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Mechanisms of Selective Autophagy

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Abstract

Selective autophagy is the lysosomal degradation of specific intracellular components sequestered into autophagosomes, late endosomes, or lysosomes through the activity of selective autophagy receptors (SARs). SARs interact with autophagy-related (ATG)8 family proteins via sequence motifs called LC3-interacting region (LIR) motifs in vertebrates and Atg8-interacting motifs (AIMs) in yeast and plants. SARs can be divided into two broad groups: soluble or membrane bound. Cargo or substrate selection may be independent or dependent of ubiquitin labeling of the cargo. In this review, we discuss mechanisms of mammalian selective autophagy with a focus on the unifying principles employed in substrate recognition, interaction with the forming autophagosome via LIR-ATG8 interactions, and the recruitment of core autophagy components for efficient autophagosome formation on the substrate.

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INTRODUCTION

Autophagy is a set of evolutionarily conserved lysosomal degradation pathways for cytoplasmic constituents. Autophagy serves important roles in cellular and organismal physiology, including adaptation to nutrient starvation and organelle homeostasis with protective roles upon microbial infections and in innate immunity, inflammation, and counteracting aging. The relationship between autophagy and human diseases including neurodegenerative and cardiovascular diseases, diabetes, and cancer is actively being studied (Dikic & Elazar 2018, Levine & Kroemer 2019). The term autophagy is often used synonymously with macroautophagy. However, there are also microautophagy and chaperone-mediated autophagy pathways. In microautophagy, cytoplasmic contents are taken up directly by invaginations of the limiting membrane of lysosomes or late endosomes (Schuck 2020). Chaperone-mediated autophagy involves the recognition of misfolded proteins exposing KFERQ(-like) motifs by cytosolic HSC70 and direct lysosomal uptake of single polypeptides via LAMP2A (Kaushik & Cuervo 2018). In macroautophagy (hereafter autophagy), evolutionarily conserved autophagy-related (ATG) protein complexes orchestrate the formation of the double-membrane-bound autophagosome. The autophagosome sequesters cytoplasmic components that are subsequently degraded upon fusion with lysosomes (or vacuoles in fungi and plants) (Ohsumi 2014). A few nuclear proteins are also known to be exported to the cytoplasm and degraded by autophagy under certain circumstances (Dou et al. 2015, Xu et al. 2020). Autophagy may act as a nonselective bulk degradation process but may also be highly selective. In selective autophagy, a set of soluble or membrane-bound cargo receptors recognize cargo and mediate autophagosome formation. The interactions between the cargo-bound receptors and the

ATG8 family proteins anchored in the membrane of the forming autophagosome and the recruitment of core autophagy machinery components are crucial for selective sequestration into autophagosomes (Johansen & Lamark 2020, Kirkin & Rogov 2019). The mechanisms involved in selective autophagy are the focus of this review.

THE FORMATION OF AUTOPHAGOSOMES

Upon initiation of autophagosome formation, a membrane structure known as the phagophore (or isolation membrane) forms. The originally flat phagophore expands, curves, engulfs part of the cytoplasm (cargo), and closes in on itself to form the autophagosome. Upon fusion with lysosomes, the inner membrane and the contents of the autophagosomes are degraded by lysosomal hydrolases, releasing amino acids, lipids, and carbohydrates to enable them to engage in recycling processes (Shen & Mizushima 2014). In mammals, autophagosomes may also fuse with late endosomes to form amphisomes that subsequently fuse with lysosomes (Seglen et al. 1991). Autophagosome formation is initiated at ER (endoplasmic reticulum)-proximal phagophore-assembly sites (PASs). In mammals, autophagosomes form in quantity throughout the cytoplasm upon amino acid starvation at parts of the ER enriched in phosphatidylinositol-3-phosphate (PI3P), emerging from a ringlike structure named the omegasome that is marked by the PI3P-binding protein DFCP1 /ZFYVE1 (Axe et al. 2008). In yeast, autophagosomes form at a single PAS that is in contact with both the ER and the vacuole (Hollenstein & Kraft 2020, Melia et al. 2020, Nakatogawa 2020).

