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Diverse Cellular Roles of Autophagy

Hideaki Morishita* and Noboru Mizushima*

Department of Biochemistry and Molecular Biology, Graduate School and Faculty of Medicine, The University of Tokyo, Tokyo 113-0033, Japan; email: morishita@m.u-tokyo.ac.jp, nmizu@m.u-tokyo.ac.jp

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*These authors contributed equally to this article

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Abstract

Macroautophagy is an intracellular degradation system that delivers diverse cytoplasmic materials to lysosomes via autophagosomes. Recent advances have enabled identification of several selective autophagy substrates and receptors, greatly expanding our understanding of the cellular functions of autophagy. In this review, we describe the diverse cellular functions of macroautophagy, including its essential contribution to metabolic adaptation and cellular homeostasis. We also discuss emerging findings on the mechanisms and functions of various types of selective autophagy.

Contents

INTRODUCTION

Autophagy is an intracellular degradation system that delivers cytoplasmic materials to lysosomes (Mizushima et al. 2011, Nakatogawa et al. 2009, Soreng et al. 2018). Autophagy can be classified into three types: macroautophagy, microautophagy (uptake of cytoplasmic components by inward invagination of lysosomal membranes) (Oku & Sakai 2018), and chaperone-mediated autophagy (direct transport of cytosolic proteins into lysosomes through translocons) (Kaushik & Cuervo 2018). The best-characterized class of autophagy is macroautophagy (hereafter referred to as autophagy), which is the focus of this review. During autophagy, the isolation membrane (also known as the phagophore) nucleates, elongates, and encloses a small portion of the cytoplasm, forming a double-membrane organelle termed the autophagosome (**Figure 1**). Autophagosomes fuse with lysosomes to form autolysosomes in which lysosomal hydrolases digest internal contents. Degradation products are recycled after being released into the cytosol.

Autophagosome: a double-membrane structure enclosing cytoplasmic materials

The molecular mechanisms and functions of autophagy have been extensively investigated since the discovery of *autophagy-related* (*ATG*) genes in yeast in the 1990s (Klionsky et al. 2003, Takeshige et al. 1992, Tsukada & Ohsumi 1993). To date, 42 *ATG* genes have been identified, and many of them are conserved among eukaryotes (Mizushima et al. 2011, Nakatogawa et al. 2009). Additional genes essential for autophagy in most eukaryotes, but not present in yeast, have also been identified: *ATG101*, *EI24*, *EPG5*, *TMEM41B*, and *VMP1* (Mizushima et al. 2011, Moretti

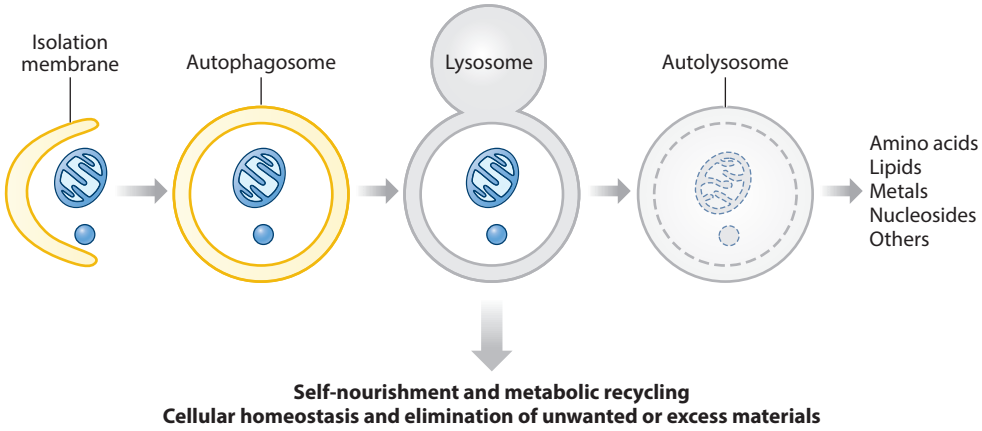

Figure 1

Processes and functions of autophagy. Membrane dynamics of macroautophagy in mammals are shown. Upon induction of autophagy, a small portion of the cytoplasm is enclosed by the isolation membrane. Then, the isolation membrane is closed, forming a double-membrane structure termed the autophagosome. The autophagosome fuses with the lysosome to degrade internal contents, forming the autolysosome, from which amino acids, lipids, metals (e.g., iron), nucleosides, and other materials are recycled back into the cytosol. In general, autophagy has two major functions: (*1*) self-nourishment and metabolic recycling and (*2*) cellular homeostasis and elimination of unwanted or excess materials.

et al. 2018, Morita et al. 2018, Shoemaker et al. 2019, Tian et al. 2010). Reverse-genetic approaches using mice and cell cultures have revealed two major roles of autophagy (**Figure 1**): (*1*) self-nourishment and metabolic recycling and (*2*) maintaining cellular homeostasis and eliminating unwanted materials (Gatica et al. 2018, Kaur & Debnath 2015, Levine et al. 2015, Mizushima & Komatsu 2011).

In this review, we describe these functions at the cellular rather than the organismal level, particularly emphasizing the roles and molecular mechanisms of various types of selective autophagy. We do not include the roles of autophagy in general physiology and diseases (e.g., degenerative disorders, cancers, inflammatory disorders, and aging), which have been reviewed in detail elsewhere (Amaravadi et al. 2016, Deretic et al. 2013, Hansen et al. 2018, Kroemer 2015, Leidal et al. 2018, Mizushima & Komatsu 2011).

MECHANISM OF AUTOPHAGY

Over the last two decades, a large body of research has revealed the functions of ATG proteins. Autophagosome formation requires a subset of core ATG proteins comprising several functional units: (*1*) Atg1/Unc-51-like kinase (ULK) complexes, (*2*) ATG9 vesicles, (*3*) class III phosphatidylinositol 3-kinase (PtdIns3K) complexes, (*4*) ATG2-Atg18/WIPI complexes, (*5*) the ATG12 conjugation system, and (*6*) the Atg8/microtubule-associated protein 1 light chain 3 (LC3) conjugation system (Mizushima et al. 2011, Nakatogawa et al. 2009, Soreng et al. 2018). Here, we summarize the principal mechanisms of the formation and maturation of autophagosomes and recognition of selective substrates.

Selective autophagy: a form of autophagy that can selectively sequester specific cargos into the autophagosome

Autophagosome Formation and Maturation

In mammals, the most upstream autophagy factors are the ULK complex [consisting of ATG101, ATG13, FIP200 (also termed RB1CC1), and ULK1/2] and ATG9 vesicles, both of which

translocate independently to the autophagosome formation site on or close to the endoplasmic reticulum (ER) (Axe et al. 2008, Itakura et al. 2012, Karanasios et al. 2016). The ULK complex is responsible for nucleating the isolation membrane (Zachari & Ganley 2017). ATG9 vesicles likely compose a portion of the autophagosome membrane (Noda 2017). These upstream factors then recruit a subtype of the class III PtdIns3K complex (consisting of ATG14, Beclin 1, VPS15, and VPS34) to generate phosphatidylinositol 3-phosphate (PtdIns3P). ATG2A/B and PtdIns3P-binding WIPI2 and two ER transmembrane proteins, VMP1 and TMEM41B, are required to form isolation membranes (Dooley et al. 2014, Mizushima et al. 2011, Moretti et al. 2018, Morita et al. 2018, Shoemaker et al. 2019). In yeast, the Atg1 complex is composed of Atg1, Atg13, Atg17, Atg29, and Atg31, and Atg18 is a WIPI2 homolog (Mizushima et al. 2011).

