THE JOURNAL OF CELL BIOLOGY

Quality control

Organellophagy: Eliminating cellular building blocks via selective autophagy

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Maintenance of organellar quality and quantity is critical for cellular homeostasis and adaptation to variable environments. Emerging evidence demonstrates that this kind of control is achieved by selective elimination of organelles via autophagy, termed organellophagy. Organellophagy consists of three key steps: induction, cargo tagging, and sequestration, which involve signaling pathways, organellar landmark molecules, and core autophagy-related proteins, respectively. In addition, posttranslational modifications such as phosphorylation and ubiquitination play important roles in recruiting and tailoring the autophagy machinery to each organelle. The basic principles underlying organellophagy are conserved from yeast to mammals, highlighting its biological relevance in eukaryotic cells.

Introduction

Organelles are fundamental subunits of eukaryotic cells that possess structurally and functionally distinct characteristics that allow them to perform unique activities crucial for viability. It is thus a matter of the utmost importance for cells to maintain organellar quality and integrity. In addition, cells modulate the quantity of organelles in order to balance organellar activities and cellular demands, which can act as an adaptive mechanism to diverse environmental changes. Both dysfunctional and surplus organelles are cleared from cells through autophagy, a widely conserved self-eating process by which cytoplasmic constituents are sequestered as cargoes by intracellular membranes that fuse with lysosomes for hydrolytic breakdown (Mizushima and Komatsu, 2011; Mizushima et al., 2011; Weidberg et al., 2011).

Although autophagy has primarily been recognized as a nonselective degradation pathway, recent studies reveal that it also plays a vital role in digesting specific cargoes such as proteins and organelles (Mizushima, 2011; Suzuki, 2013). The latter process, termed selective autophagy, includes the following three critical stages: first, signaling from degradation cues induces downstream events specific for a particular target; second, regulation of landmark molecules that tag the target as disposable cargo; third, assembly of core autophagy-related (Atg) proteins to sequester the cargo. In many cases, malfunction in or decreased cellular metabolism related to a protein or organelle leads to expression and activation of a landmark molecule. Core Atg proteins then localize to the cargo via direct or indirect interactions with the landmark molecule and ultimately mediate selective autophagy.

In this short review, we summarize recent findings on organellophagy, autophagy-related pathways selective for organelles such as the peroxisome, mitochondrion, lipid droplet (structure surrounded by a phospholipid monolayer), lysosome, nucleus, ER, and even nonmembraneous structures like the ribosome. Despite the diversity of their degradation cues and landmark molecules, organellophagy seems to be regulated by common basic principles involving protein phosphorylation and ubiquitination. In particular, these two major posttranslational modifications promote targeting of core Atg proteins to the organellar surface. Defects in several organellophagy pathways are associated with various disorders including renal injury, neurodegeneration, obesity, and atherosclerosis (Mizushima and Komatsu, 2011), underscoring their physiological significance in health and disease.

Modes of autophagy in organellophagy

Three morphologically distinct modes of autophagic processes have so far been defined: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA; Fig. 1; Mizushima and Komatsu, 2011; Li et al., 2012; Cuervo and Wong, 2014; Feng et al., 2014). Macro- and microautophagy are conserved from yeast to humans, whereas CMA has been found only in mammals. Upon macroautophagy induction, newly formed double membrane–bound structures enclose proteins and organelles, eventually generating mature vesicles, called autophagosomes.

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Abbreviations used in this paper: AIM, Atg8 family–interacting motif; Atg, autophagy related; CK-2, casein kinase-2; LIR, LC3-interacting region; Mfn, mitofusin; TOM, translocase of the outer membrane; Ubl, ubiquitin-like.

The Rockefeller University Press
J. Cell Biol. Vol. 205 No. 4 435–445
www.jcb.org/cgi/doi/10.1083/jcb.201402054