The core autophagy machinery consists of about 20 ATG proteins conserved from yeast to human that can be divided into six functional groups (Mizushima et al. 2011, Nakatogawa 2020). These groups are the Atg1/ULK protein kinase complex, Atg9/ATG9-containing vesicles, the phosphatidylinositol 3-kinase class III complex 1 (PI3KC3-C1), Atg2-Atg18/ATG2A- or B-WIPI1–4 (WD-repeat protein interacting with phosphoinositides) complex, the Atg12-5:16/ATG12-5:16L1 complex, and the Atg8/ATG8 protein–lipid conjugation system including the Atg4/ATG4A–D proteases. The two kinase complexes and the Atg9-containing vesicles are involved in initiation, whereas the others are involved in the expansion of phagophores. The ULK complex is made up of four components (ULK1 or 2, ATG13, FIP200/RB1CC1, and ATG101) in mammals and five components (Atg1, Atg13, Atg17, Atg29, and Atg31) in yeast. Both FIP200 and ULK1 bind to ER-integral VAPA and VAPB proteins via their FFAT (two phenylalanines in an acidic tract) motifs (Zhao et al. 2018). FIP200 also interacts with phosphatidylinositol synthase (PIS)-enriched ER subdomains. Thus, the ULK1/2-FIP200 autophagy-initiation complex, together with the PIS-enriched ER subdomain and ATG9A vesicles, initiates autophagosome formation (Nishimura et al. 2017). ATG9A vesicles transport PI4KIIIβ to the ER, promoting PI4P formation at the initiation site for recruitment of the ULK complex via ATG13 binding to PI4P (Judith et al. 2019). In yeast, the single PAS is a membraneless organelle formed by liquid–liquid phase separation (LLPS) with Atg13 and its phosphorylation state playing a crucial role in PAS formation (Fujioka et al. 2020). In vitro reconstitution studies (Sawa-Makarska et al. 2020) demonstrate that Atg9 vesicles can act as seeds in phagophore formation by establishing membrane contact sites to initiate lipid transfer from, for example, the ER. ATG9A-mediated lipid scrambling plays a crucial role in lipid transport from the ER to enable phagophore expansion (Maeda et al. 2020, Matoba et al. 2020). The PI3KC3-C1 comprising the lipid kinase Vps34/ PI3KC3, the regulatory subunit Vps15/PI3KR4, Vps30/Beclin-1, and the autophagy-specific subunit Atg14/ATG14L gives rise to an autophagy-specific pool of PI3P that recruits the PI3P-binding WIPI1–4 proteins and DFCP1. A fifth subunit called Atg38/NRBF2 facilitates phagophore formation and induces dimerization of the PI3KC3-C1 complex. PI3KC3-C1

is phosphorylated and activated by ULK1 (Nishimura & Tooze 2020). PI3P is bound by the PROPPIN (β-propellers that bind polyphosphoinositides) proteins Atg18 and Atg21 in yeast and WIPI1–4 proteins in mammals. In the Atg2-Atg18/ATG2A- or B-WIPI complexes, the rod-shaped Atg2/ATG2A or B act to tether the ER membrane to the phagophore and mediate lipid transfer for phagophore expansion. The N-terminal end of ATG2 binds to the ER and the C-terminal end to the PAS (Nishimura & Tooze 2020). In yeast, Atg9 vesicles act as acceptors for lipid transfer by Atg2 and contribute to phagophore expansion (Gómez-Sánchez et al. 2018, Sawa-Makarska et al. 2020). To mediate phagophore expansion and closure to mature autophagosomes, two ATG conjugation systems are needed to covalently attach ATG8 proteins to phosphatidylethanolamine (PE) on autophagic membranes. First, the E1 and E2 enzymes ATG7 and ATG10 are involved in conjugating the ubiquitin-like protein Atg12/ATG12 to a Lys residue in Atg5/ATG5. The Atg12-Atg5:Atg16/ATG12-ATG5:ATG16L1 complex forms and acts as an E3 to stimulate conjugation of PE to a free C-terminal Gly residue in Atg8/ATG8 proteins exposed by Atg4/ATG4B cleavage. ATG16L1 interacts with membranes and with WIPI2 to place the PE conjugation of ATG8s on the phagophore. Atg7/ATG7 and Atg3/ATG3 act as E1 and E2 enzymes in the PE conjugation (Mizushima et al. 2011, Nakatogawa 2020, Nishimura & Tooze 2020). The two multispanning ER membrane proteins VMP1 (TMEM49) and TMEM41B form a complex and are also required for autophagosome formation (Nishimura & Tooze 2020). In the nascent autophagosome, the two double membrane edges form a pore that is closed by ESCRT-III mediating the membrane scission events required to seal the autophagosome (Takahashi et al. 2018, Zhen et al. 2019).