Autophagy receptor: a factor that tethers a cargo to autophagic membranes and is degraded together with the cargo

Two ATG conjugation systems lead to the covalent attachment of Atg8/LC3 to phosphatidylethanolamine on autophagic membranes. The Atg8/LC3 family in mammals consists of two subfamilies: the LC3 and gamma-aminobutyric acid receptor–associated protein (GABARAP) families. Atg8/LC3 promotes the maturation of autophagosomes, including expansion and closure of the isolation membrane, fusion with the lysosome, and degradation of the inner autophagosome membrane (Nguyen et al. 2016, Noda et al. 2009, Tsuboyama et al. 2016). The closure of the isolation membrane is mediated by the ESCRT machinery (Takahashi et al. 2018). Once autophagosomes are closed, they undergo maturation to fuse with lysosomes (Bas et al. 2018, Zhao & Zhang 2018).

Selective Autophagy

Diverse cargos have been recognized as substrates for selective autophagy, including proteins, organelles, and pathogens (Farré & Subramani 2016, Gatica et al. 2018, Khaminets et al. 2016) (**Table 1**). Cargo selectivity can be conferred by direct or indirect interaction of cargo with Atg8/LC3 on autophagic membranes (**Figure 2**). Indirect interactions are achieved by autophagy receptors, which can tether cargo to autophagic membranes by binding to both the cargo and Atg8/LC3 on autophagic membranes. Although both cargos and receptors are subjected to lysosomal degradation, only the latter function as part of the autophagy apparatus (Galluzzi et al. 2017). The interaction of the cargo or receptor with Atg8/LC3 is mostly mediated by Atg8-interacting motifs (AIMs), LC3-interacting regions (LIRs), or GABARAP-interacting motifs (GIMs) on the cargo or receptor (Noda et al. 2010, Rogov et al. 2017). The canonical AIM/LIR/GIMs are composed of a consensus motif [W/F/Y]*xx*[L/I/V] (where *x* is any amino acid), surrounded by one or more proximal acidic residues (Noda et al. 2010, Rogov et al. 2017). Two hydrophobic binding pockets in Atg8/LC3s recognize the first and fourth hydrophobic residues in the AIM/LIR/GIM (Noda et al. 2010).

The autophagic receptors recognize cargos in a ubiquitin-dependent or -independent manner (**Figure 2**). When cargos (e.g., damaged mitochondria or lysosomes) are polyubiquitinated, the ubiquitin tag is recognized by autophagy receptors that can bind ubiquitinated proteins (Khaminets et al. 2016). For example, during PTEN-induced putative kinase 1 (PINK1)–PARKIN-mediated mitophagy, ubiquitinated mitochondrial proteins are recognized by two cytosolic autophagy receptors, NDP52 and optineurin (OPTN), which have both LIR and ubiquitin-binding domains (Lazarou et al. 2015). One example of ubiquitin-independent recognition is the binding of yeast aminopeptidase I precursors by the AIM-containing autophagy receptor Atg19 for transport to the vacuole by the autophagy-related cytoplasm-to-vacuole targeting (Cvt) pathway (Gatica et al. 2018).

However, cargo selectivity can be achieved by other mechanisms that are not necessarily mutually exclusive of the above mechanism (Mizushima 2018). Some cargos can trigger autophagosome

Table 1 Cargos and receptors of selective autophagy

Cargo (process)	Receptor [species, ubiquitin (Ub) dependency]	Reference(s)
Ams1, prApe1 (Cvt pathway)	Atg19 (yeast)	Gatica et al. 2018
Bacterial and viral pathogens (xenophagy)	OPTN, p62, NDP52, TAX1BP1 (mammals, Ub) TRIM5α (mammals)	Mandell et al. 2014; Thurston et al. 2009, 2012; Wild et al. 2011; Zheng et al. 2009
Endoplasmic reticulum (ER-phagy, reticulophagy)	Atg39, Atg40 (yeast)	Mochida et al. 2015
	ATL3, CCPG1, FAM134B, RTN3, SEC62, TEX264 (mammals) p62 (mammals, Ub)	An et al. 2019, Chen et al. 2019, Chino et al. 2019, Fumagalli et al. 2016, Grumati et al. 2017, Khaminets et al. 2015, Smith et al. 2018, Yang et al. 2016
Ferritin (ferritinophagy)	NCOA4 (mammals)	Dowdle et al. 2014, Mancias et al. 2014
Glycogen (glycophagy)	STBD1 (mammals)	Jiang et al. 2010
Lipid droplet (lipophagy)	Unknown	Singh et al. 2009
Lysosome (lysophagy)	p62 (mammals, Ub)TRIM16 (mammals)	Chauhan et al. 2016, Maejima et al. 2013, Papadopoulos et al. 2017
Membranous organelles in *Caenorhabditis elegans* sperm	ALLO-1 (*C. elegans*, Ub)	Sato et al. 2018
Mitochondria (mitophagy)	Atg32 (yeast)	Kanki et al. 2009, Okamoto et al. 2009
	ALLO-1 (*C. elegans*, Ub)	Sato et al. 2018
	BCL2L13, BNIP3, BNIP3L/NIX, FKBP8, FUNDC1, PHB2 (mammals)	Bhujabal et al. 2017, Hanna et al. 2012, Liu et al. 2012, Murakawa et al. 2015, Novak et al. 2010, Schweers et al. 2007, Wei et al. 2017
	NDP52, OPTN (mammals, Ub)	Lazarou et al. 2015, Wong & Holzbaur 2014
	Cardiolipin (mammals)	Chu et al. 2013
Nuclear envelope (nucleophagy)	Atg39 (yeast)	Mochida et al. 2015
Peroxisome (pexophagy)	Atg36, PpAtg30, PpAtg37, Pex3, PpPex14, PpPex3 [yeast (Pp denotes *Pichia pastoris*)]	Farré & Subramani 2016, Farré et al. 2008, Motley et al. 2012, Nazarko et al. 2014
	NBR1, p62 (mammals, Ub)	Deosaran et al. 2013, Yamashita et al. 2014
P granules (aggrephagy)	SEPA-1 (*C. elegans*)	Zhang et al. 2009
Proteasome (proteaphagy)	RPN10 (plants, Ub)	Marshall et al. 2015
	Cue5 (yeast, Ub)	Marshall et al. 2016
	p62 (mammals, Ub)	Cohen-Kaplan et al. 2016
Stress granules and P-bodies (granulophagy)	p62 (mammals)	Buchan et al. 2013
Ubiquitinated protein aggregates (aggrephagy)	Cue5 (yeast, Ub)	Lu et al. 2014
	NBR1, OPTN, p62, TOLLIP (mammals, Ub)	Kirkin et al. 2009, Korac et al. 2013, Lu et al. 2014, Pankiv et al. 2007

formation by recruiting upstream autophagy-initiating ATG factors such as the Atg1/ULK complex (**Figures 2** and **3**). For example, in yeast, several cargo receptors [e.g., Atg19 (the Cvt pathway), Atg32 (mitophagy), Atg36, *Pichia pastoris* (Pp) Atg30 (pexophagy), Atg39, and Atg40 (ER-phagy)] interact with the scaffold protein Atg11, which can recruit ATG1 complexes to induce autophagy (Gatica et al. 2018). In mammals, during PINK1–PARKIN-mediated mitophagy,