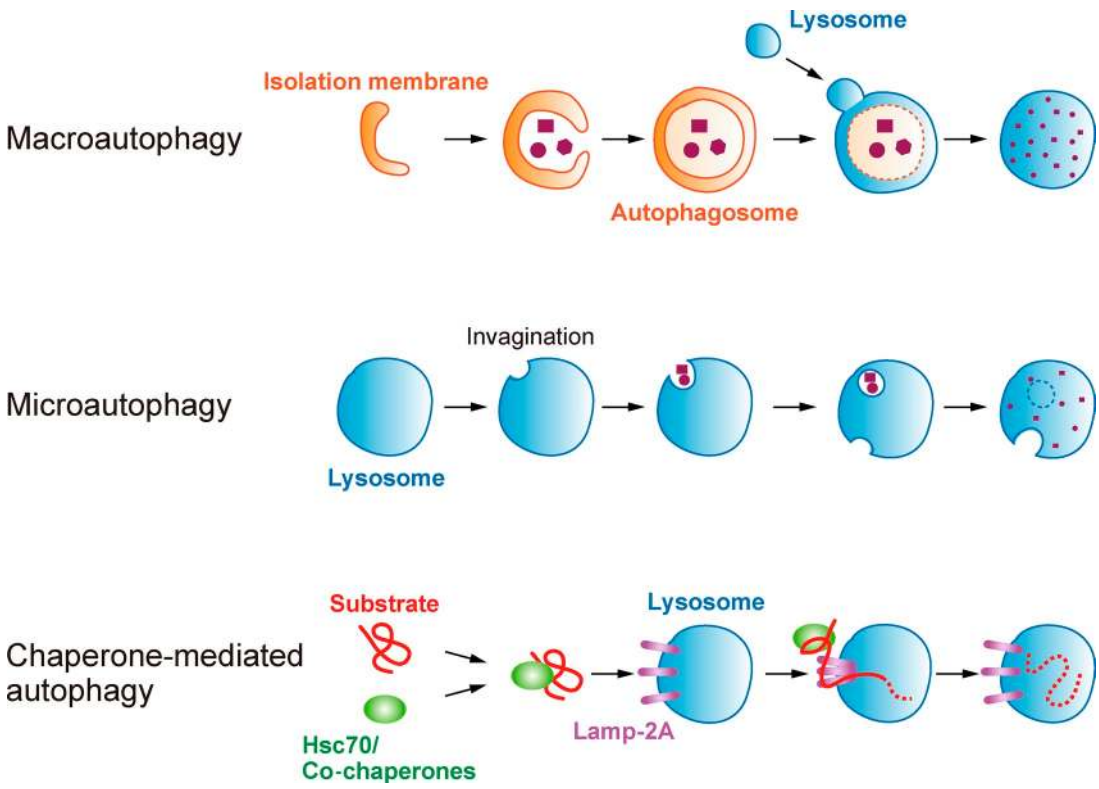

Figure 1. **Three distinct modes of autophagy.** In macroautophagy, newly generated cup-shaped structures, called isolation membranes, expand to surround cytoplasmic components. The two edges of isolation membranes then fuse to form double membrane–bound autophagosomes. Subsequently, autophagosomes fuse to lysosomes, and the engulfed cargoes are digested by hydrolytic enzymes. In microautophagy, invagination of the lysosomal membrane occurs to sequester proteins and organelles in the cytosol. The resulting vesicular structures are then pinched off and released into the lysosomal lumen for digestion. In chaperone-mediated autophagy (CMA), the Hsc70/co-chaperone complex delivers specific substrate proteins to lysosomes. The substrate polypeptides are then translocated one by one through the lysosomal membrane protein Lamp-2A and digested in the lysosomal lumen. Macro- and microautophagy are conserved from yeast to humans, whereas CMA has been found only in mammals. Unlike macro- and microautophagy, CMA has been suggested to degrade only proteins but not whole organelles.

Core Atg proteins play essential roles in autophagosome formation. The engulfed cargoes are then mixed with the lysosomal hydrolases via autophagosome–lysosome fusion and digested into small molecules for recycling. During microautophagy, the lysosomal membrane invaginates to sequester proteins and organelles. In some cases, accompanying membrane structures function in closure of the cargoes, which requires core Atg proteins. The lysosomal lipase then digests the internalized vesicles, leading to breakdown of the cargoes by hydrolases. By contrast, CMA recruits specific protein substrates associated with the molecular chaperone Hsc70 to lysosomes and translocates the substrates one by one into the lysosomal lumen through the receptor protein Lamp-2A in a manner independent on core Atg proteins. Unlike macro- and microautophagy, CMA has been suggested to degrade only proteins but not whole organelles.

Morphological classification of organelle-specific autophagy in yeast and mammals is summarized in Table 1. Both macro- and microautophagy mediate selective elimination of the peroxisome (pexophagy; Manjithaya et al., 2010b; Oku and Sakai, 2010), mitochondrion (mitophagy; Ashrafi and Schwarz, 2013; Feng et al., 2013), lipid droplet (lipophagy; Liu and Czaja, 2013), and nucleus (nucleophagy; Mijaljica and Devenish, 2013). These degradation pathways appear to be conserved from yeast to humans. Macroautophagy-related turnover processes specific for lysosome (lysophagy; Hung et al., 2013; Maejima et al., 2013) and ER (reticulophagy/ER-phagy; Bernales et al., 2006) have been found in mammals and yeast, respectively. Although whether ribosome degradation in yeast occurs via macro- or microautophagy remains to be clarified, it seems to be a selective event (ribophagy) because ribosomal subunits are degraded significantly faster than other cytosolic proteins in an autophagy-dependent fashion (Kraft et al., 2008). To date, there has been no evidence suggesting selective degradation of the Golgi apparatus (golgiphagy).

Common features of organellophagy

Studies on pexophagy and mitophagy have extensively explored molecular mechanisms underlying cargo recognition, implicating two common types, receptor- and ubiquitin-mediated processes (Fig. 2). Both types involve protein phosphorylation that activates or inactivates downstream events.

In the receptor-mediated process, specific proteins membrane-anchored or tightly associated on the organellar surface interact directly, or indirectly via adaptor proteins, with Atg8 (LC3, GABARAP, and GATE-16 in mammalian cells), a highly conserved ubiquitin-like protein essential for all autophagy-related pathways (Shpilka et al., 2011; Rogov et al., 2014; Wild et al., 2014). Notably, receptor proteins contain tetrapeptide

Table 1. **Classification of organellophagy**

Cargo organelle	Macroautophagy		Microautophagy	
	Yeast	Human	Yeast	Human
Peroxisome	✓	✓	✓	ND
Mitochondrion	✓	✓	✓	ND
Lipid droplet	ND	✓	✓	ND
Nucleus	ND	✓	✓	ND
Lysosome	ND	✓	ND	ND
Endoplasmic reticulum	✓	ND	ND	ND
Ribosome	✓[a]	ND	ND	ND

ND, not determined.
[a]Ribophagy seems to depend on macroautophagy rather than microautophagy, although this has not yet been confirmed morphologically.

