

FORUM REVIEW ARTICLE

An Overview of Autophagy: Morphology, Mechanism, and Regulation

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Abstract

Significance: Autophagy is a highly conserved eukaryotic cellular recycling process. Through the degradation of cytoplasmic organelles, proteins, and macromolecules, and the recycling of the breakdown products, autophagy plays important roles in cell survival and maintenance. Accordingly, dysfunction of this process contributes to the pathologies of many human diseases. **Recent Advances:** Extensive research is currently being done to better understand the process of autophagy. In this review, we describe current knowledge of the morphology, molecular mechanism, and regulation of mammalian autophagy. **Critical Issues:** At the mechanistic and regulatory levels, there are still many unanswered questions and points of confusion that have yet to be resolved. **Future Directions:** Through further research, a more complete and accurate picture of the molecular mechanism and regulation of autophagy will not only strengthen our understanding of this significant cellular process, but will aid in the development of new treatments for human diseases in which autophagy is not functioning properly. *Antioxid. Redox Signal.* 20, 460–473.

Introduction

AUTOPHAGY IS A cellular degradation and recycling process that is highly conserved in all eukaryotes. In mammalian cells, there are three primary types of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). While each is morphologically distinct, all three culminate in the delivery of cargo to the lysosome for degradation and recycling (Fig. 1) (154). During microautophagy, invaginations or protrusions of the lysosomal membrane are used to capture cargo (101). Uptake occurs directly at the limiting membrane of the lysosome, and can include intact organelles. CMA differs from microautophagy in that it does not use membranous structures to sequester cargo, but instead uses chaperones to identify cargo proteins that contain a particular pentapeptide motif; these substrates are then unfolded and translocated individually directly across the lysosomal membrane (95). In contrast to microautophagy and CMA, macroautophagy involves sequestration of the cargo away from the lysosome. In this case, *de novo* synthesis of double-membrane vesicles—autophagosomes—is used to sequester cargo and subsequently transport it to the lysosome (157).

Of the three types of autophagy, macroautophagy is the best studied. Macroautophagy occurs at a low level constitutively and can be further induced under stress conditions, such as nutrient or energy starvation, to degrade cytoplasmic material into metabolites that can be used in biosynthetic processes or energy production, allowing for cell survival (157). Under normal growing conditions, macroautophagy aids in cellular maintenance by specifically degrading damaged or superfluous organelles (154). Thus, macroautophagy is primarily a cytoprotective mechanism; however, excessive self-degradation can be deleterious. Accordingly, autophagic dysfunction is associated with a variety of human pathologies, including lung, liver, and heart disease, neurodegeneration, myopathies, cancer, ageing, and metabolic diseases, such as diabetes (148).

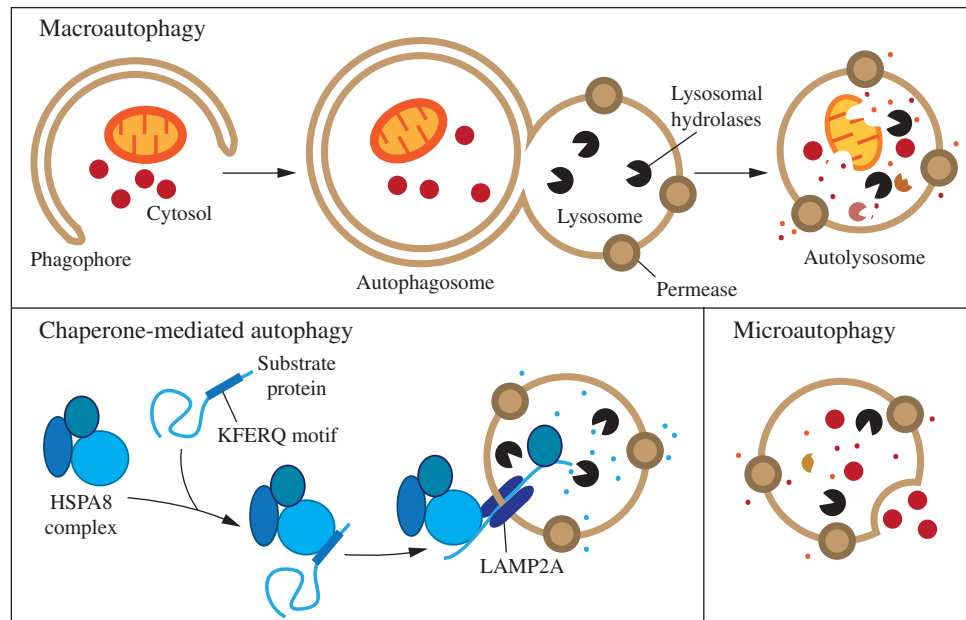
This review provides an overview of the current state of knowledge of autophagy, with an emphasis on the morphology, molecular mechanism, regulation, and selectivity of mammalian macroautophagy.

Microautophagy

Microautophagy refers to a process by which cytoplasmic contents enter the lysosome through an invagination or

FIG. 1. Three types of autophagy in mammalian cells.

Macroautophagy relies on *de novo* formation of cytosolic double-membrane vesicles, autophagosomes, to sequester and transport cargo to the lysosome. Chaperone-mediated autophagy transports individual unfolded proteins directly across the lysosomal membrane. Microautophagy involves the direct uptake of cargo through invagination of the lysosomal membrane. All three types of autophagy lead to degradation of cargo and release of the breakdown products back into the cytosol for reuse by the cell. See the text for details. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars



deformation of the lysosomal membrane (94). In one early study, isolated rat liver lysosomes were shown by electron microscopy to engulf Percoll particles *in vitro* by way of protrusions or cup-like invaginations of the lysosomal membrane, forming vesicles within the lysosome. Some of these particles were seen free-floating within the lysosomal lumen, presumably through rupture/lysis of the vesicles (93). A very recent study presented evidence that a microautophagy-like process called endosomal microautophagy transports soluble cytosolic proteins to the vesicles of late endosomal multivesicular bodies (123). Due to the limited number of tools available for the study of microautophagy, we know relatively little about this process, including its regulation and possible roles in human health and disease (101).

