagophore assembly site (PAS), in a sub-domain of the endoplasmic reticulum (ER) in mammalian cells or near the vacuole (a functional equivalent of the lysosome) in yeast [5,8-14]. In addition, substantial membrane mobilization from multiple locations, including ATG9-vesicles, the Golgi, the ER-Golgi intermediate compartment (ERGIC), ER exit sites(ERES), the plasma membrane (PM) and mitochondria, is necessary to deliver lipids and protein components to the PAS for autophagy initiation and phagophore growth [6,15,16]. Below, we briefly discuss the latest knowledge about how membranes are mobilized under autophagic conditions as well as how these membranes converge in the PAS for nucleating the phagophore precursor.

Mobilizing the ATG9 vesicles

Autophagosome biogenesis begins with a membrane nucleation step at the PAS [12,14]. One factor essential for phagophore nucleation is ATG9, a multiple transmembrane protein [17-20]. In yeast, Atg9 cycles between the Trans-Golgi Network (TGN), mitochondria, the PAS and some distinct tubulovesicular peripheral structures [21-25]. Under starvation conditions, these peripheral compartments become highly dynamic reflecting an increased membrane exchange between these structures and the PAS [25]. Mobilization of Atg9 vesicles from the TGN to the peripheral structures is crucial for subsequent delivery of Atg9 vesicles to the PAS for phagophore nucleation [24,25]. This process requires protein complex formation of Atg9 with two partners, Atg23 and Atg27, as well as the self-dimerization of Atg9 [25-28]. It has been proposed that proper stoichiometric formation of the Atg9/Atg23/Atg27 complex facilitates the clustering and sorting of Atg9 into a specific sub-domain in the TGN, which is essential for the generation of the tubulovesicular structure as an intermediate station for the delivery of Atg9 to the PAS [27].

A similar cycling of ATG9 between the TGN and certain peripheral compartments also occurs in mammalian cells [29]. These peripheral structures are a combination of both endosomes and endosome-like compartments [30]. After starvation, ATG9 shifts from the TGN to the peripheral compartments in a ULK1 and phosphatidylinositol 3-kinase (PI3K) dependent manner [29]. In addition, Bif-1 (an N-Bar domain protein), p38IP (p38-interacting protein) and myosin II are also required for this process [31-33]. In the peripheral compartment, ATG9 vesicles transiently associate with a growing phagophore for membrane delivery [30]. A recent study has also reported another route of ATG9 cycling between the PM and recycling endosomes. In the recycling endosome ATG9vesicles fuse with ATG16-positive vesicles as an essential step for producing a phagophore precursor [34].

Mobilizing the ER-derived membranes through COPII

Although ATG9 vesicles are essential for autophagosome nucleation, they are thought to only contribute a small portion of the autophagosomal membrane [25]. Consequently, a substantial amount of membrane should be acquired elsewhere. LC3, a mammalian homologue of yeast Atg8, is a ~15kD cytosolic protein that is extensively conjugated to phosphatidyl ethanolamine on autophagosomal membrane via aubiquitin-conjugation like pathway with the assistance of ATG12-ATG5/ATG16 protein complex (E3), ATG3 (E2) and ATG7 (E1) [35-38]. This process, called LC3 lipidation, is a critical step in autophagosome biogenesis. The membrane template for LC3 lipidation could also be a bulk source of the autophagosomal membrane. However, the origin of these membranes has been difficult to pinpoint due to the lack of a robust functional assay.

We have established a cell-free LC3 lipidation assay with mammalian cell cytosol and membranes that recapitulates many regulatory landmarks of autophagy [39]. Combining the assay with a membrane fractionation approach, we recently identified an ER-related compartment, termed the ERGIC, as a major membrane source supporting LC3 lipidation [39, 40]. In mammalian cells, the ERGIC is a sorting station for cargo traffic between the ER and the Golgi. Under steady states, the ERGIC constantly undergoes dynamic membrane exchange by receiving COPII and COPI vesicles derived from the ERES and cis-Golgi; it also generates COPI vesicles for antero/retro-grade transport [41-43]. Upon starvation, activation of the autophagic PI3K complex induces the translocation of COPII machineries, which are otherwise concentrated on the ERES for cargo export out of the ER, to the ERGIC to bud ERGIC-derived COPII vesicles [44]. These are one potential membrane template for LC3 lipidation [44]. This suggests that PI3K-induced COPII budding from the ERGIC could provide one essential membrane source for the phagophore.

