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Review

Autophagy machinery in the context of mammalian mitophagy☆

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ABSTRACT

Autophagy is an intracellular catabolic system that degrades cytoplasmic proteins and organelles. Damaged mitochondria can be degraded by a selective type of autophagy, which is termed mitophagy. PINK1-Parkin-dependent mitophagy has been extensively studied in the mammalian system. PINK1 accumulates on damaged mitochondria to recruit Parkin, which subsequently ubiquitinates a broad range of outer mitochondrial membrane proteins. Ubiquitinated mitochondria associate with the autophagosome formation site, and are selectively incorporated into autophagosomes. During this process, damaged mitochondria first associate with the autophagosome formation site together with upstream autophagy factors, then are efficiently incorporated into autophagosomes through binding with autophagosome adaptors. This "two-step model" may be applied to other selective types of autophagy. This article is part of a Special Issue entitled: Mitophagy.

1. Introduction

Autophagy is an intracellular degradation system that is conserved in eukaryotes. An isolation membrane (also termed as phagophore) surrounds a portion of the cytoplasm to form a double-membraned organelle, the autophagosome. The autophagosome then fuses with a lysosome to degrade its contents into amino acids and other nutrients. Autophagy is known to be highly induced under starvation conditions. Under these conditions, substrates are thought to be degraded mainly in a non-selective manner. However, it is becoming clear that there are selective types of autophagy. Mitophagy is a form of selective autophagy in which damaged or unwanted mitochondria are engulfed by autophagosomes.

PTEN-induced putative kinase 1 (*PINK1*)/*Park6* and *Parkin*/*Park2* were identified as causative genes of familial Parkinson's disease [1,2]. In 2008, Youle's group reported that Parkin mediates the degradation of damaged mitochondria by autophagy [3]. Carbonyl cyanide *m*-chlorophenylhydrazone or valinomycin treatment causes loss of the mitochondrial membrane potential, which mimics mitochondrial damage. PINK1, which is rapidly degraded under normal conditions, is stabilized on depolarized mitochondria and recruits and activates Parkin [4–11]. Parkin then ubiquitinates proteins on the outer mitochondrial membrane (OMM) to target the damaged mitochondria for mitophagy. During this process, damaged mitochondria are recognized by the autophagy machinery in at least two steps: 1) accumulation of damaged mitochondria and upstream autophagy-related (ATG) proteins at the autophagosome formation site and 2) incorporation into autophagosomes [12] (Fig. 1). The aim of this review is to focus on the ultrastructure and functions of ATG proteins in these two steps of mitophagy.

2. Function of ATG proteins in canonical autophagy

The ULK1 complex and ATG9A are the most upstream ATG proteins in the mammalian system [12,13]. The ULK1 complex consists of ULK1, ATG13, FIP200 and ATG101 and the complex is regulated by mechanistic target of rapamycin (mTor) in starvation-induced autophagy [14–17]. Upon starvation, the ULK1 complex is recruited to punctate structures close to the endoplasmic reticulum (ER) [13,18], which has been suggested to be a possible origin or formation platform of autophagosomes [19–21]. ATG9A resides on a vesicular structure

Abbreviations: PINK1, PTEN-induced putative kinase 1; CCCP, carbonyl cyanide *m*-chlorophenylhydrazone; OMM, outer mitochondrial membrane; ATG, autophagy-related; ULK1, unc-51 like kinase 1; FIP200, focal adhesion kinase family interacting protein of 200 kDa; mTor, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PI3P, phosphatidylinositol 3-phosphate; DFCP1, double-FYVE domain containing protein 1; SQSTM1, sequestosome 1; VMP1, vacuole membrane protein 1; WIPI, WD-repeat protein interacting with phosphoinositides; LC3, microtubule-associated protein light chain 3; GABARAP, gamma-aminobutyric-acid-type-A-receptor-associated protein; PE, phosphatidylethanolamine; ER, endoplasmic reticulum; STX, syntaxin; SNARE, soluble NSF attachment protein receptor; HOPS, homotypic fusion and protein sorting; VPS33A, vacuolar sorting-associated protein 33A; HSP90, heat shock protein 90; Cdc37, cell division control protein 37; NBR, neighbor of BRCA1 gene 1; LIR, LC3-interacting region; GAP, GTPase-activating protein; Fis1, mitochondrial fission 1 protein; Nix, NIP3-like protein X; Bnip3, Bcl-2/adenovirus E1B 19-kDa-interacting protein 3; FUNDC1, FUN14 domain-containing protein 1; HDAC6, histone deacetylase 6; NDP52, nuclear dot protein 52; TAX1BP1, human T-cell leukemia virus type 1 binding protein 1; SMURF1, SMAD specific E3 ubiquitin protein ligase 1NCOA4, nuclear receptor coactivator 4; NCOA4, nuclear receptor coactivator 4