Chaperone-Mediated Autophagy

A second type of autophagy, which has so far only been described in mammalian cells, is CMA. Unlike microautophagy and macroautophagy, which can both nonspecifically engulf bulk cytoplasm, CMA is highly specific; common to all CMA substrates is a pentapeptide targeting motif biochemically related to KFERQ (24). Based on sequence analysis and immunoprecipitation experiments, it is estimated that ~30% of cytosolic proteins contain such a sequence (16). Target proteins containing the KFERQ consensus motif are unfolded through the action of cytosolic chaperones and translocated directly across the lysosomal membrane where they are degraded in the lumen (114). CMA degrades a wide range of substrate proteins, including certain glycolytic enzymes, transcription factors and their inhibitors, calcium and lipid binding proteins, proteasome subunits, and proteins involved in vesicular trafficking (3).

During CMA, the KFERQ motif is recognized by the heat shock 70 kDa protein 8 (HSPA8/HSC70), as well as other cochaperones (Fig. 1) (17). HSPA8 can then deliver the

substrate to the lysosomal membrane, where it likely assists in substrate unfolding (1). At the lysosomal membrane, the substrate binds to monomers of the CMA substrate receptor, lysosomal-associated membrane protein 2A (LAMP2A) (18). This substrate-receptor binding leads to the multimerization of LAMP2A (8, 18). As the multimeric translocation complex forms, subunits of the complex are stabilized on the luminal side of the lysosomal membrane by HSP90 (8). Following translocation of the substrate into the lysosomal lumen—in part, through the action of luminal HSPA8—the translocation complex is actively disassembled by cytosolic HSPA8, and LAMP2A returns to a monomeric state where it can bind new substrate and initiate a new round of translocation (8).

Regulation of the translocation process occurs at the level of substrate binding to LAMP2A, which is rate-limiting for CMA (19). Changes in LAMP2A levels at the lysosomal membrane modulate the level of CMA activity and primarily result from changes in degradation and organization of LAMP2A rather than synthesis of the protein (8, 19, 20). Some data support the idea that redistribution of LAMP2A between fluid regions of the lysosomal membrane and lipid-enriched microdomains influences the degradation of LAMP2A (65). While much is known about translocation regulation, far less is clear about overall CMA regulation (3). Mild oxidative stress (66), protein-damaging toxins (21), and extended periods of nutrient deprivation all upregulate CMA (6, 22), but the intracellular signaling pathways that facilitate this change are not fully understood (3).

It is suggested that HSPA8 and LAMP2A also participate in a type of macroautophagy called chaperone-assisted selective autophagy. During this process, chaperones aid in the clearance of selectively ubiquitinated organelles and protein complexes (76). Association of these ubiquitinated targets with receptors, such as SQSTM1/p62 and NBR1, and with enzymes, including HDAC6, allows for recognition by the macroautophagy machinery, delivery to the lysosome, and degradation (74, 76, 81).

Macroautophagy

Basic morphological progression

As stated above, macroautophagy is distinct from microautophagy and CMA in part because the initial site of sequestration occurs away from the limiting membrane of the lysosome, and involves the formation of cytosolic vesicles that transport the cargo to this organelle. The morphological feature that makes macroautophagy unique from other intracellular vesicle-mediated trafficking processes is that the sequestering vesicles, termed autophagosomes, form *de novo* rather than through membrane budding; that is, the autophagosome forms by expansion, and does not bud from a preexisting organelle, already containing cargo (152). Upon induction of macroautophagy in yeast, formation of autophagosomes begins at a single perivacuolar site called the

phagophore assembly site (PAS) (14). In mammalian systems, autophagosome generation is initiated at multiple sites throughout the cytoplasm rather than at a single PAS (14, 57). Several studies suggest that endoplasmic reticulum (ER)-associated structures called omegasomes may serve as initiation sites in mammals (41, 155).

Following initiation, the membrane begins to expand. At this stage, it is called a phagophore, which is the primary double-membrane sequestering compartment (Fig. 2) (43). The source of membrane that makes up the phagophore is highly debated, but various studies have implicated the plasma membrane (120, 121), ER (41, 155), Golgi complex (134), and mitochondria (36) as possible sources (107, 145). As the phagophore expands, the membrane bends to ultimately generate a spherical autophagosome. The factors that drive curvature of the membrane during nonspecific