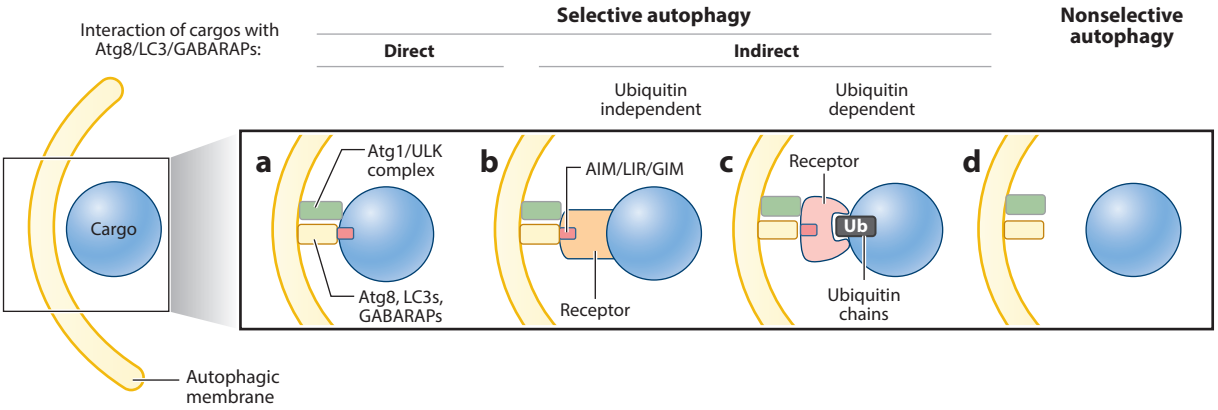

Figure 2

Types of cargo selection for autophagy. (*a*) When cargos have AIM/LIR/GIMs (e.g., p62 and NCoR1), they can directly bind to Atg8/LC3/GABARAPs on autophagic membranes. (*b*) When cargos lack AIM/LIR/GIMs or ubiquitin tags (e.g., ApeI and ferritin), they use autophagy receptors with AIM/LIR/GIMs (e.g., Atg19 and NCOA4, respectively). (*c*) When cargos lack AIM/LIR/GIMs but are ubiquitinated (e.g., damaged mitochondria), they interact with cytosolic receptors (e.g., NDP52 and OPTN) that have both ubiquitin-binding domains and AIM/LIR/GIMs. In some types of selective autophagy, the Atg1/ULK complex associates with cargos (e.g., p62) or autophagy receptors (e.g., CCPG1 and NDP52) to initiate autophagy (*a–c*). (*d*) Nonselective autophagy randomly sequesters the cytoplasm. Abbreviations: AIM, Atg8-interacting motif; GIM, GABARAP-interacting motif; LIR, LC3-interacting region; NCOA4, nuclear receptor coactivator 4.

damaged mitochondria can recruit the ULK complex through the autophagy receptors (NDP52 and OPTN), independently of LC3/GABARAPs (Lazarou et al. 2015, Nguyen et al. 2016). NDP52 interacts with FIP200, an ULK complex component, to initiate autophagy (Vargas et al. 2019). The ER-phagy receptor cell-cycle progression 1 (CCPG1) and testis-expressed protein 264 (TEX264) can bind not only LC3/GABARAPs but also FIP200 (An et al. 2019, Smith et al. 2018). During xenophagy, NDP52 binds to FIP200 to induce autophagy (Ravenhill et al. 2019). Some TRIM family proteins, which act as autophagy receptors, also bind ULK1 and Beclin 1 to induce lysophagy and xenophagy (Chauhan et al. 2016). p62 also directly interacts with FIP200 to induce autophagic degradation of p62-ubiquitin condensates (Turco et al. 2019). Thus, some autophagy receptors play active roles in autophagy in both initiation and later sequestration steps.

APPROACHES TO UNDERSTANDING CELLULAR ROLES OF AUTOPHAGY

The identification of core *ATG* genes has enabled three key approaches that have greatly contributed to the current understanding of the cellular roles of autophagy: monitoring of autophagy, reverse genetics, and genome-wide screens of selective cargos and receptors.

Monitoring of Autophagy

Autophagic flux: the rate at which lysosomes degrade autophagic substrates

Using ATG factors as markers for monitoring autophagic structures has enabled investigations of the spatiotemporal dynamics of autophagy. This has mainly been achieved through LC3-based biochemical and microscopic assays, including the use of transgenic mice expressing GFP-LC3 (Kabeya et al. 2000, Mizushima et al. 2004). To quantify the process of autophagic degradation, termed autophagic flux, several methods have been developed (Klionsky et al. 2016, Mizushima et al. 2010). One common method compares autophagic substrates [e.g., LC3 and p62 (also termed