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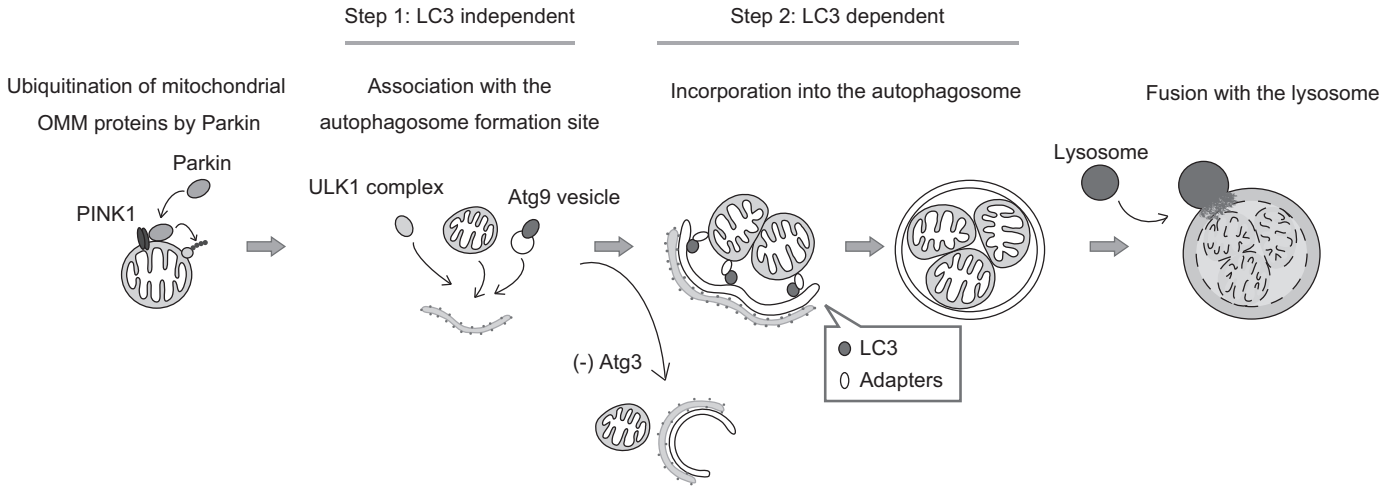

Fig. 1. The two-step model for mitochondrial recognition by the autophagy machineries. Damaged mitochondria are ubiquitinated by Parkin. These ubiquitinated mitochondria as well as early ATG proteins such as the ULK1 kinase complex (ULK1, Atg13, FIP200 and Atg101) and ATG9 vesicles associate with the autophagosome formation site (Step 1). The first step does not require LC3–PE or isolation membrane formation. Isolation membranes are formed closely enwrapping the damaged mitochondria (Step 2). This second step depends on LC3–PE. The isolation membranes fail to incorporate mitochondria in Atg3 KO cells where LC3 is not conjugated to PE. Adaptor proteins which bridges mitochondria and LC3 are involved. Putative adapters for Parkin-mediated mitophagy include p62, NBR1 and/or optineurin which can bind both to ubiquitinated (mitochondrial) proteins and LC3 [36–39,43], and TBC1D15/17 which can bind to mitochondrial outer membrane protein Fis1 as well as LC3/GABARAPs [45]. Finally, completely sealed autophagosomes fuse with the lysosome, and the mitochondria are degraded.

(ATG9 vesicle) and shuttles between organelles such as the Golgi apparatus, endosomes and autophagic structures [22]. Both the ULK1 complex and ATG9A are required for the recruitment of the autophagy-specific class III phosphatidylinositol 3-kinase (PI3K) complex. The PI3K complex in turn recruits downstream ATG factors by the generation of phosphatidylinositol 3-phosphate in the isolation membrane and omegasome (adjacent ER structure defined by the existence of double-FYVE domain-containing protein 1, DFCP1) [13,23]. The deletion or inactivation of one of the upstream autophagy factors, the ULK1 complex, ATG9A or the PI3K complex, results in a very similar ultrastructure [24]. Autophagy cargoes, such as p62/SQSTM1 aggregates and ferritin clusters colocalize with the ULK1 complex and/or ATG9A vesicles at the autophagosome formation site in the absence of the isolation membrane. These aggregated autophagy substrates are surrounded by the ER. The mechanisms underlying the recruitment of upstream ATG factors as well as autophagy cargoes to the putative autophagosome formation site remain unknown.