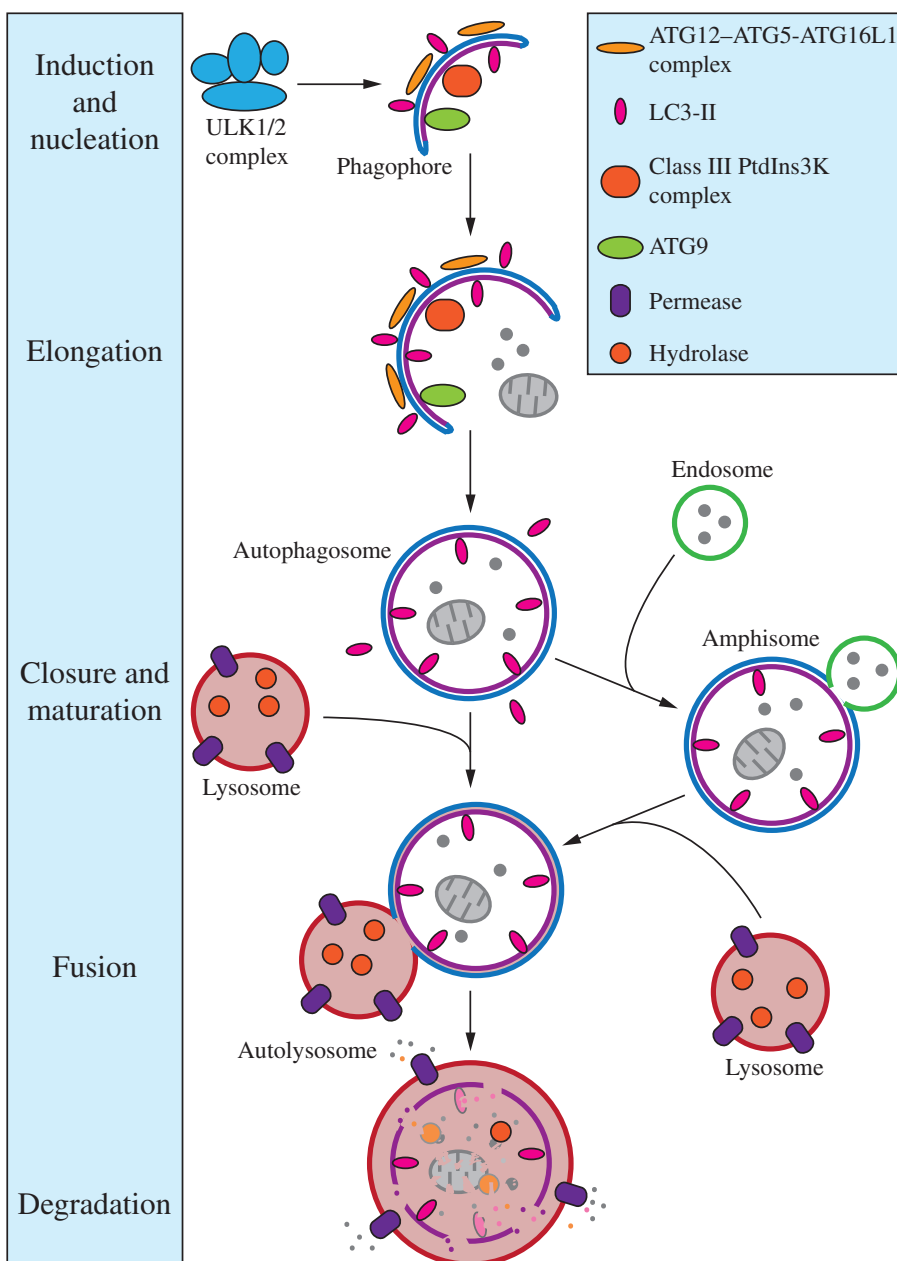


FIG. 2. Morphology of macroautophagy. Nucleation of the phagophore occurs following induction by the ULK1/2 complex. Elongation of the phagophore is aided by the ATG12-ATG5-ATG16L1 complex, the class III PtdIns3K complex, LC3-II, and ATG9. Eventually, the expanding membrane closes around its cargo to form an autophagosome and LC3-II is cleaved from the outer membrane of this structure. The outer membrane of the autophagosome will then fuse with the lysosomal membrane to form an autolysosome. In some instances, the autophagosome may fuse with an endosome, forming an amphisome, before fusing with the lysosome. The contents of the autolysosome are then degraded and exported back into the cytoplasm for reuse by the cell. See the text for details. This figure was modified from Figure 1 in Yang and Klionsky (153). ATG, autophagy-related; PtdIns3K, phosphatidylinositol 3-kinase; ULK, unc-51-like kinase (*C. elegans*). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

macroautophagy are not known. In the case of selective macroautophagy, the membrane appears to essentially wrap around the cargo; thus, adjusting to fit the specific target (102). Upon completion, the phagophore fully surrounds its cargo and fuses to form the double-membrane autophagosome. The size of the autophagosome varies based on organism and cargo type. For example, the diameter of autophagosomes ranges from ~ 0.4 to $0.9 \mu\text{m}$ in yeast, and 0.5 to $1.5 \mu\text{m}$ in mammals (104, 117, 127, 136).

Once the autophagosome is formed, it must deliver its cargo to the lysosome in mammals or the functionally related vacuole in yeast and plants. As it reaches its destination, the outer membrane of the autophagosome will fuse with the lysosomal/vacuolar membrane. In yeast and plants, due to the relatively large size of the vacuole, this releases a single-membrane autophagic body into the vacuolar lumen. Fusion between autophagosomes and lysosomes in mammals, however, does not generate autophagic bodies (23). The product of fusion between an autophagosome and lysosome in mammalian cells is referred to as an autolysosome (152). Exposed to the acidic lumen and resident hydrolases of the lysosome/vacuole, the autophagosome inner membrane and, subsequently, the autophagic cargo are degraded and the component parts are exported back into the cytoplasm through lysosomal permeases for use by the cell in biosynthetic processes or to generate energy (157). In mammals, macroautophagy often converges with the endocytic pathway. Hence, before fusion with lysosomes, autophagosomes may also fuse with early or late endosomes to form amphisomes, which then fuse with lysosomes to become autolysosomes (9, 140).

Macroautophagy machinery

Induction. In yeast macroautophagy, induction of autophagosome formation is regulated by the Atg1-Atg13-Atg17-Atg31-Atg29 kinase complex (43). In mammalian cells, this complex is made up of an Atg1 homolog from the Unc-51-like kinase family (either ULK1 or ULK2), the mammalian homolog of Atg13 (ATG13), and RB1-inducible coiled-coil 1

(RB1CC1/FIP200), which is required for the induction of macroautophagy and may be an ortholog of yeast Atg17 (Fig. 3) (33, 38, 47, 62). Also in this complex is C12orf44/ATG101, which binds directly to ATG13, is essential for macroautophagy, and has no known yeast homolog (48, 100). The mammalian ULK1/2-ATG13-RB1CC1 complex is stable and forms regardless of nutrient status (47, 62).

The association of the mechanistic target of rapamycin complex 1 (MTORC1) with the induction complex is, however, influenced by nutrient status. Under nutrient-rich conditions, MTORC1 associates with the complex, but dissociates upon nutrient starvation (47). When MTORC1 is complex-associated, it phosphorylates ULK1/2 and ATG13, inactivating them. However, when cells are treated with rapamycin or starved for nutrients, MTORC1 dissociates from the induction complex, resulting in dephosphorylation at these sites and induction of macroautophagy (47, 62). The phosphatases responsible at this stage are as yet unknown. The involvement of MTORC1 in the regulation of macroautophagy is an active area of research and will be discussed in greater detail below, as well as in another review in this Forum series.