ATG8 FAMILY PROTEINS AND LIR INTERACTIONS

ATG8 proteins are small ubiquitin-like proteins with two extra N-terminal α-helices (Johansen & Lamark 2020). Yeast has a single Atg8, while vertebrates have six ATG8 proteins grouped into the microtubule-associated protein 1 light chain 3 (MAP1-LC3) and GABA type A receptor–associated protein (GABARAP) subfamilies. Human ATG8 proteins are encoded by seven genes expressing LC3A (two alternatively spliced isoforms with different N-termini), LC3B, LC3B2 (with only one amino acid different from LC3B), LC3C, GABARAP, GABARAPL1 (GABARAP-like 1), and GABARAPL2 (Shpilka et al. 2011). Lipidated ATG8s act as adaptors to recruit proteins containing the short sequence motif LC3-interacting region (LIR), often called ATG8-interacting motif (AIM) in yeast and plants, to the phagophore. A canonical LIR consists of a four-residue core motif $[W/F/Y]_0$-X_1-X_2-$[L/V/I]_3$ flanked by N- and C-terminal sequences contributing to binding. The conserved residues in positions 0 and 3 fit into two hydrophobic pockets (HP1 and HP2) in the LIR docking sites (LDSs) of the ATG8s. The LDS has a basic surface surrounding the two pockets, and LIR sequences are characterized by a high frequency of acidic residues (E or D) in positions 1 and 2 and/or adjacent to the core motif. Many LIR motifs also contain residues that can be phosphorylated to increase the ATG8 interaction (Johansen & Lamark 2020). In addition to the LIR-LDS interaction, ATG8s can also use other interaction surfaces [reviewed in Johansen & Lamark (2020) and Wesch et al. (2020)].

Lipidated ATG8s help to scaffold core autophagy components on the phagophore membrane via LIR-LDS interactions for the efficient expansion of the phagophore through a positive feedback loop to amplify autophagosome formation. Both human ULK1/2 and ATG13 harbor avid binding LIR motifs (Alemu et al. 2012, Wirth et al. 2019), as does yeast Atg1 (Kraft et al. 2012, Nakatogawa et al. 2012). In the PI3KC3-C1 complex, human ATG14, Beclin-1, and VPS34 bind ATG8s via LIR motifs (Birgisdottir et al. 2019). Human ATG2A/B contain a LIR motif in close proximity to the ATG2-WIPI4 interaction site that interacts with GABARAP and GABARAPL1.

This interaction is crucial for phagophore expansion and pore closure (Bozic et al. 2020).The LIR-containing core ATG proteins bind preferentially to GABARAP and GABARAPL1. Consistent with the role of ATG8s in phagophore expansion, yeast lacking Atg8 have small autophagosomes (Xie et al. 2008). ATG4B and yeast Atg4 interact with ATG8s/Atg8 through both catalytic binding sites and LIR motifs (Abreu et al. 2017, Skytte Rasmussen et al. 2017). In human cells lacking all ATG8s, autophagosomes are formed very inefficiently and fusion with lysosomes is impaired. GABARAP family proteins can compensate for the loss of all ATG8s, while LC3 family members cannot (Nguyen et al. 2016, Vaites et al. 2018). Surprisingly, the ATG conjugation system is required for the degradation of the inner autophagosomal membrane (Tsuboyama et al. 2016). In addition to roles in autophagosome–lysosome fusion, ATG8 proteins are important in the trafficking of autophagosomes [reviewed in Kriegenburg et al. (2018)].

SELECTIVE AUTOPHAGY RECEPTORS

Selective autophagy is distinguished from bulk autophagy by the use of selective autophagy receptors (SARs) (Johansen & Lamark 2011). Two unifying criteria for a SAR are that it is attached to a cargo and uses a LIR motif to interact with ATG8s on the inner membrane surface of the phagophore. The cargo is recognized, attached to the phagophore, and ultimately degraded by autophagy. This process requires large amounts of ATG8s. The present concept of selective autophagy was initiated by the discovery of p62/SQSTM1 (Sequestosome-1) as a selective autophagy substrate and a SAR responsible for the degradation of ubiquitinated cargos by autophagy (Bjørkøy et al. 2005, Pankiv et al. 2007). Since then, an increasing number of SARs have been identified, both in mammals and other eukaryotes (**Table 1**). They are associated with all types of cargos and have different ways of interacting with those cargos (Johansen & Lamark 2020; Kirkin & Rogov 2019). SARs are commonly divided into soluble and membrane-associated forms (**Table 1**). Soluble SARs can be sorted into ubiquitin-dependent and -independent SARs.