consensus sequences called Atg8 family–interacting motif (AIM) and LC3-interacting region (LIR) that consist of W/YxxI/L/V and W/F/YxxL/I/V, respectively (Noda et al., 2010; Birgisdottir et al., 2013). AIM/LIR directly associates with Atg8/LC3 through the side chains of their conserved residues bound deeply into the hydrophobic pocket of Atg8/LC3. Mutations in AIM and LIR impair degradation of cargo organelles, suggesting the significance of these interactions. Because Atg8 is covalently linked to the phospholipid phosphatidylethanolamine and localized predominantly to autophagosomes, the receptor–Atg8/LC3 interactions could assist generation and expansion of cup-shaped structures called isolation membranes surrounding cargo organelles. In yeast, pexophagy and mitophagy receptors also interact with Atg11 or Atg17, scaffold proteins that serve as platforms for core Atg protein assembly (Farré et al., 2008; Kanki et al., 2009; Okamoto et al., 2009; Motley et al., 2012). Importantly, protein kinases and phosphatases modify receptors and appear to play regulatory roles in stabilizing or destabilizing the interactions of receptor proteins with Atg8/LC3 and Atg11/Atg17 (Farré et al., 2008, 2013; Novak et al., 2010; Aoki et al., 2011; Kondo-Okamoto et al., 2012; Liu et al., 2012; Kanki et al., 2013; Zhu et al., 2013).

In the ubiquitin-mediated process, peripheral and/or membrane-anchored proteins on the surface of cargo organelles are ubiquitinated by specific E3 ligases (Shaid et al., 2013). These ubiquitin chains act as "degradation tags" recognized by soluble adaptor proteins such as p62 and NBR1 that also interact with LC3 (Johansen and Lamark, 2011). Targeting of other core Atg proteins to these cargo organelles seems to be independent of p62 and LC3 (Itakura et al., 2012), which may be mediated directly by ubiquitin, or indirectly via unknown ubiquitin-binding proteins. In some cases, mitophagy-specific E3 ligases are regulated by phosphorylation. For example, the protein kinase PINK1 phosphorylates the ubiquitin E3 ligase Parkin to promote mitophagy (Kondapalli et al., 2012; Shiba-Fukushima et al., 2012; Iguchi et al., 2013). This type of mitophagy has so far been found in mammals, but not in yeast. Finally, it should be noted that the receptor- and ubiquitin-mediated processes are not mutually exclusive, as the LC3 receptor Pex14 is also involved in the ubiquitin/NBR1-mediated pexophagy in mammalian cells (Deosaran et al., 2013).

Pexophagy

In response to changes in the intra- and extracellular environments, peroxisome number dynamically increases or decreases in order to maintain the appropriate levels of the metabolic reactions including fatty acid oxidation and H_2O_2 detoxification (Smith and Aitchison, 2013). For example, the methylotrophic yeasts *Pichia pastoris* and *Hansenula polymorpha* can proliferate large peroxisome clusters when they grow in media containing methanol as the sole carbon source (van der Klei et al., 2006). Pexophagy is then drastically triggered upon a shift from methanol to glucose or ethanol media in which the peroxisomal metabolism is not critical for cell growth and viability (Manjithaya et al., 2010b; Oku and Sakai, 2010). Thus, molecular mechanisms underlying the selectivity of pexophagy have mostly been uncovered in these methylotrophic yeasts.

Macro- and microautophagy mediate pexophagy (macro- and micropexophagy, respectively) in *P. pastoris* that requires the soluble receptor protein Atg30 that interacts with Pex3 and Pex14, two peroxisomal membrane proteins, and recruits Atg8, Atg11, and Atg17 to the surface of peroxisomes (Farré et al., 2008, 2013). Similarly, Atg36 acts as a soluble receptor protein in the budding yeast *Saccharomyces cerevisiae*, localizes to the peroxisomal surface via Pex3, and binds Atg8 and Atg11 to promote macropexophagy (Motley et al., 2012; Farré et al., 2013). Interestingly, both Atg30 and Atg36 contain AIMs flanked with putative phosphoserine residues (Farré et al., 2013). These amino acids modified by unknown kinase(s) may stabilize the Atg30–Atg8 and Atg36–Atg8 interactions. Additional phosphorylation sites are also required for binding of Atg30 and Atg36 to Atg11 (Farré et al., 2008, 2013). In *S. cerevisiae*, the MAPK cascade Mid2–Pkc1–Bck1–Mkk1/Mkk2–Slt2 is necessary for peroxisome degradation, but not for pexophagosome formation (Manjithaya et al., 2010a; Mao et al., 2011). Hence, Slt2 is unlikely to regulate the interactions of Atg36 with Atg8 and Atg11. Nonetheless, pexophagy in *S. cerevisiae* is enhanced in a set of mutants containing dysfunctional peroxisomes through yet-uncharacterized modifications of Atg36 (Nuttall et al., 2014). Despite the common role in recruiting the pexophagy receptors to the peroxisomal surface in *P. pastoris* and *S. cerevisiae*, Pex3 in *H. polymorpha* is degraded via the ubiquitin–proteasome pathway in order to initiate macropexophagy by unknown mechanisms (Bellu et al., 2002; Williams and van der