Nucleation. The next complex recruited to the putative site of autophagosome formation is the ATG14-containing class III phosphatidylinositol 3-kinase (PtdIns3K) complex (57). The PtdIns3K complex generates PtdIns3P, which is required for macroautophagy in both yeast and mammals (13). This complex is involved in the nucleation of the phagophore and consists of PIK3C3/VPS34, PIK3R4/p150 (Vps15 in yeast), and BECN1 (Vps30/Atg6 in yeast) (Fig. 4) (32, 55, 67, 87, 151). As in yeast, this complex can either function in macroautophagy by associating with ATG14 or in the endocytic pathway through an interaction with UVRAG (an ortholog of yeast Vps38) (55, 85, 132). While some data suggest that the UVRAG-associated PtdIns3K complex is involved in autophagosome formation (85), other reports suggest that it may act in later stages of autophagosome development (86). Another study found that siRNA knockdown of UVRAG in HeLa cells does not affect macroautophagy (55). It is clear that further

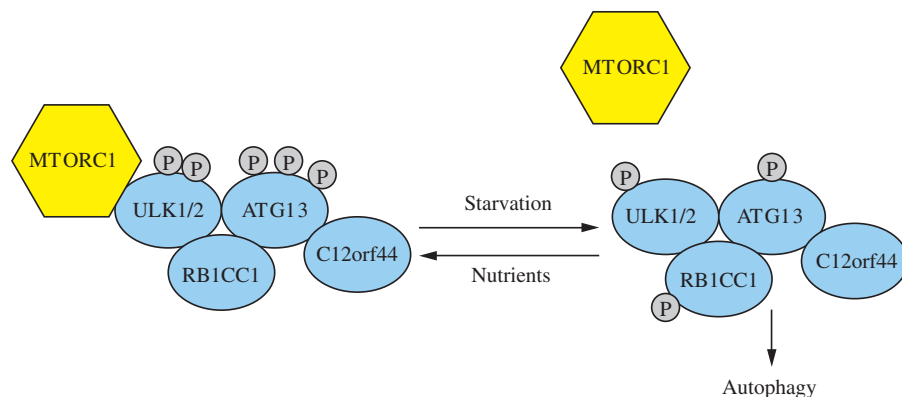


FIG. 3. The induction complex consists of ULK1/2, ATG13, RB1CC1, and C12orf44. Under nutrient-rich conditions, MTORC1 associates with the complex and inactivates ULK1/2 and ATG13 through phosphorylation. During starvation, MTORC1 dissociates from the complex and ULK1/2 and ATG13 become partially dephosphorylated by as yet unidentified phosphatases, allowing the complex to induce macroautophagy. RB1CC1/FIP200 and C12orf44/ATG101 are also associated with the induction complex and are essential for macroautophagy. RB1CC1/FIP200 may be the ortholog of yeast Atg17, whereas the function of C12orf44/ATG101 is not known. This figure was modified from Figure 1 in Yang and Klionsky (154). MTORC1, mechanistic target of rapamycin complex 1; RB1CC1, RB1-inducible coiled-coil 1. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

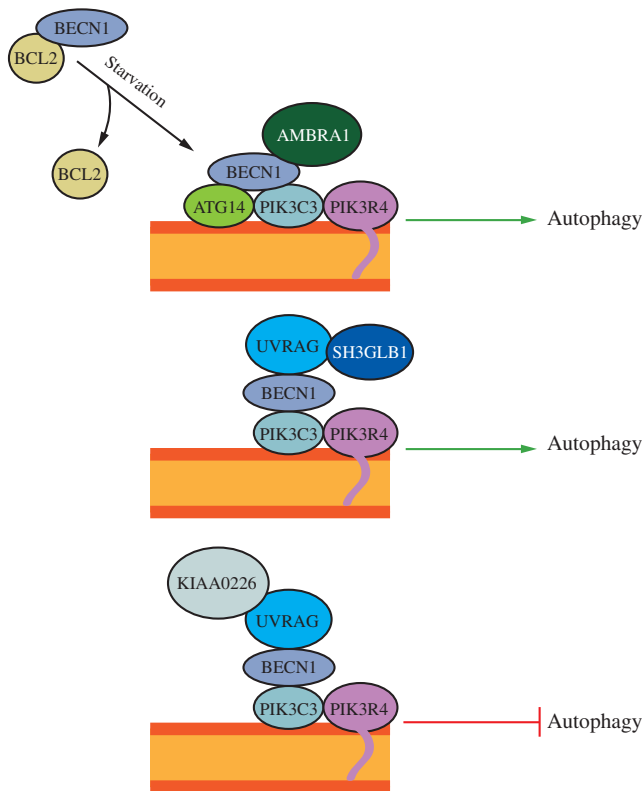


FIG. 4. The activity of the class III PtdIns3K complex is regulated by subunit composition. The ATG14 complex (ATG14-BECN1-PIK3C3-PIK3R4) is required for macroautophagy. It can be positively regulated by AMBRA1 and negatively regulated by BCL2 binding to BECN1 and preventing association with the complex. The UVRAG (UVRAG-BECN1-PIK3C3-PIK3R4) complex is involved in the endocytic pathway and also participates in macroautophagy. SH3GLB1/Bif-1 positively regulates this complex by binding UVRAG. The KIAA0226/Rubicon complex (KIAA0226-UVRAG-BECN1-PIK3C3-PIK3R4) negatively regulates macroautophagy. This figure was modified from Figure 1 in Yang and Klionsky (154). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

work is required to fully understand the role of UVRAG in the endocytic and macroautophagic pathways.

Regulation of the PtdIns3K complex occurs largely through proteins that interact with BECN1, which is essential for macroautophagy (87, 160). The antiapoptotic protein BCL2 binds BECN1 and prevents its interaction with PIK3C3; thus, inhibiting macroautophagy (32, 88, 116). Another BECN1-binding protein, KIAA0226/Rubicon, inhibits PIK3C3 activity in UVRAG-associated PtdIns3K complexes (Fig. 4) (96, 163). Two positive regulators of the PtdIns3K complex are AMBRA1 (which directly binds BECN1) and SH3GLB1/Bif-1 (which interacts with BECN1 through UVRAG, and may be involved in generating membrane curvature) (29, 133, 135). Very little is known, however, about upstream events regulating the constituents of the various PtdIns3K complexes.