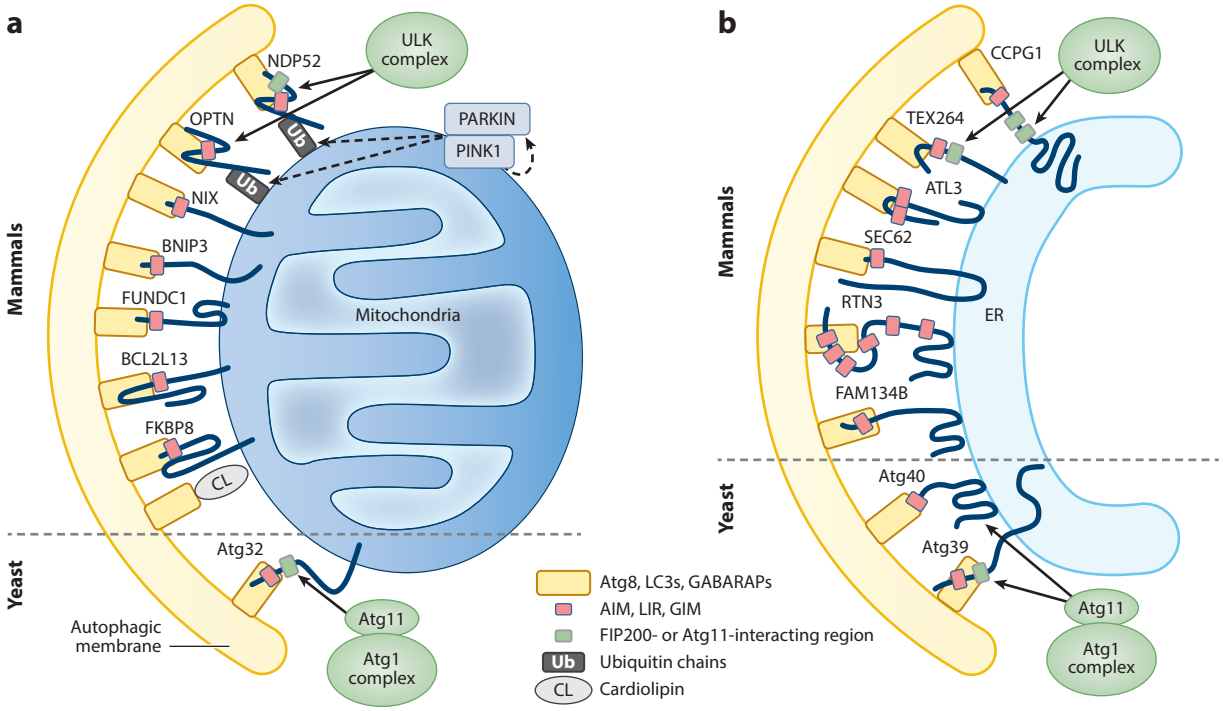

Figure 3

Mechanisms of mitophagy and ER-phagy. (*a*) A model of mitophagy in yeast and mammals. In yeast, Atg32 binds to Atg8 via its Atg8-interacting motif (AIM) as well as to the scaffold protein Atg11 via its Atg11-binding region. Atg11 recruits the autophagy-initiating Atg1 complex (*arrow at bottom*). In mammals, the LIR-containing integral outer mitochondrial proteins (BCL2L13, BNIP3, BNIP3L/NIX, FKBP8, and FUNDC1) and cardiolipin, a phospholipid, can directly bind to LC3/GABARAP family proteins on autophagic membranes. In contrast, during PINK1–PARKIN-mediated mitophagy, upon mitochondrial depolarization, PINK1 recruits and activates PARKIN by phosphorylation. PARKIN ubiquitinates many mitochondrial proteins, and PINK1 phosphorylates ubiquitin on them (*dashed arrows*). The ULK complex can be recruited by two receptors, OPTN and NDP52, to induce mitophagy (*arrows at top*). (*b*) A model of ER-phagy in yeast and mammals. In yeast, Atg39 and Atg40 bind to Atg11, which mediates binding with the Atg1 complex (*arrows at bottom*). In mammals, there are six types of receptors (ATL3, CCPG1, SEC62, RTN3, FAM134B, and TEX264). CCPG1 and TEX264 can recruit FIP200, an ULK complex component, via FIP200-interacting regions (*arrows at top*).

SQSTM1)] between samples with or without lysosomal inhibitors, where differences indicate autophagic degradation; however, the results of this method can be easily affected by substrate expression levels and lysosomal inhibitor side effects. Alternatively, fluorescent probes that do not need to be used with lysosomal inhibitors, such as RFP-GFP-LC3 (Kimura et al. 2007), Keima(-LC3) (Katayama et al. 2011), and GFP-LC3-RFP(-LC3ΔG) (Kaizuka et al. 2016), have also been developed. Nevertheless, there remains a demand for new methods (e.g., biomarkers) that are simpler, more quantitative, more specific to autophagy, and more applicable to organisms, including humans.

Loss-of-Function Analysis of Autophagy

Studies using cells and organisms lacking several core *Atg* genes have greatly expanded our knowledge about the physiological functions of autophagy (Levine et al. 2015, Mizushima & Komatsu 2011). However, autophagic functions cannot be conclusively confirmed from the

results of deleting one *ATG* gene, because the phenotypes caused by the deletion of various core *ATG* genes are not always identical. In mice, for example, deletion of upstream *Atg* genes (e.g., *Becn1* and *Fip200*) is embryonically lethal, while deletion of downstream *Atg* genes (e.g., *Atg5* and *Atg7*) is neonatally lethal (Kuma et al. 2017). Similarly, in mammalian cell cultures, deletion of some upstream genes (*ATG101*, *ATG9A*, and *FIP200*) induces more severe phenotypes than does deletion of the downstream gene *ATG7* on the basis of the degradation of substrates such as NBR1 (Shoemaker et al. 2019).

What causes these phenotypic differences? One explanation could be that downstream *ATG* genes are not essential for autophagy. Indeed, in mammals, autophagosomes can be formed and fused with lysosomes without downstream ATG conjugation systems, although at a reduced rate (Nguyen et al. 2016, Tsuboyama et al. 2016). Thus, the phenotypes of ATG conjugation system–deficient cells and mice can be leaky (Kuma et al. 2017). The contribution of so-called alternative autophagy, in which autophagosomes are purportedly formed from the *trans*-Golgi (Nishida et al. 2009), to the phenotypic differences remains unclear.

Alternatively, some *ATG* genes have been reported to have nonautophagic functions, which have been reviewed in detail elsewhere (Cadwell & Debnath 2018, Solvik & Debnath 2016). For example, Beclin 1, Vps15, and Vps34 play essential roles in endocytic pathways, whereas a subset of ATG factors are involved in LC3-associated phagocytosis, unconventional secretion, or apoptotic pathways (Cadwell & Debnath 2018, Solvik & Debnath 2016). Additionally, a subset of ATG factors and receptors may be involved in ESCRT-III-dependent endosomal microautophagy (Goodwin et al. 2017, Mejlvang et al. 2018). Thus, the phenotypes caused by *ATG* gene deletion should be interpreted with caution, and studies using more than two models lacking different *ATG* genes at different steps (e.g., *FIP200* and *ATG5*) would be required.

Identification of Selective Cargos and Receptors

The third approach is the identification of selective cargos and receptors to reveal the functions of selective autophagy. To identify selective cargos or receptors, three methods, usually combined with mass spectrometry and bioinformatics, have been widely used. The first method is the identification of Atg8/LC3-interacting proteins, which is based on the principle that most cargos and receptors for selective autophagy are recognized by ATG8/LC3s via AIM/LIR/GIMs. Through the use of interaction screens with Atg8/LC3s, several novel autophagy receptors have been identified, such as ER-phagy receptors (Atg39, Atg40, CCPG1, FAM134B, and TEX264) (Chino et al. 2019, Khaminets et al. 2015, Mochida et al. 2015, Smith et al. 2018) and the yeast aggrephagy receptor Cue5 (Lu et al. 2014). The second method is the identification of proteins enriched in autophagosome or lysosome fractions. By using purified autophagosome fractions, selective cargos such as the proteasome (Dengjel et al. 2012) and Fas1/2 (subunits of fatty acid synthetase) (Suzuki et al. 2014) and the ferritinophagy receptor nuclear receptor coactivator 4 (NCOA4) (Mancias et al. 2014) have been identified. The ribophagy receptor nuclear FMR1-interacting protein 1 (NUFIP1) was also identified by comparing the proteomes of purified lysosomes before and after autophagy induction (Wyant et al. 2018). The third method is the identification of proteins accumulated in autophagy-deficient cells. By using autophagy-deficient cells and ubiquitin-affinity proteomics, NCOA4 was also identified (Dowdle et al. 2014). TEX264 was also identified by proteome analysis as one of the proteins that were degraded upon nutrient deprivation in wild-type but not autophagy-deficient cells (An et al. 2019). For large cargos, ultrastructural observation of autophagy-deficient cells has also helped identify selective cargos such as yeast retrotransposons (K. Suzuki et al. 2011) and mammalian ferritin (Kishi-Itakura et al. 2014). In the future, the use of genome-wide CRISPR screens may facilitate the discovery of additional selective autophagy receptors and their regulators.