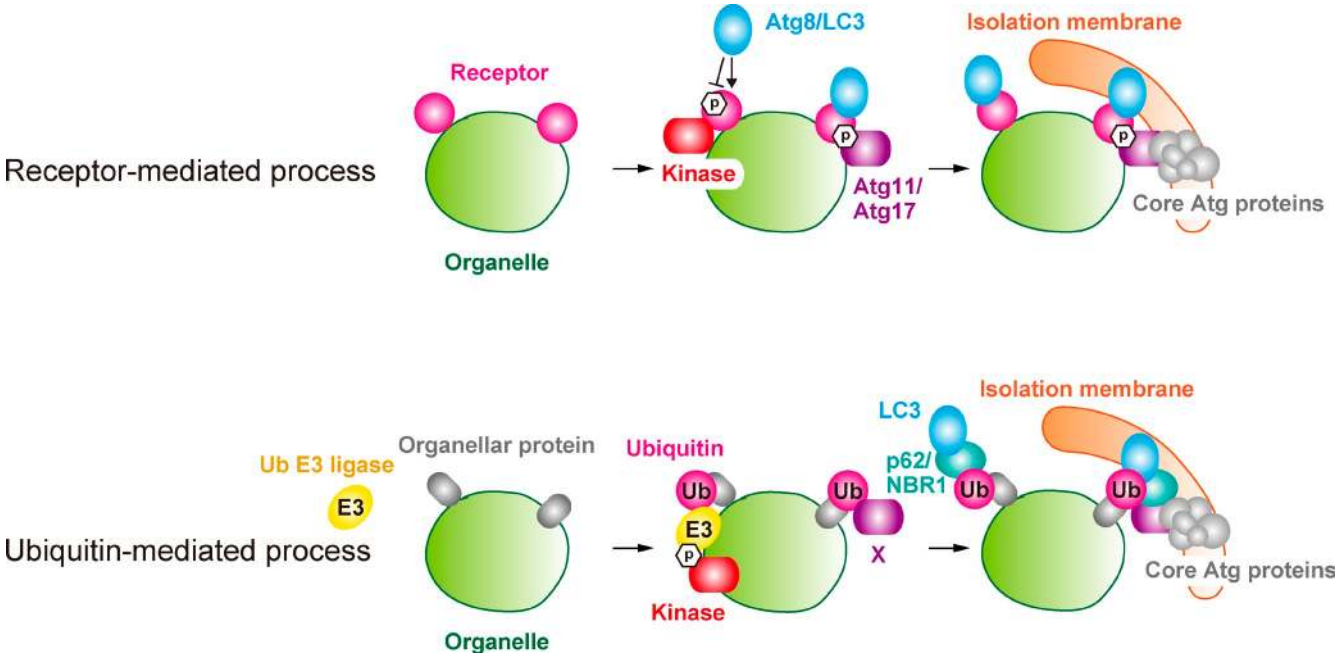

Figure 2. **Two common mechanisms of organellophagy.** Molecular mechanisms underlying cargo recognition in pexophagy and mitophagy have extensively been explored, including two common types, receptor- and ubiquitin-mediated processes. Both types involve protein phosphorylation that activates or inactivates their downstream events. In the receptor-mediated process, membrane-anchored or peripherally associated receptors on the organellar surface interact with Atg8/LC3, ubiquitin-like proteins conjugated to the phospholipid phosphatidylethanolamine and localized to autophagosomes, and Atg11/Atg17, scaffold proteins required for core Atg protein assembly. Protein kinases phosphorylate receptors and regulate receptor interactions with Atg8/LC3 and Atg11/Atg17. In the ubiquitin-mediated process, E3 ubiquitin ligases target to the organelle and ubiquitinate proteins on the organellar surface. The ubiquitin chains then interact with LC3-binding adaptors such as p62/NBR1, or unknown factors (X) that may promote core Atg protein assembly. Protein kinases phosphorylate the ubiquitin ligases and promote targeting and activation of the E3 enzymes.

Klei, 2013), suggesting the diversity of peroxisome turnover mechanisms among yeast species. It should also be noted that dynamin-related GTPases, Dnm1 and Vps1, target to peroxisomes, and promote peroxisomal fission, which is a critical step before pexophagy in *H. polymorpha* and *S. cerevisiae* (Manivannan et al., 2013; Mao et al., 2014).

A study using Chinese hamster ovary cells demonstrates that pexophagy can be induced upon a shift from starvation to nutrient-rich media (Hara-Kuge and Fujiki, 2008). Under this condition, Pex14 interacts with LC3-II, a phosphatidylethanolamine-conjugated form anchored on autophagosomes (Hara-Kuge and Fujiki, 2008). When monoubiquitinated peroxisomal membrane proteins are overexpressed in COS-7 cells, pexophagy occurs in a manner dependent on p62 (Kim et al., 2008). More recently, down-regulation of either p62 or NBR1 has been shown to suppress degradation of peroxisomes in HeLa cells (Deosaran et al., 2013). Overexpression of NBR1, but not p62, can facilitate pexophagy through its LIR, coiled-coil domain (for homo-oligomerization), JUBA domain (for membrane association), and UBA domain (for ubiquitin binding; Deosaran et al., 2013). Notably, an NBR1 mutant defective in p62 interaction is not fully functional for pexophagy (Deosaran et al., 2013). Thus, p62 may not be a major adaptor, but still contributes to pexophagy in cooperation with NBR1. Nonetheless, it seems likely that ubiquitination of peroxisomal proteins promotes recruitment of LC3 to peroxisomes via p62 and NBR1, ultimately leading to pexophagy in mammalian cells. How the core factors of the autophagy machinery are targeted to peroxisomes remains to be clarified.

Mitophagy

Mitochondria are major organelles that are platforms for many important processes including energy conversion, calcium homeostasis, and programmed cell death (Nunnari and Suomalainen, 2012). These organelles concomitantly generate reactive oxygen species (ROS) as hazardous byproducts during respiration. Consequently, accumulation of ROS causes mitochondrial dysfunction. Elimination of damaged mitochondria is therefore critical for cell homeostasis (Okamoto and Kondo-Okamoto, 2012). The other problem related to their energy metabolism is that cells need to maintain the balance between ATP supply and demand. Upon a shift from high to low energy consumption state, surplus mitochondria become vital targets for clearance (Okamoto and Kondo-Okamoto, 2012). Numerous studies demonstrate that mitophagy contributes to mitochondrial quality and quantity control, and that its selectivity is established via common mechanisms (Youle and Narendra, 2011; Jin and Youle, 2012; Narendra et al., 2012; Ashrafi and Schwarz, 2013; Feng et al., 2013).