In yeast, there are several proteins that bind to PtdIns3P generated by the Vps34 complex. Of these, Atg18 and Atg21 have a role in macroautophagy and localize to the PAS (78). Mammalian cells express two Atg18 orthologs, WIPI1 and WIPI2, which are also involved in macroautophagy and as-

sociate with phagophores during amino acid starvation by binding to PtdIns3P (60, 118, 119). Another PtdIns3P-binding protein in mammalian cells is the zinc finger, FYVE domain containing 1 (ZFYVE1/DFCP1), which associates with PtdIns3P-enriched omegasomes (7). The precise functions of WIPI1/2 and ZFYVE1 in macroautophagy are still unknown.

Elongation. In both yeast and mammals, there are two conjugation systems involving ubiquitin-like (UBL) proteins that contribute to the expansion of the phagophore (145). The first system involves formation of the Atg12-Atg5-Atg16 complex. In yeast, the UBL protein Atg12 is covalently conjugated to Atg5 in a manner dependent on the E1 activating enzyme Atg7 and the E2 conjugating enzyme Atg10 (70, 113, 129). This process differs from ubiquitination in that the conjugation of Atg12 to Atg5 is irreversible and does not require an E3 ligase enzyme (34). Following Atg12-Atg5 conjugation, Atg16 binds to Atg5 noncovalently and dimerizes to form a larger complex (79). Mammalian orthologs of this system,

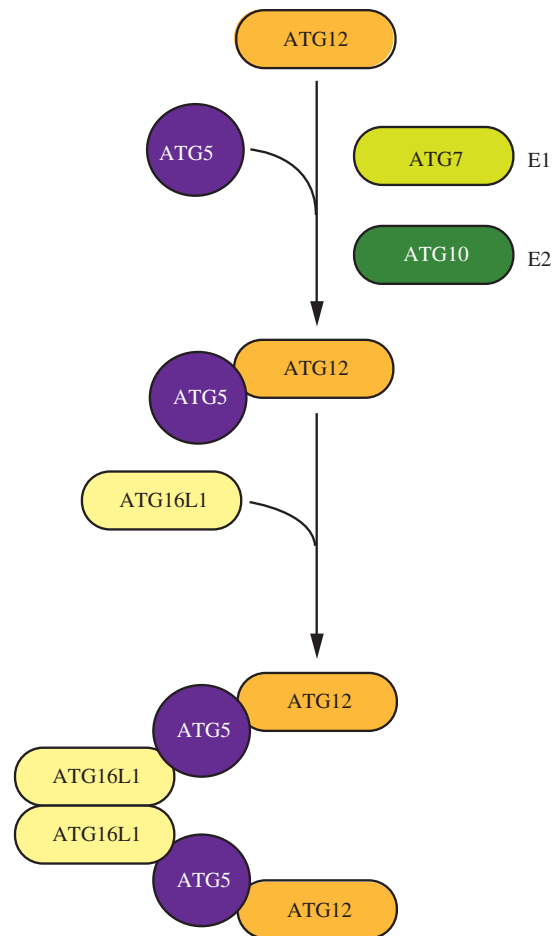


FIG. 5. ATG12-ATG5-ATG16L1 conjugation complex. The ubiquitin-like protein ATG12 is irreversibly conjugated to ATG5 in an ATG7- and ATG10-dependent manner. ATG7 and ATG10 function as E1 activating and E2 conjugating enzymes, respectively. The ATG12-ATG5 conjugate binds ATG16L1 through ATG5. ATG16L1 dimerizes and allows association with the phagophore, promoting membrane expansion. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

ATG5, ATG12 and ATG16L1, have been identified, and function as in yeast (Fig. 5) (105, 113). The mammalian ATG12–ATG5–ATG16L1 complex associates with the phagophore membrane, but dissociates following autophagosome completion (105, 106). One way in which this complex is regulated is through the Golgi protein RAB33A, which can bind to and inhibit ATG16L1 (58). Additionally, ATG5, ATG7, and ATG12 are inhibited through acetylation by the acetyltransferase KAT2B/p300 (82).

The second UBL system involved in phagophore expansion is the Atg8/LC3 system. This conjugation pathway in yeast begins with processing of Atg8 by the cysteine protease Atg4 to expose a glycine residue at the C terminus of Atg8 (73). The E1-like enzyme Atg7 activates the processed Atg8 and transfers it to the E2-like enzyme Atg3 (52). Finally, the C-terminal glycine of Atg8 is covalently conjugated to the lipid phosphatidylethanolamine (PE). The Atg12–Atg5 conjugate, which may act as an E3 ligase, facilitates this final step (30, 37, 52). Atg8–PE is membrane-associated, but can be released from membranes as a result of a second Atg4-mediated cleavage (73). The mechanism of regulation of the second Atg4-dependent processing event, referred to as deconjugation, is not known; however, this appears to be an important step in macroautophagy because defects in cleavage result in partial autophagic dysfunction (111).

Mammalian homologs of the Atg8/LC3 system function much like their yeast counterparts (Fig. 6) (34). Unlike yeast, which have only one Atg4 and one Atg8, mammals have four isoforms of ATG4 and several ATG8-like proteins, the latter of which are divided into the LC3 and GABARAP subfamilies (44, 91, 146). Whereas both subfamilies can localize with autophagosomes (64), it has been proposed that they function at different steps in phagophore elongation and completion, with the LC3 subfamily acting before the GABARAP subfamily (146). Among the Atg8-like proteins in mammals, LC3 has been the best characterized. The ATG4-processed form of LC3 is referred to as LC3-I and the PE-conjugated form is called LC3-II (34). Lipidation of LC3 in mammalian cells is accelerated under conditions of nutrient starvation or other types of stress (63). While the mechanism of the conjugation system of Atg8/LC3 in macroautophagy is still unclear, Atg8, and to some extent LC3 (92, 138), shows a substantial increase in synthesis during macroautophagy induction (72), and in yeast this is a determining factor in autophagosome size (149).