AUTOPHAGY FOR SELF-NOURISHMENT AND METABOLIC RECYCLING

Self-nourishment and metabolic recycling are major essential functions of autophagy. When nutrients are scarce or growth is necessary, autophagy can supply metabolites for producing macromolecules and energy (Kaur & Debnath 2015). Autophagy also regulates the recycling of metals such as iron (Asano et al. 2011) and zinc (Kawamata et al. 2017). These functions are important for cellular and organismal viability under severe starvation. Here, we discuss recent progress in elucidating these functions, focusing on amino acids, lipids, iron, and nucleosides.

Supply of Amino Acids

Starvation-induced autophagy is required to maintain pools of amino acids in yeast (Onodera & Ohsumi 2005) and neonatal and adult mice (Karsli-Uzunbas et al. 2014, Komatsu et al. 2005, Kuma et al. 2004). Autophagy is tightly regulated by mechanistic target of rapamycin complex 1 (mTORC1) in mammals and TOR in yeast. The ULK complex is phosphorylated and suppressed by mTORC1 under conditions rich in amino acids or growth factors such as insulin (Zachari & Ganley 2017). Energy deprivation (i.e., glucose starvation or increase in the AMP/ATP ratio) can also induce autophagy by activating AMP-activated protein kinase, which in turn activates the ULK1 complex and suppresses mTORC1 (Zachari & Ganley 2017).

Amino acids produced by autophagy during starvation are primarily used for protein synthesis. In particular, the synthesis of mitochondrial antioxidant enzymes and respiratory chain proteins is important for survival in yeast because defective translation of these mitochondrial factors during nitrogen starvation causes mitochondrial dysfunction and cell death in autophagy-deficient yeasts (S.W. Suzuki et al. 2011). In mammals, autophagy is required for translation of newly synthesized proteins and survival during preimplantation development (Tsukamoto et al. 2008). However, the role of autophagy in protein synthesis during starvation remains largely uncharacterized, especially in mammals.

Additionally, autophagy has been proposed to supply amino acids for gluconeogenesis and energy production. Loss of *Atg7* in the liver leads to reduced levels of blood glucose and amino acids after starvation in mice (Ezaki et al. 2011). Likewise, acute and whole-body deletion of *Atg7* in adult mice causes fatal hypoglycemia after 24 h of starvation (Karsli-Uzunbas et al. 2014). Autophagy also maintains energy homeostasis during starvation in neonatal mice (Kuma et al. 2004) and in *Kras*-driven tumor cells (Guo et al. 2016).

Several lines of evidence have demonstrated that cancer cells, which have an increased metabolic demand for energy and macromolecular building blocks to proliferate, show elevated levels of autophagy to recycle nutrients like amino acids; however, autophagy suppresses tumor initiation, likely through intracellular quality control (Amaravadi et al. 2016). Indeed, autophagy suppression can reduce tumor growth in various models and is thus a promising therapeutic target against cancer (Karsli-Uzunbas et al. 2014). Autophagy contributes to tumor growth both cell autonomously (via direct effects on tumor growth) and non–cell autonomously (via effects on tumor growth through other cell types). For example, the metabolism of pancreatic ductal adenocarcinoma cells can be supported using extracellular alanine, which is generated by autophagy in neighboring pancreatic stellate cells upon stimulation by cancer cells (Sousa et al. 2016). Similarly, in a *Drosophila* malignant tumor model, both neighboring epithelial cells and distal tissues supplied amino acids to tumor cells by inducing autophagy (Katheder et al. 2017). Both cell-autonomous autophagy and non-cell-autonomous autophagy support tumor growth in mice (Karsli-Uzunbas et al. 2014, Yang et al. 2018) and can be mediated by controlling the circulating levels of the arginine-degrading enzyme arginase I (Poillet-Perez et al. 2018).

Supply of Lipids

Autophagy also mediates the supply of lipids, especially fatty acids, by degrading lipid storage through different mechanisms (Kaur & Debnath 2015, Martinez-Lopez & Singh 2015). Fatty acids, which are stored in cytosolic lipid droplets (LDs), are important energy sources; they undergo β-oxidation in mitochondria to support ATP production. Although the release of free fatty acids from LDs is largely dependent on LD-associated neutral lipases (Rambold et al. 2015), autophagy could deliver LDs to lysosomes for hydrolysis, which is referred to as lipophagy (Martinez-Lopez & Singh 2015, Singh et al. 2009). Lipophagy can be observed in several cell types (e.g., hepatocytes, macrophages, and hypothalamic neurons) under different conditions (e.g., serum starvation and lipid overload) (Martinez-Lopez & Singh 2015, Rambold et al. 2015, Singh et al. 2009).

Other studies have shown that loss of autophagy decreases LD abundance (Ma et al. 2013, Shibata et al. 2009), suggesting that autophagy is involved in LD formation or lipogenesis. Indeed, during nutrient starvation, autophagy-derived fatty acids, which are likely produced by degradation of endomembranes rather than LDs, induce LD formation (Rambold et al. 2015). Fatty acids derived from LDs are mobilized to mitochondria that may escape from autophagic degradation by forming tubular networks, which can permit mitochondria to maximize energy production (Rambold et al. 2011). Alternatively, autophagy has been reported to be important for lipogenesis and lipolysis by regulating genes involved in de novo lipogenesis, triglyceride synthesis, and fatty acid β-oxidation (Ma et al. 2013). Autophagy was recently shown to regulate lipid metabolism (e.g., β-oxidation) by selective degradation of GIM-containing cargo protein nuclear receptor corepressor 1 (NCoR1), which suppresses peroxisome proliferator–activated receptor-α (PPARα), a master regulator of lipid metabolism that activates the transcription of genes involved in β-oxidation (Iershov et al. 2019, Saito et al. 2019).

Supply of Iron

Iron is important for multiple biological processes as a cofactor for several heme- and non-heme-containing proteins (Arosio et al. 2009). Excess iron is stored in ferritin to prevent the generation of free radicals via the Fenton reaction. Ferritin is a large complex of 24 subunits composed of H (heart/heavy) and L (liver/light) chains in ratios that vary among tissues. In the ferritin cage, Fe(II) is oxidized to Fe(III), which is unavailable for use or generation of reactive oxygen species (ROS). To release iron from ferritin, ferritin is delivered to the lysosome, where Fe(III) is converted into Fe(II) (Arosio et al. 2009).

Ferritin can be degraded by autophagy (Asano et al. 2011), and this process is selective (Dowdle et al. 2014, Mancias et al. 2014). The selective autophagy of ferritin, termed ferritinophagy, is mediated by the autophagy receptor NCOA4, which binds both ferritin and LC3/GABARAPs (Dowdle et al. 2014, Mancias et al. 2014). NCOA4 is required for erythropoiesis and for prevention of excess iron accumulation in the liver and spleen of mice (Bellelli et al. 2016, Mancias et al. 2015). Ferritin can accumulate at the autophagosome formation site independently of any ATG factors (Kishi-Itakura et al. 2014), suggesting the presence of yet-unknown ATG-independent mechanisms for recruiting ferritin to sites of autophagosome formation.