In addition to cargo recognition and efficient binding to ATG8s, a soluble SAR must link to the core autophagy apparatus and form a structure that can be encapsulated by a phagophore. Efficient docking of the SAR–cargo complex to the phagophore depends on multivalent LIR interactions. This is achieved by oligomerization of the SAR, as seen for p62 (Jakobi et al. 2020, Klionsky et al. 2016, Zaffagnini et al. 2018), or the SAR may contain multiple LIRs. This was first described for yeast Atg19 (Sawa-Makarska et al. 2014) and taken to the extreme by the ER-phagy receptor RTN3L containing six LIRs (Grumati et al. 2017).

UBIQUITIN-DEPENDENT SOLUBLE SELECTIVE AUTOPHAGY RECEPTORS

The most-studied soluble SARs in mammals are the Sequestosome-1-like receptors (SLRs) p62, NBR1, NDP52, TAX1BP1, and OPTN (Johansen & Lamark 2020, Kirkin & Rogov 2019). SLRs are characterized by containing oligomerization domains (PB1- or coiled-coil domains), ATG8-binding LIR domains, and ubiquitin-binding domains. Substrates targeted by SLRs are in most cases ubiquitinated. SLRs are widely expressed, multifunctional proteins recruited to a wide variety of cargos including specific protein complexes, protein aggregates, organelles, and intracellular bacteria (**Table 1**). This distinguishes them from ubiquitin-independent SARs that usually have only a single type of cargo (see section titled Ubiquitin-Independent Soluble Selective Autophagy Receptors). Yeast lack SLRs, but a pathway for the clearance of ubiquitinated protein aggregates mediated by the ubiquitin-binding SAR Cue5 has been identified in yeast. Tollip was suggested as a homologous SAR in mammals (Lu et al. 2014).

Table 1 Selective autophagy receptors

Pathway	Substrate	Autophagy receptors	Reference(s)
Aggrephagy	Protein aggregate	p62, NBR1, OPTN, TAX1BP1, yeast Cue5	Bjørkøy et al. 2005, Kirkin et al. 2009, Korac et al. 2013, Lu et al. 2014, Pankiv et al. 2007, Sarraf et al. 2020
Cvt pathway (yeast)	Ams1, prApe1	Yeast Atg19, Atg34	Lynch-Day & Klionsky 2010, Nakatogawa et al. 2009
Ub-dependent mitophagy	Mitochondria	NDP52, OPTN, p62, TAX1BP1, AMBRA1	Heo et al. 2015, Lazarou et al. 2015, Strappazzon et al. 2015, Van Humbeeck et al. 2011, Wong & Holzbaur 2014
Ub-independent mitophagy	Mitochondria	NIX, BNIP3, FUNDC1, Bcl2L13, FKBP8, PHB2, NLRX1, AMBRA1, cardiolipin, ceramide, yeast Atg32	Bhujabal et al. 2017, Chu et al. 2013, Hanna et al. 2012, Liu et al. 2012, Murakawa et al. 2015, Novak et al. 2010, Sentelle et al. 2012, Strappazzon et al. 2015, Wei et al. 2017, Zhang et al. 2019
Ub-dependent pexophagy	Peroxisome	NBR1, p62	Deosaran et al. 2013
Lysophagy	Lysosome	p62, TRIM16	Chauhan et al. 2016, Koerver et al. 2019
Zymophagy	Secretory granule	p62	Grasso et al. 2011
ER-phagy	ER	FAM134B, SEC62, RTN3, CCPG1, ATL3, TEX264, yeast Atg39 and Atg40	An et al. 2019, Chen et al. 2019, Chino et al. 2019, Fumagalli et al. 2016, Grumati et al. 2017, Khaminets et al. 2015, Mochida et al. 2015, Smith et al. 2018
Ferritinophagy	Ferritin	NCO4A	Dowdle et al. 2014, Mancias et al. 2014
Glycophagy	Glycogen	Stbd1	Jiang et al. 2011
Nuclear lamina autophagy	Nuclear lamina	Lamin B1	Dou et al. 2015
Xenophagy	Bacteria	NDP52, p62, OPTN, TAX1BP1	Thurston et al. 2009, Tumbarello et al. 2015, Wild et al. 2011, Zheng et al. 2009
Virophagy	Viral capsids	TRIM5α, p62	Mandell et al. 2014, Orvedahl et al. 2010
Ribophagy	Ribosomes	NUFIP1	Wyant et al. 2018
Midbody autophagy	Midbody rings	p62, NBR1, TRIM17	Isakson et al. 2013, Mandell et al. 2016, Pohl & Jentsch 2009
Clockophagy	Circadian clock protein ARNTL	p62	Yang et al. 2019

Abbreviations: Atg, autophagy-related protein; Cvt, cytoplasm-to-vacuole-targeting; ER, endoplasmic reticulum; Ub, ubiquitin.