Another protein thought to function in elongation of the phagophore is the transmembrane protein ATG9. In yeast, Atg9 may cycle between the PAS and peripheral sites (122). These peripheral sites are referred to as Atg9 reservoirs or tubulovesicular clusters (TVCs). The TVCs may be direct membrane precursors to the PAS, and thus, to phagophores (90, 110). The movement of Atg9 is dependent on the Atg1-kinase complex, as well as multimerization of Atg9 (42, 122). The abilities of Atg9 to traffic and multimerize are necessary for autophagosome formation, suggesting that these properties of Atg9 contribute to a role for this protein in recruiting membrane to the expanding phagophore (42, 122).

The mammalian homolog of Atg9 (ATG9) is also seen to shift localization within the cell and is proposed to have a similar role in membrane recruitment (159). Under nutrient-rich conditions, ATG9 localizes to the *trans*-Golgi network and late endosomes (159). When cells are starved for nutri-

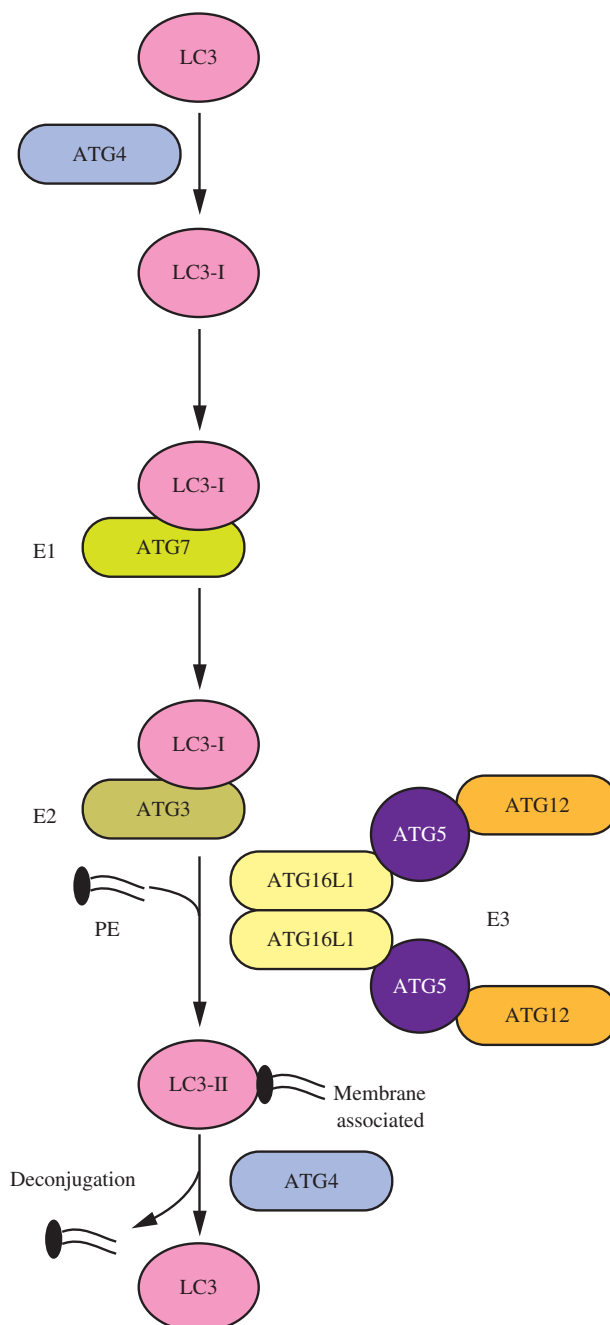


FIG. 6. The LC3 conjugation system. LC3 is processed by ATG4 to reveal a C-terminal glycine (LC3-I). ATG7, an E1-like enzyme, activates LC3-I and transfers it to the E2-like enzyme ATG3. The ATG12–ATG5–ATG16L1 complex may participate as an E3 ligase in the conjugation of PE to LC3-I to create LC3-II, which can associate with the phagophore. LC3-II can subsequently be cleaved by ATG4 to release LC3 (deconjugation). PE, phosphatidylethanolamine. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

ents, however, ATG9 colocalizes with autophagosomal markers (159). This cycling to autophagosomes is dependent on both ULK1 and PtdIns3K activity and is negatively regulated by MAPK14/p38 α (144, 159). The exact functions of ATG9 in the cell, and how the ULK1 complex regulates ATG9 movement, are poorly understood.

Autophagosome completion and fusion. In what is perhaps the least understood step of macroautophagy, the expanding phagophore must eventually mature and close to form a completed autophagosome, which traffics to and fuses with an endosome and/or lysosome, becoming an autolysosome. Movement of autophagosomes to lysosomes is dependent on microtubules (108). Fusion of autophagosomes with endosomes involves the protein VTIIB (5). UVRAG, which can associate with the PtdIns3K complex, can activate the GTPase RAB7, which promotes fusion with lysosomes (59, 86). It has also been suggested that components of the SNARE machinery, such as VAM7 and VAM9, have a role in fusion (28, 31). Recent work has identified another SNARE, syntaxin 17, which localizes to completed autophagosomes and is required for fusion with the endosome/lysosome through an interaction with SNAP29 and the endosomal/lysosomal SNARE VAMP8 (56).

Regulation of macroautophagy

Macroautophagy helps cells respond to a wide range of extra- and intracellular stresses including nutrient starvation, the presence/absence of insulin and other growth factors, hypoxia, and ER stress (Fig. 7) (43). Two pathways involved in nutrient starvation are regulated by the cAMP-dependent protein kinase A (PKA) and TOR pathways, which sense primarily carbon and nitrogen, respectively (130). In yeast, PKA is an inhibitor of macroautophagy under nutrient-rich conditions (12). In mammals, this inhibition occurs at least partially through the phosphorylation of LC3 by PKA (15). For its role in nitrogen sensing, MTORC1 is positively regulated by the presence of amino acids. Amino acids regulate RAG proteins, RAS-related small GTPases that activate MTORC1 (68, 124). There is thought to be some crosstalk