In the yeast *S. cerevisiae*, the mitophagy receptor Atg32 is induced in response to oxidative stress and anchored on the surface of mitochondria with its N- and C-terminal regions exposed to the cytosol and mitochondrial intermembrane space (IMS), respectively (Fig. 3 A; Kanki et al., 2009; Okamoto et al., 2009). Atg32 contains an AIM near the N terminus that is embedded into the hydrophobic pocket of Atg8 (Okamoto et al., 2009; Kondo-Okamoto et al., 2012). The C-terminal coiled-coil domain of Atg11 physically associates with Atg32 via a consensus

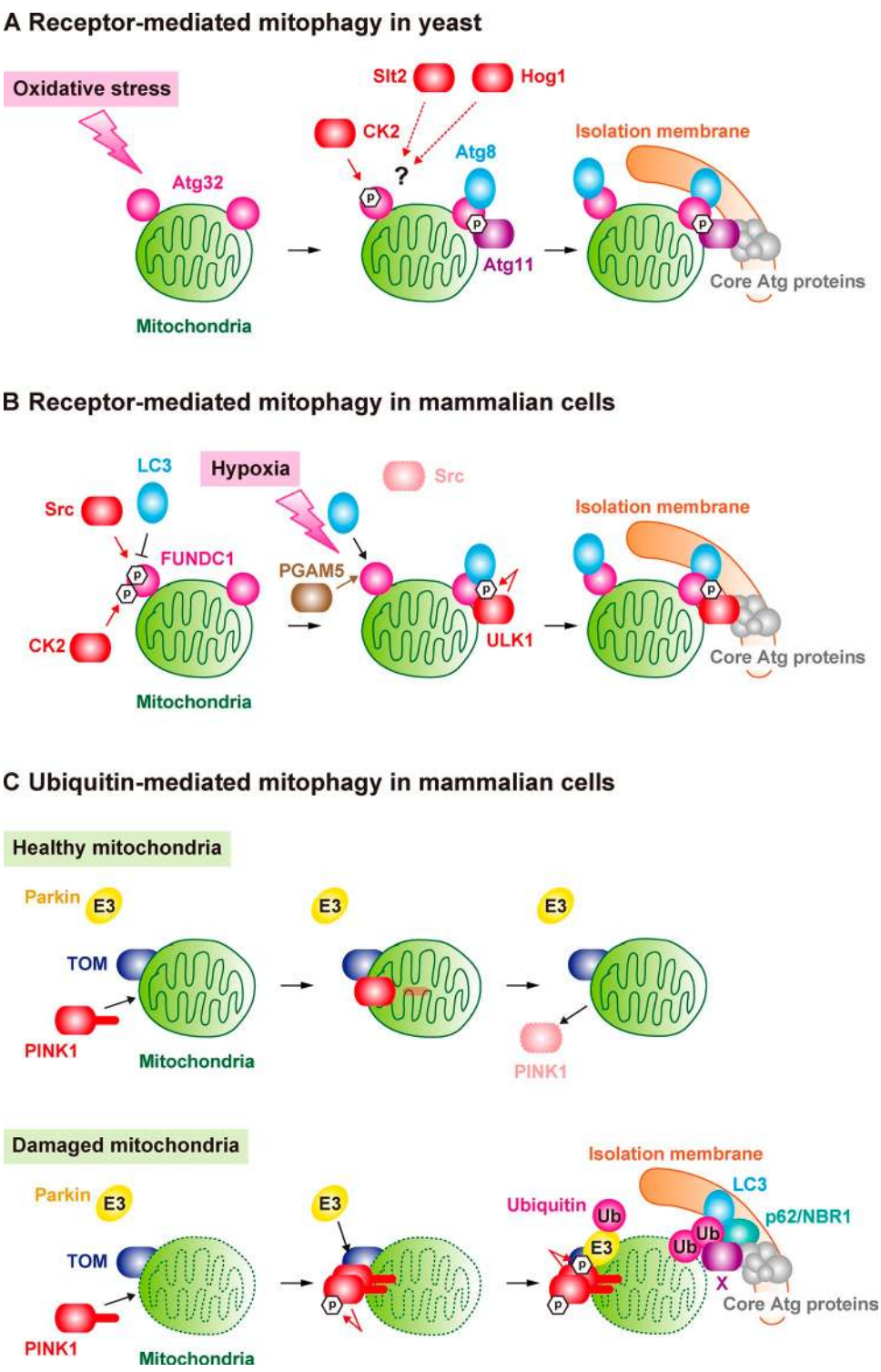

Figure 3. **Models for mitophagy in yeast and mammalian cells.** (A) Atg32-mediated mitophagy in *S. cerevisiae*. Under respiratory conditions, the mitophagy receptor Atg32 is induced in response to oxidative stress, targeted, and anchored to the mitochondrial surface. Atg32 recruits Atg8 and Atg11 to mitochondria via distinct domains. CK2 phosphorylates Atg32 to stabilize the interaction between Atg32 and Atg11. This tertiary complex and core Atg proteins cooperatively generate isolation membranes to sequester mitochondria. The protein kinases Slt2 and Hog1 are also critical for mitophagy in yeast, although their targets remain unknown. (B) FUNDC1-mediated mitophagy in mammals. Under normoxic conditions, the mitochondrial outer membrane protein FUNDC1 is phosphorylated by Src and CK2, thereby preventing LC3 binding. Upon hypoxia, the expression of Src is strongly suppressed, and the protein phosphatase PGAM5 dephosphorylates FUNDC1 and promotes LC3 binding. In addition, ULK1, a mammalian Atg1 kinase homologue, interacts with FUNDC1 and phosphorylates the mitophagy receptor. This posttranslational modification also stabilizes the interaction between FUNDC1 and LC3. (C) PINK1/Parkin-mediated mitophagy in mammals. When targeted to healthy mitochondria, PINK1 is partially translocated across the mitochondrial membranes, proteolytically processed, released back to the cytosol, and rapidly degraded. In cells containing damaged mitochondria, PINK1 is stalled in the outer membrane and associated with the TOM complex. Two molecules of PINK1 undergo self-activation via autophosphorylation. Active PINK1 then phosphorylates Parkin and stabilizes the E3 ligase on the surface of mitochondria. Mitochondria-associated Parkin promotes ubiquitination of multiple substrates, ultimately leading to LC3 and p62/NBR1 recruitment and core Atg protein assembly. Ubiquitin chains and these proteins are bridged by an unknown factor (X).