Delivery of ferritin to lysosomes can also be independent of canonical autophagy but is dependent on ESCRT as well as TAX1BP1, FIP200, ATG9A, and VPS34 (Goodwin et al. 2017). Additionally, several autophagy receptors, including NCOA4 and ferritin, are degraded by ESCRT-III-dependent late endosomes/multivesicular bodies during the acute phase of starvation (Mejlvang et al. 2018). Thus, both autophagy and endocytic microautophagy can contribute to iron recycling. Further investigations are required to reveal the relative contributions of these two degradation pathways.

Supply of Nucleosides

Recent studies have suggested that autophagy is critical for supplying nucleosides during nutrient starvation by degrading ribosomal RNAs (Frankel et al. 2017). Ribosomes, one of the most abundant cytoplasmic constituents composed of proteins and RNAs, can be taken up by autophagy during nutrient starvation (Huang et al. 2015, Takeshige et al. 1992). Turnover of ribosomal RNA in vacuoles and lysosomes is mediated by vacuolar/lysosomal T2-type ribonucleases (Frankel et al. 2017, Huang et al. 2015, Liu et al. 2018). In *Caenorhabditis elegans*, autophagic degradation of ribosomal RNA as well as de novo synthesis of pyrimidine nucleotides is important for maintaining nucleotide homeostasis, which is essential for development (Liu et al. 2018).

Ribosomes can be selectively degraded, a process termed ribophagy. In yeast, ribophagy depends on the Ubp3/Bre5 ubiquitin proteases (Kraft et al. 2008). In mammals, NUFIP1 functions as a receptor for starvation-induced ribophagy (Wyant et al. 2018); NUFIP1 associates with ribosomes, translocates from the nucleus to the cytosol, and is sequestered by autophagosomes in a LIR-dependent manner. Levels of all nucleosides in lysosomes increase upon mTORC1 inhibition; however, this increase is lost in cells lacking NUFIP1 or ATG7 (Wyant et al. 2018). The survival defect of cells lacking NUFIP1 can be rescued by supplementation with nucleosides, as shown in ATG7-deficient cancer cells (Guo et al. 2016). Thus, by degrading ribosomes, autophagy can reuse nucleosides for cellular functions that are essential during starvation (Guo et al. 2016, Wyant et al. 2018). In addition to having a role in nucleotide recycling, autophagic degradation of ribosomes is important for supporting yeast growth under zinc depletion by releasing zinc from ribosomal proteins (Kawamata et al. 2017).

AUTOPHAGY FOR CELLULAR HOMEOSTASIS AND ELIMINATION OF UNWANTED MATERIALS

The other essential functions of autophagy are the maintenance of cellular homeostasis and elimination of unwanted materials. Although nonselective autophagy could partially contribute to refreshing the cytoplasm by random sequestration, increasing evidence indicates that selective autophagy specifically eliminates unwanted or surplus materials (Gatica et al. 2018). This autophagic function is critical for both intracellular quality control and intracellular remodeling. For example, the loss of autophagy in mouse neurons and hepatocytes causes neurodegeneration and hepatic disorders, respectively, through the accumulation of polyubiquitinated protein- and p62-containing aggregates and abnormal mitochondria (Hara et al. 2006; Komatsu et al. 2005, 2006). Here, we discuss these functions for various autophagic substrates.

Regulation of the Levels of Specific Proteins

To maintain cellular homeostasis, autophagy needs to regulate the levels of specific proteins such as p62. As discussed above, p62 is degraded by autophagy as an autophagy receptor together with ubiquitinated cargos (Bjorkoy et al. 2005, Komatsu et al. 2007, Pankiv et al. 2007). In addition to having a role in autophagy, p62 has multiple functions as a hub protein in several signaling pathways involved in cell survival, growth, and death [e.g., NF-κB, mTOR, caspase 8, and nuclear factor erythroid 2–related factor 2 (NRF2)] (Sánchez-Martín & Komatsu 2018). Thus, p62 can be not only a receptor but also a cargo of autophagy. Indeed, when autophagy is suppressed, p62 highly accumulates and activates NRF2, a transcription factor that induces the expression of antioxidant, anti-inflammatory, and detoxifying proteins (Sánchez-Martín & Komatsu 2018). Additionally, p62 binds to Kelch-like ECH-associated protein 1 (KEAP1), an adaptor of the Cul3/ubiquitin E3 ligase complex that constitutively degrades NRF2 under quiescent conditions, and inhibits its

E3 activity, thereby stabilizing and activating NRF2. The binding of p62 to KEAP1 is enhanced by p62 phosphorylation (Ichimura et al. 2013). The persistent hyperactivation of NRF2 caused by autophagy deficiency can promote tumor growth by metabolic reprogramming (Saito et al. 2016). Accordingly, autophagy-deficient mice develop benign liver tumors with p62- and NRF2-dependent growth (Komatsu et al. 2007, Ni et al. 2014, Takamura et al. 2011), but the activation of other pathways (e.g., NF-κB, mTORC1, and c-Myc) (Sánchez-Martín & Komatsu 2018) and other factors (e.g., defects in mitochondria) is also involved in this process. Thus, the tight regulation of p62 levels as an autophagy cargo is critical for maintaining homeostasis of various signaling pathways and suppressing tumor growth.

p62 forms condensates that contain p62 and polyubiquitinated proteins, in which p62 organizes flexible polymers (probably filamentous) through the N-terminal Phox and Bem1 domains and interacts with ubiquitinated proteins through the C-terminal ubiquitin-associated (UBA) domain (Sánchez-Martín & Komatsu 2018). Phosphorylation of the UBA domain by certain kinases [e.g., casein kinase 2 and TANK-binding kinase 1 (TBK1)] enhances the p62 binding affinity of ubiquitinated proteins (Sánchez-Martín & Komatsu 2018). Recent studies have shown that p62 undergoes liquid-liquid phase separation, which is enhanced by phosphorylation of the UBA domain (Sun et al. 2018, Zaffagnini et al. 2018). p62 associates with FIP200 to recruit the ULK1 complex to p62-ubiquitin condensates (Turco et al. 2019). Phase separation is also implicated in the degradation of germline P granules by using the SEPA-1 receptor during *C. elegans* embryogenesis (Zhang et al. 2018). An interesting question is whether phase separation is generally involved in autophagic degradation of aggregate-prone proteins.

Selective Degradation of Mitochondria

Selective autophagic degradation of unnecessary or damaged mitochondria, termed mitophagy, is important for maintaining mitochondrial homeostasis (Palikaras et al. 2018, Pickles et al. 2018) (**Figure 3**). Several types of mitophagy occur throughout cellular stress, differentiation, and development.