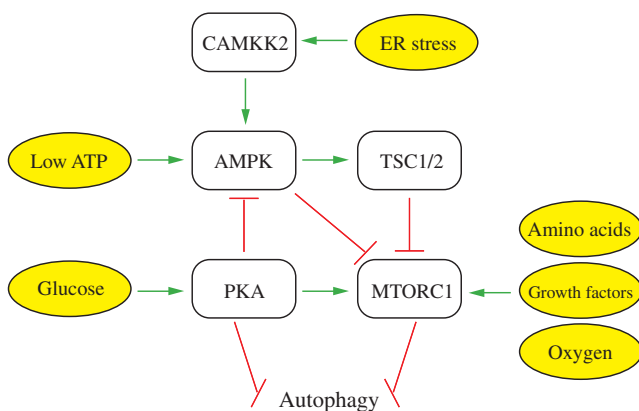


FIG. 7. Regulation of macroautophagy. Three of the major kinases that regulate macroautophagy are PKA, AMPK, and MTORC1. These kinases, along with proteins such as TSC1/2 and CAMKK2/CaMKK β , respond to a variety of intracellular and extracellular signals to regulate macroautophagy. *Green arrows* indicate activation of a target and *red bars* indicate inhibition of a target. See the text for details. This figure was modified from Figure 4 of Chen and Klionsky (14). PKA, cAMP-dependent protein kinase A; AMPK, AMP-activated protein kinase; CAMKK2/CaMKK β , calcium/calmodulin-dependent protein kinase kinase 2, beta. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

between the carbon- and nitrogen-sensing pathways, based on studies that demonstrated that mammalian PKA can phosphorylate, and thus activate, MTORC1 (11, 97). PKA can also indirectly activate MTORC1 through inactivation of the AMP-activated protein kinase (AMPK) (26).

AMPK is not simply a substrate of PKA. It is the major energy-sensing kinase in the cell and responds to intracellular AMP/ATP levels to regulate a variety of cellular processes, including macroautophagy (2, 99). AMP and ATP have opposite effects on the activity of AMPK, with AMP binding activating the kinase activity of AMPK (40). When activated by low energy levels, AMPK can phosphorylate and activate the TSC1/2 complex, which indirectly inhibits the activity of MTORC1 (53). Alternatively, AMPK can directly inhibit MTORC1 (35, 154). Several studies have also reported that AMPK can phosphorylate and activate ULK1 to induce macroautophagy (27, 71, 84, 128). The modulation of macroautophagy by energy sensing is conserved in yeast where Snf1, the yeast ortholog of AMPK, serves as a positive regulator (50, 143).

It has also been observed that an increase in cytosolic Ca²⁺ concentrations resulting from ER stress causes calcium/calmodulin-dependent protein kinase kinase 2, beta (CAMKK2/CaMKK β) to activate AMPK and induce macroautophagy (49). Another way in which ER stress can induce macroautophagy is through unfolded protein response (UPR) signaling. Accumulation of unfolded proteins in the ER can be caused by a variety of cellular stressors, and induces macroautophagy in both yeast and mammals. However, the role of macroautophagy in response to ER stress seems to vary, with some studies reporting that it enhances cell survival, while others suggest that it may result in autophagic cell death (25, 43).

Additional signals that cause the induction of macroautophagy include hypoxia and the absence of growth factors. Even in the presence of adequate nutrients, the absence of growth factors leads to the induction of macroautophagy (89). Both growth factor concentrations and hypoxia regulate macroautophagy at least in part through MTORC1, and hypoxia can inhibit MTORC1 even in the presence of adequate nutrients and growth factors (2, 4). Given its complex regulation by a variety of cellular signaling pathways, the involvement of MTORC1 in the regulation of macroautophagy is a very intriguing and active area of research, and is discussed in greater detail in another review in this Forum series.

Selective macroautophagy and cellular maintenance

While nonspecific macroautophagy can be induced in response to nutrient or energy deprivation to enable cell survival, macroautophagy can also be highly specific, and in this mode functions more in cell maintenance and homeostasis (14, 54). Specific autophagic cargoes can include, but are not limited to peroxisomes, mitochondria, and ubiquitinated proteins (83, 139, 145).

The selective macroautophagic degradation of peroxisomes, termed pexophagy, is important for a majority of the turnover of peroxisomes under normal growth conditions (51). For example, in mouse livers, macroautophagy is responsible for degradation of 70%–80% of the peroxisomal mass (156). Peroxisomes can also be degraded under

starvation conditions, during which they can be specifically recognized by autophagosomes through binding of LC3-II to PEX14, a component of the peroxisomal translocon complex found on the peroxisomal membrane (39). Given the role of peroxisomes in a variety of metabolic functions and the negative effects of peroxisomal dysfunction on human health, pexophagy has an important role in maintaining proper cellular physiology (139).

Mitophagy is another type of selective macroautophagy that involves the selective degradation of mitochondria, and has been shown to be important in mammals not only for steady-state turnover of these organelles (137), but also for the development of certain cell types and the clearance of damaged mitochondria (69, 80, 126). For example, in order for mammalian red blood cells to mature, mitophagy is used to remove mitochondria from the immature cells (80, 109, 161). During this process, it is thought that a mitochondrial outer membrane protein called BNIP3L/NIX interacts through a WXXL-like motif (also called the LC3-interacting region) with LC3 and GABARAP on the expanding phagophore, allowing for recognition (Fig. 8) (158).

The clearance of damaged mitochondria, however, is thought to proceed in a slightly different way. In this case, the cytosolic E3 ubiquitin ligase PARK2/Parkin is recruited to damaged mitochondria by the mitochondrial outer membrane kinase PINK1, whereupon PARK2 ubiquitinates mitochondrial substrates, leading to mitophagy (158). In healthy mitochondria, PINK1 is imported into the mitochondrial inner membrane, and subsequent cleavage by the mitochondrial processing peptidase (PMPCB) and presenilin associated, rhomboid-like protease (PARL) leads to its eventual degradation. This prevents the accumulation of PINK1 on the mitochondrial outer membrane, which would otherwise lead to mitophagy of healthy mitochondria (61, 98). The genes encoding both PINK1 and PARK2 are mutated in autosomal recessive Parkinson disease (77, 142), emphasizing the importance of mitophagic clearance of damaged mitochondria in maintaining cellular and, thus, organismal health.