At intermediate steps of autophagosome formation, VMP1, ATG2 proteins and WIPI proteins (mammalian ATG18s) are required. Knockdown of VMP1 or ATG2A/B causes similar aggregation formation as observed in FIP200 or ATG9A knockout (KO) cells. However, LC3-positive small isolation membrane/autophagosome-like structures are formed in or around the p62 aggregates [24]. The small isolation membrane/autophagosome-like structures in VMP1 knockdown (KD) or ATG2A/B KD cells do not seem to mature into complete autophagosomes, suggesting that VMP1 and ATG2A/B are required for elongation and maturation of the isolation membrane.

Finally, downstream factors involved in two ubiquitin-like systems, the ATG12 (ATG12, ATG7, ATG10, ATG5 and ATG16L1) and LC3/gamma-aminobutyric-acid-type-A-receptor-associated protein (GABARAP) systems (LC3/GABARAP family proteins, ATG7 and ATG3) are involved in conjugation of LC3/GABARAPs with phosphatidylethanolamine (PE) [25]. ATG5- or ATG3-deficient cells can form isolation membranes with nearly normal morphology [12,19,21,24,26,27]. However, most isolation membranes have obvious open ends and are still surrounded by the ER, suggesting that the isolation membrane cannot close to form mature autophagosomes. PE conjugation of LC3/GABARAPs is required for the final step of autophagosome formation [24].

Complete autophagosomes detach from the ER and recruit STX17, an autophagosome-localizing soluble NSF attachment protein receptor (SNARE), and homotypic fusion and protein sorting (HOPS)-tethering complex [18,28–31]. KD of STX17 or VPS33A (a HOPS component) causes accumulation of complete autophagosomes, suggesting that STX17 and HOPS complexes are required for the fusion between autophagosomes and lysosomes.

3. Step 1: Accumulation of damaged mitochondria and upstream ATG proteins at the autophagosome formation site

Once damaged mitochondria are ubiquitinated by Parkin, these mitochondria cluster at the perinuclear region. The first step of mitophagy is the association between these damaged mitochondria and the autophagosome formation site and upstream ATG proteins. In FIP200 KO cells, damaged mitochondria aggregate at the perinuclear region but almost no isolation membrane is formed around them [12,32]. ATG9 vesicles accumulate near the damaged mitochondria in FIP200 KO cells, indicating that both mitochondria and ATG9A vesicles accumulate at the autophagosome formation sites [12]. Similarly, damaged mitochondria colocalize with ULK1 in ATG9A KO cells [12]. Finally, if PI3K is inhibited by wortmannin (suppression of the formation of the isolation membrane), both ULK1 and ATG9A colocalize with mitochondria [12]. These data indicate that damaged mitochondria can associate with the autophagosome formation site in the absence of upstream ATG factors such as FIP200, ATG9 and PI3K and even in the absence of the isolation membrane.

It is generally believed that the recruitment of damaged mitochondria to autophagic structures is mediated by LC3 family proteins and ubiquitin-binding adaptor proteins such as p62 [33,34]. However, association between damaged mitochondria and the autophagosome formation site is independent of membrane-bound LC3 (the PE-conjugated form). For example, ATG16L1 can localize on damaged mitochondria in ATG3 KO cells in which LC3/GABARAPs are not PE-conjugated and cannot localize on membranes. An unexpected observation is that LC3 can be detected on damaged mitochondria in FIP200 KO and ATG9A KO cells, in which isolation membranes cannot be formed [12]. A possible explanation of this finding is that LC3 is mislocalized to some structures other than the isolation membranes in these cells. Nonetheless, the observation in ATG3 KO cells suggests that early events as part of Parkin-dependent mitophagy are independent of membrane-bound LC3.

How upstream ATGs are recruited onto the damaged mitochondria at the autophagosome site remains largely unknown. One study showed that the recruitment of ATG13 onto damaged mitochondria depends on the kinase activity of ULK1 and a cytosol chaperon HSP90 [35]. HSP90 and its kinase-specific co-chaperon Cdc37 regulate the kinase activity of ULK1, which in turn regulates the interaction between ULK1 and ATG13 as well as the localization of the ULK1 complex to the damaged mitochondria. Whether accumulation of damaged mitochondria and ATG9A at the autophagosome formation site also depends on HSP90 and Cdc37 remains unknown. Further studies will be required to elucidate the mechanism by which upstream ATGs are recruited to damaged mitochondria.