One of the most extensively studied types of mitophagy is PINK1–PARKIN-mediated mitophagy, which occurs in metazoans and is driven by two proteins mutated in early-onset Parkinson's disease: the E3 ubiquitin ligase PARKIN/PARK2 and PINK1/PARK6 (Pickles et al. 2018). When mitochondria are depolarized, PINK1 is stabilized and phosphorylates preexisting ubiquitin on the outer mitochondrial membrane to recruit, phosphorylate, and activate PARKIN, which amplifies the amount of ubiquitin on mitochondria (Kane et al. 2014, Kazlauskaite et al. 2014, Koyano et al. 2014). Then, autophagy receptors such as NDP52 and OPTN bind these ubiquitinated proteins to recruit ATG factors to form autophagosomes (Lazarou et al. 2015, Nguyen et al. 2016, Vargas et al. 2019). TBK1 modulates the phosphorylation status of OPTN, NDP52, and p62 to enhance their binding affinity to ubiquitin chains (Richter et al. 2016). PARKIN also mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane (Chan et al. 2011, Yoshii et al. 2011). The LIR-containing inner mitochondrial protein PHB2 (prohibitin 2) can also act as a receptor for PARKIN-mediated mitophagy (Wei et al. 2017).

The physiological function of PINK1–PARKIN-mediated mitophagy remains unclear. In *Drosophila*, loss of PINK1 or PARKIN leads to mitochondrial defects and muscle degeneration, but basal mitophagy can still occur in most tissues (Lee et al. 2018). Similarly, basal mitophagy normally occurs in mice lacking PINK1 (McWilliams et al. 2018). However, PINK1 becomes essential for mitophagy induction in heart muscles during mitochondrial stress caused by exhaustive exercise (Sliter et al. 2018). Furthermore, loss of PARKIN can elicit motor deficits and degeneration of dopaminergic substantia nigral neurons in a mouse model that accumulates mutations in

mitochondrial DNA (Pickrell et al. 2015), and these phenotypes can be rescued by loss of STING, a central regulator of the proinflammatory response to cytosolic DNA (Sliter et al. 2018). Thus, PINK1 and PARKIN can suppress innate immune responses that may contribute to Parkinson's disease.

Stress-induced mitophagy also occurs upon starvation, hypoxia, and iron depletion. These types of mitophagy are mediated by several integral mitochondrial outer membrane receptors that have AIM/LIR/GIMs. In yeast, mitophagy occurs under post-log-phase growth in nonfermentable carbon sources using Atg32 as a receptor. Atg32 binds Atg8 and Atg11 (Kanki et al. 2009, Okamoto et al. 2009). In mammals, there are no obvious homologs of Atg32, but there are several functional counterparts of Atg32, including BCL2L13, BNIP3, BNIP3L/NIX, FKBP8, and FUNDC1 (Bhujabal et al. 2017, Pickles et al. 2018). Among them, BNIP3, FUNDC1, and NIX drive hypoxia-induced mitophagy (Pickles et al. 2018). For example, under hypoxic conditions, FUNDC1 is dephosphorylated, thus enhancing interactions with LC3 (Liu et al. 2012). Mitophagy upon iron depletion occurs in a PINK1–PARKIN-independent manner (Allen et al. 2013). In neurons under mitochondrial stress, cardiolipin, a phospholipid, is externalized from the inner mitochondrial membrane to the outer mitochondrial membrane, allowing cardiolipin to interact with LC3 to induce mitophagy (Chu et al. 2013).

Programmed degradation of mitochondria has been reported to occur during cellular differentiation and development. Mitophagy has been implicated in the programmed elimination of mitochondria during reticulocyte differentiation. This role is mediated by NIX, which is upregulated during reticulocyte differentiation. Mice lacking NIX develop anemia, with an increase in the number of reticulocytes in which autophagy fails to degrade mitochondria (Novak et al. 2010, Schweers et al. 2007). Because ATG5 and ATG7 are unnecessary for degrading organelles in reticulocytes (Matsui et al. 2006, Nishida et al. 2009), other autophagic or nonautophagic mechanisms of organelle degradation may exist.

Another example of programmed degradation of mitochondria is sperm mitophagy. In some animals, autophagy has been implicated in the elimination of paternal mitochondria and their mitochondrial DNA in fertilized eggs. In *C. elegans*, fertilization-triggered autophagy is required for this process (Al Rawi et al. 2011, Sato & Sato 2011) by using the ALLO-1 receptor, which binds to both Atg8 homologs and ubiquitinated proteins of sperm mitochondria, and the kinase IKKE-1 (Sato et al. 2018). In *Drosophila*, the involvement of both endocytic and autophagic pathways in this process is p62 dependent but not PARKIN dependent (Politi et al. 2014). In mammals, evidence suggests that autophagic degradation of paternal mitochondria depends on p62, VCP/p97 (Song et al. 2016), PINK1, and two E3 ubiquitin ligases (PARKIN and MUL1) (Rojansky et al. 2016). Thus, the ubiquitin-dependent mechanism is likely responsible for sperm mitophagy. However, more studies are required to reveal whether mitophagy is a central mechanism of eliminating paternal mitochondria from embryos. If paternal mitochondria are already undergoing dysfunction or elimination [e.g., fertilization-induced mitochondrial DNA degradation by mitochondrial endonuclease G in *C. elegans* (Zhou et al. 2016)], autophagy may have only a supportive role in the process.

Selective Degradation of the ER

Selective autophagic elimination of ER fragments is termed ER-phagy (or reticulophagy) (**Figure 3**). Two AIM-containing ER-phagy receptors, Atg39 and Atg40, have been identified in yeast (Mochida et al. 2015). Atg39 is enriched in the perinuclear ER (or the nuclear envelope) and induces autophagic sequestration of a portion of the perinuclear ER and nucleus, while Atg40, which has a reticulon-homology domain that promotes curvature of the ER membrane, localizes

to and sequesters the cortical and cytoplasmic ER into autophagosomes. Additionally, Atg39 is required for cell survival under nitrogen deprivation.

In mammals, six LIR-containing integral ER membrane ER-phagy receptors have been identified: ATLASTIN-3 (ATL3) (Chen et al. 2019), CCPG1 (Smith et al. 2018), FAM134B (Khaminets et al. 2015), RTN3 (Grumati et al. 2017), SEC62 (Fumagalli et al. 2016), and TEX264 (An et al. 2019, Chino et al. 2019). FAM134B and the longest variant of RTN3 have a reticulon-homology domain and regulate autophagic degradation of ER sheets and tubules, respectively, during nutrient starvation (Grumati et al. 2017, Khaminets et al. 2015). FAM134B is mutated in severe sensory neuropathy, and loss of FAM134B in mice leads to similar sensory neuropathy with an ER expansion (Khaminets et al. 2015). SEC62, a translocon component, drives autophagic degradation of excess ER membranes and proteins during the recovery phase of ER stress (Fumagalli et al. 2016). CCPG1, which is induced during ER stress, mediates autophagic elimination of peripheral ER (Smith et al. 2018). CCPG1 has two FIP200-interacting domains that recruit FIP200 to initiate autophagy. Mice lacking CCPG1 exhibit defective ER luminal proteostasis in pancreatic acinar cells (Smith et al. 2018). ATL3, which is mutated in hereditary sensory and autonomic neuropathy type I, is a tubular ER-phagy receptor (Chen et al. 2019). TEX264 interacts with LC3/GABARAP family proteins more efficiently and is expressed more ubiquitously than other ER-phagy receptors (An et al. 2019, Chino et al. 2019). A long, intrinsically disordered region of TEX264 is required for its ER-phagy receptor function to bridge the gap between the ER and autophagic membrane (Chino et al. 2019). TEX264 binds to FIP200 as well as to components of the class III PtdIns3K complex to initiate autophagy (An et al. 2019). In addition to these integral ER receptors, p62 plays a role in autophagic removal of excess ER membranes and proteins in mouse liver after withdrawal of phenobarbital-like xenobiotics (Yang et al. 2016).