The role of COPII in mobilizing the membrane for autophagosome biogenesis was also implicated in two other studies performed in yeast; one investigating macroautophagy and the other focusing on the cytoplasm to vacuole targeting (Cvt) pathway, a selective form of autophagy in yeast [45-47]. These studies indicate a physiological and functional link between the COPII-enriched spot, the ERES (a functional equivalent of both the ERGIC and ERES of mammalian cells) and the PAS in yeast. As another support of this notion, depletion of COPII components has been shown to compromise autophagy in both yeast and mammalian cells [44,45,48-50].

Mobilizing membrane from other sources

In addition to ATG9 and COPII vesicles, evidence has been provided that membrane mobilization from the PM [51,52], endosomes [34,53,54], the Golgi [55-58], mitochondria [59] and lipid droplets [60] also contributes to autophagosome biogenesis under different cellular backgrounds. Coat proteins [51,57], small GTPases [49,53], curvature generating proteins [54], organelle junctions [61] as well as lipases [60] have all been implicated in membrane mobilization from these organelles under autophagy-inducing conditions. It is worth mentioning that the ER has been generally considered the cradle for autophagosome biogenesis through the formation of the PAS followed by a PI3P-enriched structure, termed omegasome, in mammalian cells [10,11,61,62]. Therefore, the ER could be a major contributor to autophagosome biogenesis not just by supplying membrane but also acting as an organizing center to receive multiple sources of membrane for nucleation and growth of the phagophore. It is still unknown how bulk amount of ER membrane is directly mobilized for phagophore growth. COPII vesicle involvement could be one way [44,50,61]. However, other mechanisms may also exist.

Converging on the PAS

The autophagosome cradle (the PAS) is assembled by a hierarchical action of ATG proteins almost in parallel with the membrane mobilization events mentioned above [12,14,63]. In yeast, early steps involve the activation of a serine/threonine kinase complex, Atg1/Atg13/Atg17/Atg29/Atg31 complex, together with other ATG proteins like PI3K complex builds the initial architecture of the PAS for subsequent membrane recruitment, tethering and fusion [64-70]. Genetic, biochemical and structural analyses have revealed scaffolding and tethering functions of this protein complex in respect to receiving membranes from different sources as well as organizing the pre-autophagosomal structure [65,71]. Atg17 acts together with Atg11, a molecular scaffold for the yeast Cvt pathway, to recruit Atg9 vesicles to the PAS [72]. Structural analysis of the Atg17/Atg29/Atg31 complex showed a crescent shape of Atg17 with a curvature that fits the range to capture a small, highly curved vesicle similar to an Atg9 vesicle [65]. Together with the C-terminal EAT domain of Atg1,which senses membrane curvature, the Atg17/Atg29/Atg31 complex dimerizes and may act as a tether for two Atg9 vesicles to facilitate homotypic fusion possibly via SNARE proteins [52,65,73]. In addition to theAtg1/Atg13/Atg17/Atg29/Atg31 complex, another tethering complex, the transport protein particle III (TRAPPIII), also translocate to the PAS through direct association with Atg9 and Atg17 via Trs85, a specific subunit of TRAPPIII [74,75]. The TRAPPIII complex associates withSec23, an integral component of COPII, and is a GTP Exchange Factor (GEF) of a small GTPase Ypt1 in yeast. Therefore COPII vesicles and Ypt1 are recruited to the PAS, where COPII vesicles supply membrane and Ypt1 regulates vesicular events [50, 74-76]. Furthermore, it is proposed that the TRAPPIII complex may also be a tether to facilitate heterotypic fusion between an Atg9 vesicle and a COPII vesicle in the PAS [50, 77]. It has been shown, in mammalian systems, that a similar hierarchy of ATG proteins orchestrates PAS formation. However, the protein tethers and scaffold are still elusive. The protein FIP200 in a serine/threonine kinase complex (ULK1/FIP200/ATG13/ATG101) could be a functional homologue of Atg17 [78]. In addition, TRAPPIII also exists in mammalian cells. It would be interesting to know if the mechanism is conserved from yeast to mammals.

In summary, cells prepare for autophagosome biogenesis through substantial membrane rearrangements in multiple locations. Over the past few decades, our knowledge on this early autophagy step has been rapidly advanced by molecular genetics, advanced imaging techniques and biochemical reconstitution. Some questions, notably the source of the membrane for phagophore nucleation as well as the molecular details for mobilizing membrane from these sources have persisted. Future studies will be necessary to understand how and which membranes are mobilized for autophagosome biogenesis under each cellular situation or pathological condition as well as to identify specific factors involved as targets for the development of therapeutic modulators of autophagy to treat or relieve related pathological conditions.

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