Another mechanism used by the cell to identify cargo for selective degradation by macroautophagy involves ubiquitination. The ubiquitin-binding protein SQSTM1/p62 targets intracellular bacteria for degradation by a specific type of macroautophagy called xenophagy (162). SQSTM1 is also important for the clearance of ubiquitinated protein aggregates by acting as an adaptor protein that interacts with LC3-II to target aggregates for macroautophagy-specific degradation in a process termed aggrephagy (10, 115, 141). NBR1 and OPTN are other receptors that function in targeting ubiquitinated proteins or pathogens to autophagosomes (75, 147).

Conclusions

Given the wide array of extra- and intracellular signals that can regulate autophagy and the range of possible cargos, it is not surprising to learn that autophagy has been implicated in various aspects of human health and pathophysiology. Several of these topics will be explored in depth in other reviews in this Forum series. One area that especially warrants further study is the regulatory network controlling macroautophagy. While several key regulators of macroautophagy have been identified, it is likely that many regulatory factors are not yet

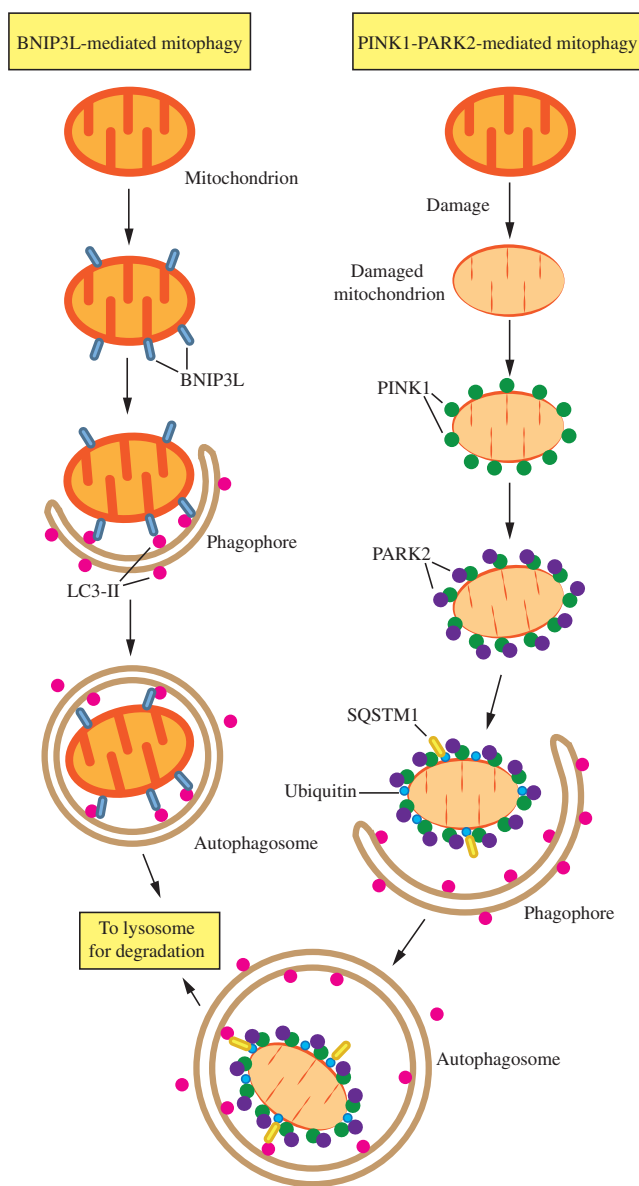


FIG. 8. Two mechanisms of mitophagy. Mitochondria are cleared from maturing red blood cells through a mechanism involving autophagic recognition of mitochondria through a BNIP3L–LC3 interaction. During removal of damaged mitochondria, PARK2 binds to PINK1 on the mitochondrial surface and ubiquitinates mitochondrial outer membrane proteins, which may then bind SQSTM1, a receptor that interacts with LC3. In either case, the interaction with LC3 leads to sequestration by the phagophore and eventual degradation. This figure was modified from Figure 2 of Youle and Narendra (158). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

defined. Even in the case of relatively well-characterized regulators, such as MTORC1, the relevant downstream targets are not completely known, as is true for most of the kinases that control macroautophagy, and very little information is available with regard to the complementary phosphatases. Similarly, the crosstalk among the different regulatory pathways has not been well elucidated. The

identification and characterization of such factors will be important in the development of therapeutics targeting regulatory proteins; without a deeper understanding of how the cell integrates various extracellular and intracellular signals into a cohesive macroautophagic response, it is difficult to predict how the regulatory network will function when perturbed by therapeutics.

Along these lines, potentially interesting targets for therapeutic applications include ULK1/2, ATG3, ATG4, ATG7, ATG10, and PIK3C3/VPS34. The crystal structures of most of these proteins have been determined from various organisms (45, 46, 103, 112, 125, 131, 150), and, importantly, they have clearly defined functions and functional motifs, making them interesting targets for rational drug design. Further elucidation of the individual steps of macroautophagy, additional structural studies, and a more complete knowledge of the role of this process in different disease conditions will provide a better understanding of this integral cellular process, and can guide the development of improved methods and/or drugs for the treatment of autophagy defects related to human disease.

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Abbreviations Used

AMPK = AMP-activated protein kinase
 ATG = autophagy-related
 CAMKK2/CaMKK β = calcium/calmodulin-dependent protein kinase kinase 2, beta
 CMA = chaperone-mediated autophagy
 ER = endoplasmic reticulum
 HSPA8 = heat shock 70kDa protein 8
 LAMP2A = lysosomal-associated membrane protein 2A
 MTORC1 = mechanistic target of rapamycin complex 1
 PAS = phagophore assembly site
 PE = phosphatidylethanolamine
 PKA = cAMP-dependent protein kinase A
 PtdIns3K = phosphatidylinositol 3-kinase
 RB1CC1 = RB1-inducible coiled-coil 1
 TVC = tubulovesicular cluster
 UBL = ubiquitin-like
 ULK = unc-51-like kinase (*C. elegans*)
 UPR = unfolded protein response
 ZFYVE1 = zinc finger, FYVE domain containing 1

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