region following the AIM (Aoki et al., 2011). Notably, this Atg11-interacting region contains serine residues that appear to be modified directly by casein kinase-2 (CK2), a housekeeping protein kinase (Kanki et al., 2013). This posttranslational modification stabilizes Atg32–Atg11 interaction (Fig. 3 A; Aoki et al., 2011; Kondo-Okamoto et al., 2012). A recent study suggests that processing of the Atg32 C-terminal region by Yme1, a catalytic subunit of the mitochondrial inner membrane AAA protease facing the IMS, is important for Atg32–Atg11 interaction (Wang et al., 2013), yet the role of Yme1 in mitophagy is currently a matter of debate (Campbell and Thorsness, 1998; Welter et al., 2013). In addition to CK2, the MAPK cascades Wsc1–Pkc1–Bck1–Mkk1/2–Slt2 and Ssk1–Pbs2–Hog1 are important for mitophagy (Aoki et al., 2011; Mao et al., 2011). Phosphorylation of Atg32 depends on Hog1, but not Slt2, while Atg32 is not a substrate for Hog1 (Aoki et al., 2011). Atg1, a protein kinase essential for all autophagy-related processes, is also involved in Atg32 phosphorylation (Kondo-Okamoto et al., 2012), although the molecular function of this modification remains unclear.

Similar to Atg32-mediated mitophagy in yeast, three mitochondria-anchored receptors, NIX, BNIP3, and FUNDC1, promote autophagic degradation selective for mitochondria in mammalian cells (Schweers et al., 2007; Sandoval et al., 2008; Zhang et al., 2008; Liu et al., 2012). All three proteins contain the LIR consensus sequences that are important for their mitophagy activities (Novak et al., 2010; Liu et al., 2012; Zhu et al., 2013). NIX is highly induced during reticulocyte maturation and interacts with LC3 and GABARAP (Schweers et al., 2007; Novak et al., 2010). BNIP3 is strongly expressed in response to hypoxia and activated by reoxygenation (Zhang et al., 2008; Zhu et al., 2013). Notably, phosphorylation of serine residues near the BNIP3 LIR is crucial for LC3 and GATE-16 binding, and efficient mitophagy (Zhu et al., 2013). Kinases regulating the BNIP3 LIR are currently unknown. Although FUNDC1 is constitutively expressed under normoxic conditions, the tyrosine residue of the LIR is phosphorylated by the Src family kinase, which prevents LC3 binding and mitophagy (Fig. 3 B; Liu et al., 2012). Strikingly, hypoxia strongly suppresses Src expression, leading to dephosphorylation of the FUNDC1 LIR by unknown protein phosphatases, subsequent binding of LC3, and ultimate activation of mitophagy (Fig. 3 B; Liu et al., 2012). Furthermore, a serine residue near the LIR is phosphorylated by CK2 under normal conditions, and conversely dephosphorylated by the mitochondrial phosphatase PGAM5 upon hypoxic stress and mitochondrial membrane potential ($\Delta\Psi$m) dissipation, leading to efficient LC3 binding and mitophagy activation (Fig. 3 B; Chen et al., 2014). Another recent study reveals that ULK1, a mammalian Atg1 kinase, targets to mitochondria via interaction with FUNDC1 and phosphorylates the mitophagy receptor to stabilize the FUNDC1–LC3 interaction (Fig. 3 B; Wu et al., 2014). It is not certain whether these mitophagy receptors could also recruit core Atg proteins to mitochondria.

In addition to the receptor-driven pathways described above, mammalian cells use the ubiquitin-dependent processes to promote degradation of mitochondria. The best known is the mitophagy involving PINK1, a mitochondrial protein kinase, and Parkin, a cytosolic E3 ubiquitin ligase, two closely related causal factors for autosomal-recessive familial Parkinsonism (Kitada et al., 1998; Valente et al., 2004). When targeted to healthy mitochondria, PINK1 is partially translocated across the mitochondrial outer and inner membranes, cleaved by several enzymes including the matrix-localized mitochondrial-processing peptidase MPP and the inner membrane protease PARL, released back into the cytosol, and rapidly degraded by the proteasome via the N-end rule pathway (Fig. 3 C; Jin et al., 2010; Matsuda et al., 2010; Narendra et al., 2010b; Deas et al., 2011; Meissner et al., 2011; Shi et al., 2011; Greene et al., 2012; Yamano and Youle, 2013). In this situation, Parkin is dispersed throughout the cytosol as an inactive form and is not stably associated with mitochondria (Narendra et al., 2008, 2010b; Matsuda et al., 2010; Chaugule et al., 2011; Chew et al., 2011) (Fig. 3 C). As a result, mitophagy is mostly suppressed in normally respiring cells. Upon mitochondrial dysfunction such as $\Delta\Psi$m dissipation, PINK1 is stalled in the outer membrane and anchored on the surface of mitochondria (Kawajiri et al., 2010; Matsuda et al., 2010; Narendra et al., 2010b; Rakovic et al., 2010). Subsequently, PINK1 forms a supermolecular complex together with the translocase of the outer membrane (TOM) components (Fig. 3 C; Lazarou et al., 2012; Okatsu et al., 2013). In this supermolecular complex, two molecules of PINK1 undergo intermolecular phosphorylation (Okatsu et al., 2013). PINK1 complex formation is correlated well with its autophosphorylation, which is prerequisite for recruitment of Parkin to damaged mitochondria (Okatsu et al., 2012, 2013). Through these processes, PINK1 becomes more active, efficiently phosphorylating a serine residue of the Parkin ubiquitin-like (Ubl) domain (Fig. 3 C; Kondapalli et al., 2012; Shiba-Fukushima et al., 2012; Iguchi et al., 2013). Phosphorylation of the Ubl domain probably induces a conformational change, at least to some extent, resulting in Parkin self-association and ubiquitin-thioester formation at the RING2 domain, which is essential for the E3 ligase activity (Chaugule et al., 2011; Iguchi et al., 2013; Lazarou et al., 2013; Spratt et al., 2013; Zheng and Hunter, 2013). Importantly, these PINK1-mediated events are consistent with the mechanisms of Parkin inactive–active state transition revealed by recent structural studies (Riley et al., 2013; Trempe et al., 2013; Wauer and Komander, 2013).