4. Step 2: LC3-dependent incorporation of damaged mitochondria into autophagosomes

Association between damaged mitochondria and upstream ATGs is followed by efficient incorporation of these mitochondria into the autophagosome. This second step is LC3 dependent. Isolation membranes can be formed in ATG3 KO cells, but those isolation membranes fail to selectively enwrap mitochondria and appear to randomly incorporate the cytoplasm [12]. How exactly PE-conjugated LC3/GABARAPs recognize damaged mitochondria has not been fully elucidated. Putative autophagy adapter proteins, such as p62, NBR1 and optineurin, have the ubiquitin-binding domain as well as the LC3-interacting region (LIR) motif [36]. Therefore, p62, NBR1 and/or optineurin may bridge ubiquitin on damaged mitochondria and LC3 on the isolation membrane. However, whereas some studies demonstrated the requirement of p62 for mitophagy [37–39], others showed that the lack of p62 does not seem to abrogate mitophagy [40–42]. One recent report suggested that optineurin and p62 are differentially recruited onto damaged mitochondria dependently on Parkin, and only optineurin but not p62 is required for the recruitment of LC3 via its LIR motif [43]. To what extent these adapters are separately or cooperatively involved in and facilitate selective autophagy needs to be further clarified.

Recently, it has been reported that the OMM protein Fis1 and its interacting Rab-GAPs, TBC1D15/17, are important for close enwrapping of damaged mitochondria by the isolation membrane [44,45]. TBC1D15/17 bind to both OMM protein Fis1 and LC3 family proteins (especially GABARAPs), therefore directly bridging damaged mitochondria and isolation membranes. It is interesting that both TBC1D15 and TBC1D17 are known as Rab-GAPs, and LC3-positive structures accumulate and elongate in the absence of TBC1D15. TBC1D15/TBC1D17 may inhibit uncontrolled elongation of isolation membranes thereby facilitating close enwrapping of mitochondria. Other factors that act like adapters include Nix/Bnip3 [46–53], FUNDC1 [54–56], HDAC6 [57,58], NDP52/TAX1BP1 [59,60] and SMURF1 [61] although the contribution of these proteins in Parkin-dependent mitophagy is not clear. Nix, Bnip3 and FUNDC1 are mitochondrial outer membrane proteins which can directly bind to LC3. Nix is required for mitophagy in reticulocytes [50,51,53], and Bnip3/Nix and FUNDC1 act in hypoxia-induced mitophagy [46,49,54–56]. The roles of these adapters are discussed elsewhere [33,62].

The two-step model of selective substrate recognition appears to be universal; it can also be applied to other types of autophagy. For example, p62, one of the best characterized selective autophagy substrates, accumulates at the autophagosome formation site in FIP200 KO or ATG9 KO cells where isolation membranes are not formed, as well as in ATG5 KO and ATG3 KO cells where LC3/GABARAPs are not conjugated to PE (step 1) [24,63]. However, efficient degradation of p62 is dependent on its LIR motif indicating the dependency on LC3/GABARAPs for incorporation into autophagosomes [64,65] (step 2). Similarly, ULK1 localizes on salmonella-containing endosomes in ATG9A KO cells whereas ATG9A localizes on the structure in FIP200 KO cells [66]. Also, early ATG factors can be recruited to the endosomes mimicking bacteria-containing vacuoles in ATG5 KO cells, suggesting that the first step is independent of LC3 [67]. Finally, the recently discovered autophagy substrate ferritin can be recruited to the autophagosome formation site independently of ATG proteins [24], whereas it can be incorporated inside an autophagosome via the novel adaptor protein NCOA4 [68]. It is likely that there is a fundamental mechanism by which autophagy substrates associate with the autophagosome formation site.

5. Perspectives

Parkin-dependent mitophagy has been extensively studied since its discovery in 2008 [3]. A number of factors have been proposed to facilitate efficient mitophagy, many of which are known to associate with LC3/GABARAPs, suggesting that they may work at the second step of mitochondrial recognition. However, little is known about the first step which is LC3 independent. How the damaged mitochondria are recruited to the autophagosome formation site (or how the site is brought onto mitochondria) and how upstream ATG factors start to accumulate on the mitochondria remain to be elucidated. One indication is that Parkin-mediated ubiquitination is essential for the initiation of mitophagy [12]. Similarly, ubiquitination is required for the recruitment of ATG factors on damaged endosomes mimicking bacteria-containing vacuoles [67]. Similar mechanisms can be expected for the autophagy of damaged lysosomes which are also ubiquitinated [69]. Therefore, ubiquitination of a certain or several proteins appears to be the trigger for the execution of the first step of selective autophagy. Another observation comes from p62 that oligomerization of the protein is required for the accumulation of p62 at the autophagosome formation site [63]. Another autophagy substrate, ferritin, also forms a clustered structure at the autophagosome formation site although the requirement for clustering remains unknown [24]. Aggregation of mitochondria does not appear to be essential [41,42], but abundant proteins on the OMM may be the equivalent of oligomerization, or OMM proteins may form oligomers prior to the first step of mitophagy. The similarity of the order of events and dependencies among factors in various types of selective autophagy suggest that there may be shared mechanisms of substrate recognition and incorporation that follow the proposed two-step model.

Conflict of interest

The authors declare that there are no conflicts of interest.

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