Selective Degradation of Peroxisomes

Degradation of excess or damaged peroxisomes is important for maintaining peroxisome homeostasis. Pexophagy, the selective autophagy of peroxisomes, plays important roles in this process, although micropexophagy is also involved in yeast (Farré & Subramani 2016). For example, in yeast such as methylotrophic Pp, when cells grow on methanol as a carbon source, they induce peroxisome proliferation to metabolize methanol; however, when the carbon source is switched from methanol to ethanol or nitrogen-depleted starvation medium, peroxisomes are no longer required and are degraded by pexophagy (Farré et al. 2008). The AIM-containing receptors Atg30 in Pp and Atg36 in *Saccharomyces cerevisiae* are required for pexophagy; these receptors interact with peroxisomal protein complexes (Pex3, PpPex14, Atg37) as well as Atg11 to induce pexophagy (Farré & Subramani 2016, Farré et al. 2008, Motley et al. 2012, Nazarko et al. 2014).

Mammals lack obvious Atg30 or Atg36 homologs. Instead, p62 or NBR1 functions as a pexophagy receptor that binds ubiquitinated proteins on peroxisomes (Deosaran et al. 2013, Kim et al. 2008, Yamashita et al. 2014). PEX3 induces ubiquitination of peroxisomal proteins to induce pexophagy (Yamashita et al. 2014). PEX2, a peroxisomal E3 ubiquitin ligase, is induced during nutrient starvation and ubiquitinates peroxisomal membrane proteins such as PEX5 and PMP70 (Sargent et al. 2016). ROS, which is a by-product of fatty acid β-oxidation in peroxisomes, can induce pexophagy by recruiting ataxia-telangiectasia mutated (ATM), a kinase that can detect ROS levels, to peroxisomes (Zhang et al. 2015). Nevertheless, the physiological functions of pexophagy and its induction mechanisms remain largely unknown in mammals.

Selective Degradation of Lysosomes

Damaged lysosomes should be eliminated from the cytoplasm because lysosomal hydrolases released into the cytoplasm upon lysosomal rupture can induce lysosomal cell death (Papadopoulos

& Meyer 2017). Autophagy can sequester and degrade damaged lysosomes selectively, a process termed lysophagy (Hung et al. 2013, Maejima et al. 2013). Lysophagy can be induced by several lysosomotropic agents (e.g., L-leucyl-L-leucine methyl ester), silica, monosodium urate, light-induced damage, invading microbes, and endocytosed tau fibrils (Papadopoulos & Meyer 2017). Under conditions of lysosomal damage, autophagy deficiency leads to the suppression of lysosomal biogenesis and worsening of acute kidney injury in mice (Maejima et al. 2013).

The mechanisms of lysophagy were recently studied in detail. After lysosomal rupture, cytosolic galectins, such as galetin-3 and galectin-8, bind to β-galactoside-containing glycoproteins exposed on the damaged lysosomes (Maejima et al. 2013, Thurston et al. 2012). Because these β-galactosides are present only on the cell surface and in the lumen of endosomes (and endomembranes), endosomal rupture allows these galectins to access the luminal glycoproteins. The ruptured lysosomes are ubiquitinated and recruit p62 and VCP/p97, both of which are required for lysophagy (Papadopoulos et al. 2017), and the autophagic machinery (Maejima et al. 2013, Thurston et al. 2012). TRIM16, a RING-type E3 ubiquitin ligase, recognizes lysosomal damage in cooperation with galectin-3 and ULK1 and ubiquitinates certain lysosomal proteins (Chauhan et al. 2016). A recent study also showed that ubiquitination of exposed glycoproteins requires the E3 ubiquitin ligase SCF^{FBXO27} [SKP1–CUL1–F-box protein 27 (FBXO27)] (Yoshida et al. 2017). SCF^{FBXO27} ubiquitinates lysosomal glycoproteins (e.g., LAMP2) in damaged lysosomes to regulate autophagic machinery recruitment. The recognition of damaged lysosomes by FBXO27 is partly mediated by its binding affinity with *N*-glycoproteins, ensuring the specific recognition of the luminal face of a ruptured membrane.

Selective Degradation of Intracellular Bacteria

Selective autophagy is also important for cell-autonomous defense against microbes, including intracellular bacteria (e.g., *Salmonella typhimurium*, group A *Streptococcus*, and *Mycobacterium tuberculosis*), through a process termed xenophagy (Deretic et al. 2013, Herhaus & Dikic 2018, Randow & Youle 2014). *S. typhimurium* is among the best-characterized bacterial targets of xenophagy. *Salmonella* invades epithelial cells and replicates within host-derived membrane vacuoles termed *Salmonella*-containing vacuoles. However, once vacuolar membranes are ruptured, bacteria and damaged vacuoles can be ubiquitinated and captured by autophagy (Fujita et al. 2013, Herhaus & Dikic 2018). Galectin-8 recognizes glycoproteins in damaged vacuoles and interacts with and recruits NDP52, followed by further ubiquitin-dependent recruitment of NDP52 (Thurston et al. 2009, 2012). NDP52 binds to FIP200 to recruit the ULK complex (Ravenhill et al. 2019). NDP52 additionally binds to LC3C by a noncanonical LIR motif (von Muhlinen et al. 2012). OPTN, p62, and TAX1BP1 are also involved in xenophagy of *Salmonella* (Thurston et al. 2009, Tumbarello et al. 2015, Wild et al. 2011, Zheng et al. 2009). Ubiquitination of *Salmonella* is mediated by E3 ubiquitin ligases of host cells (Herhaus & Dikic 2018). For example, linear ubiquitin chain assembly complex (LUBAC), a multimeric E3 ubiquitin ligase composed of HOIP, HOIL-1, and SHARPIN, generates linear polyubiquitin patches in the preexisting ubiquitin coat of bacterial proteins (Noad et al. 2017). The LUBAC-synthesized polyubiquitin then recruits OPTN and NEMO to induce xenophagy and local NF-κB activation, respectively (Noad et al. 2017). Thus, the polyubiquitin on bacteria also serves as a signaling platform to regulate host cell defense mechanisms.

CLOSING REMARKS AND FUTURE ISSUES

This review discusses diverse cellular functions of autophagy, including selective autophagy, as well as its roles in metabolic adaptation and cellular homeostasis. However, several questions and challenges remain unaddressed. For example, the role of autophagy during nutrient starvation is

still unclear; the exact roles of autophagic degradation products, including amino acids and lipids, are not fully understood. Although many selective autophagy cargos and receptors have been identified in the past decade, the physiological function of their degradation is unclear. It will be important to know when and where each type of selective autophagy is induced across physiological and pathological conditions by using reporters specific to each type of selective autophagy. Regarding the multifunctionality of many ATG factors, we should carefully distinguish between their autophagy-dependent and autophagy-independent functions. To this end, understanding of the molecular mechanisms of each autophagy-independent function is required. Finally, the development of autophagy-specific monitoring methods and modulators will be vital for advances in basic research and for the development of therapeutic applications.

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