Whether specific Parkin targets are required for mitophagy remains controversial (Geisler et al., 2010; Lee et al., 2010; Narendra et al., 2010a; Okatsu et al., 2010). A high-throughput analysis on the Parkin-dependent ubiquitylome demonstrates numerous targets on the surface of depolarized mitochondria including mitofusins (Mfns), large GTPases required for mitochondrial fusion (Sarraf et al., 2013). Parkin is responsible for degradation of mitofusins, preventing refusion of damaged mitochondria and assisting subsequent mitophagy (Gegg et al., 2010; Tanaka et al., 2010; Glauser et al., 2011; Rakovic et al., 2011). The role of Mfns in the PINK1/Parkin pathway is rather intricate, as it has been reported that Mfn2 serves as a Parkin receptor to promote mitochondrial degradation in mouse cardiomyocytes (Chen and Dorn, 2013). Notably, genome-wide siRNA screens uncover additional factors for PINK1/Parkin-mediated mitophagy, including TOMM7, a component of the

TOM complex, as essential for stabilizing PINK1 on the outer membrane of depolarized mitochondria (Hasson et al., 2013). Rab GTPase-activating proteins have recently been shown to interact with Fis1, a tail-anchored protein, and LC3/GABARAP family members on the surface of mitochondria where they promote formation of autophagosomes by regulating Rab7 activity during PINK1/Parkin-mediated mitophagy (Yamano et al., 2014). Very recently, three studies demonstrate that PINK1 phosphorylates ubiquitin to activate Parkin in a manner similar to Parkin self-activation via the phosphorylated Ubl domain (Kane et al., 2014; Kazlauskaite et al., 2014; Koyano et al., 2014). Whether ubiquitin/LC3-binding adaptors such as p62 and NBR1 are necessary for the PINK1/Parkin pathway, and how core Atg proteins are recruited to damaged mitochondria remain inconclusive.

In addition to Parkin, two ubiquitin E3 ligases, Gp78 and SMURF1, have been implicated in mammalian mitophagy. The Gp78-mediated process depends on Mfn1, but does not require Parkin (Fu et al., 2013). In contrast, SMURF1 is required for the PINK1/Parkin pathway (Orvedahl et al., 2011). Molecular mechanisms underlying Gp78 and SMURF1 functions have not yet been elucidated.

Lipophagy

Lipid droplets (LDs) consist of a core mainly containing triglycerides and sterol esters surrounded by a phospholipid monolayer and associated with various proteins. They are dynamic organelles that change their size and number in response to diverse conditions, and play key roles in lipid storage and metabolism (Walther and Farese, 2012). In addition to the cytosolic lipases, lysosomal hydrolases catabolize LDs that are transported via lipophagy (Liu and Czaja, 2013). In yeast, LDs are degraded through microautophagy (van Zutphen et al., 2014). By contrast, lipophagy occurs via macroautophagy in mouse hepatocytes and human enterocytes (Singh et al., 2009; Khaldoun et al., 2014). How the selectivity of lipophagy is established needs future studies.

Nucleophagy

Accumulating evidence suggests that portions of the nucleus, nucleus-derived components, or even a whole nucleus, are degraded by selective autophagy in a variety of eukaryotes (Mijaljica and Devenish, 2013). These processes, defined as nucleophagy, can be induced under starvation and other stress conditions such as DNA damage and cell cycle arrest (Mijaljica and Devenish, 2013). In the yeast *S. cerevisiae*, small teardrop-shaped parts of the nucleus are engulfed by the vacuole, a lytic organelle equivalent to the lysosome, at nucleus–vacuole (NV) junctions (Roberts et al., 2003). This event, termed piecemeal microautophagy of the nucleus (PMN), is induced soon after nutrient deprivation (Roberts et al., 2003). Formation of NV junctions requires Nvj1 in the nuclear envelope and Vac8 on the vacuolar membrane, two physically associated proteins that establish the vacuolar diffusion barrier, invaginate NV junctions, and generate PMN vesicles in a manner dependent on the vacuolar electrochemical gradient and lipid-modifying enzymes (Roberts et al., 2003; Dawaliby and Mayer, 2010). Atg11, Atg17, and other core Atg proteins are indispensable for PMN, as in the case of micropexophagy in the methylotrophic yeasts (Krick et al., 2008). After prolonged starvation, another type of nucleophagy also occurs through unknown mechanisms, which does not require Nvj1, Vac8, and Atg11 (Mijaljica et al., 2012).

In mammals, LC3- and several core Atg-positive structures containing nuclear components accumulate in close proximity to the nucleus in cells from nuclear envelopathies (Park et al., 2009). In addition, micronuclei, small structures containing displaced chromosomes or chromosome fragments efficiently generated in cells expose to genotoxic stress, are degraded via autophagy (Rello-Varona et al., 2012). These autophagic micronuclei are p62 positive and exhibit signs of nuclear envelope degradation and DNA damage (Rello-Varona et al., 2012). It has also been suggested that LC3-positive micronuclei represent vesicles containing DNA that has not been repaired (Erenpreisa et al., 2012). Whether macro- and microautophagy could mediate nucleophagy in mammals and how the selectivity is established remain to be clarified.

Lysophagy

Lysosomes are acidic organelles highly enriched with hydrolytic enzymes that digest macromolecules delivered via the endocytic and autophagic pathways. Recent studies demonstrate that lysosomal rupture causes release of hydrolases into the cytosol, ultimately leading to destruction of intracellular structures and functions (Boya and Kroemer, 2008). It is therefore conceivable that cells must use surveillance and quality control systems for lysosomes. Indeed, emerging evidence reveals that damaged lysosomes are selectively sequestered by macroautophagy in mammalian cells (Hung et al., 2013; Maejima et al., 2013). Lysophagy seems to be a ubiquitin-mediated process involving LC3 and p62, which could contribute to recovery of lysosomal activities (Maejima et al., 2013). How ubiquitin and core Atg proteins selectively target to damaged lysosomes awaits further investigations.

Reticulophagy/ER-phagy

ER membranes are most abundant in many cell types, and their lumens serve as major factories for protein folding and modification. Although macroautophagy in yeast under starvation conditions can nonselectively sequester the ER together with other cytoplasmic constituents, ER components are more enriched than cytosolic proteins in autophagic bodies, suggesting a selective feature of this ER turnover (Hamasaki et al., 2005). Strikingly, when yeast cells are challenged with protein folding stress, ER membrane stacks are densely enclosed in autophagosome-like structures (Bernales et al., 2006). Recently, a Ypt/Rab GTPase module containing Atg11 has been reported to regulate reticulophagy/ER-phagy in yeast (Lipatova et al., 2013). These observations raise the possibility that ER turnover occurs via unknown selective mechanisms.

Ribophagy

In yeast, a hallmark of starvation-induced, nonselective macroautophagy is that autophagic bodies in the vacuolar lumen contain myriad ribosomes (Takeshige et al., 1992). However, under the same conditions, ribosomal subunits are degraded faster

than other cytosolic proteins (Kraft et al., 2008). Intriguingly, the Rsp5 ubiquitin ligase and the Ubp3/Bre5 ubiquitin protease are involved in this preferential ribosome turnover but not bulk autophagy, supporting the existence of ribophagy (Kraft and Peter, 2008). The Ubp3–Bre5 complex interacts with the AAA ATPase Cdc48 and the ubiquitin-binding Cdc48 adaptor Ufd3 that are also required for ribophagy (Ossareh-Nazari et al., 2010). Recently, the E3 ubiquitin ligase Ltn1 has been suggested to negatively regulate ribophagy through ubiquitinating Rpl25, a 60S ribosomal subunit protein, which is also de-ubiquitinated by Ubp3 in an antagonistic action (Ossareh-Nazari et al., 2014). Whether ribosomes are recognized as disposable cargoes via ubiquitin or unknown receptor(s), and how de-ubiquitination regulates ribophagy remain to be addressed.

During starvation-induced macroautophagy in mammalian cells, the timing of ribosomal degradation is different from those of other proteins and organelles, implying that bulk autophagy can even be intimately regulated in terms of cargo recognition and sequential activation (Kristensen et al., 2008).

Perspectives

Herein, we have highlighted recent progress in our understanding of organelle-specific autophagy pathways. Despite the diversity of their degradation cues and tags, the basic principles underlying organellophagy are similar among different organelles, and are likely to be universal in almost all eukaryotes. However, many of the landmark molecules for recruiting core Atg proteins are still missing, and the molecular details of organellophagy induction and termination are largely unknown.

The origin of autophagosomal membranes is a fundamental, ongoing issue for all autophagy-related processes in unicellular and multicellular eukaryotes (Lamb et al., 2013). Recent imaging studies reveal the ER–mitochondria contacts as autophagosome formation sites for autophagy in mammals (Hamasaki et al., 2013) and mitophagy in yeast (Böckler and Westermann, 2014), whereas others implicate ER exit sites and the ER–Golgi intermediate compartment involving COPII vesicles for autophagy in yeast and mammals (Ge et al., 2013; Graef et al., 2013; Suzuki et al., 2013). In COS-7 cells under starvation conditions, COPII vesicles seem to localize at ER–mitochondria contacts (Tan et al., 2013), raising the possibility that these autophagosome formation sites may not be mutually exclusive. Whether degradation of other organelles utilizes the aforementioned sites for formation of autophagosomes remains to be addressed.

Finally, the challenging attempts will be to decipher whether there is a cross talk between organelle biogenesis and degradation, and how the organellar quality and quantity control pathways regulate higher-order functions such as cell differentiation and development in multicellular organisms. Definitely, more stimulating discoveries are yet to come.

We apologize to the many colleagues whose work could not be cited because of space limitations, and hope the readers refer to the cited reviews for more information.

This work was supported in part by the Ministry of Education, Culture, Science, and Technology of Japan Grant-in-Aid for Challenging Exploratory Research grant (25650067), Scientific Research (B) (25291045), Scientific Research on Innovative Areas (26111513), and by grants from the Ono Medical Research Foundation.

The author declares no competing financial interest.

Submitted: 11 February 2014
Accepted: 6 May 2014

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