Several members of mammalian TRIM (tripartite motif) family E3 ligases bind to ATG8s and act as SARs, forming TRIMosomes containing the core autophagy components ULK1 and/or Beclin-1 and often also the archetypical SAR p62 (Chauhan et al. 2016; Kimura et al. 2015; Mandell et al. 2014, 2016). TRIMosomes act as platforms to focus selective autophagy on highly specific targets (Kimura et al. 2015). TRIM5α is a SAR for viral capsid proteins (Mandell et al. 2014). TRIM20 targets the inflammasome components, including NLRP3, NLRP1, and

pro-caspase 1, whereas TRIM21 targets IRF3 (Kimura et al. 2015), key components of the inflammasome, and type I interferon response systems. TRIM17 targets midbodies (Mandell et al. 2016), while TRIM16 acts with Galectin-3 (GAL3) to target damaged lysosomes in lysophagy (Chauhan et al. 2016).

The Role of Ubiquitin and Other "Eat-Me" Signals

As first demonstrated for peroxisomes, the ubiquitination of a cellular structure leads to the recruitment of SLRs and the subsequent selective autophagy of that structure (Kim et al. 2008). Hence, ubiquitin decoration works as an "eat-me" signal for selective autophagy. The selective autophagy of protein substrates often depends on their assembly in p62 bodies. p62 recognizes several "eat-me" signals. These include mono- and/or polyubiquitin recognized by the UBA (ubiquitin-associated) domain of p62 and/or NBR1 (Kirkin et al. 2009, Pankiv et al. 2010). Another is the N-terminal arginylation of proteins, which labels them as degrons recognized by the ZZ domain of p62 (Cha-Molstad et al. 2017). A third signal is NIPSNAP1 and NIPSNAP2 proteins acting in mitophagy (Abudu et al. 2019). The selective autophagy pathway via p62 bodies is chosen if the protein substrate is not efficiently degraded by the ubiquitin–proteasome system (UPS) or if the capacity of the UPS is overwhelmed (Dikic 2017). The cross talk between the UPS and autophagy is dynamic and controlled by molecular chaperones (Fernandez-Fernandez et al. 2017). The ER-resident Hsp70 chaperone BiP is involved in the degradation of degrons by autophagy via p62 bodies (Cha-Molstad et al. 2015). A chaperone complex with Hsp70, BAG3, and HspB8 delivers ubiquitinated proteins to p62 (Fernandez-Fernandez et al. 2017). This chaperone complex is essential under basal conditions. Increased BAG3 expression is seen in response to aging or stress, which enhances the use of the selective autophagy of damaged proteins (Gamerdinger et al. 2009).

Another important "eat-me" signal used to label damaged lysosomes or bacteria-containing vacuoles consists of cytosolic lectins of the GAL family. GALs interact with β-galactosides, and the binding of GALs to intraluminal sugars exposed when the membrane is ruptured works as an "eat-me" signal (see section titled Lysophagy). Several TRIM family proteins interact with at least a subset of the GAL proteins, but among the SLRs only NDP52 and TAX1BP1 appear to bind to these "eat-me" signals. On both lysosomes and bacteria-containing vacuoles, the GALs induce an early response before the structures are ubiquitinated, while the addition of polyubiquitin induces a later response.

The Role of Condensates Formed by Liquid–Liquid Phase Separation

The cytoplasm and nucleoplasm harbor numerous membraneless organelles such as the nucleolus, Cajal bodies, PML bodies, and stress granules. These biomolecular condensates are formed by LLPS in which molecules are concentrated in a confined liquidlike compartment coexisting with the liquid environment in the cytoplasm or nucleoplasm (Banani et al. 2017, Bracha et al. 2018, Shin & Brangwynne 2017). LLPS structures are spherical bodies or droplets that can fuse or undergo fission; they can also become deformed upon encountering a physical barrier, a phenomenon known as wetting. The components of the droplets are kept together by multivalent weak interactions, show internal mobility, and exchange with the surrounding milieu.

As mentioned, the single PAS in yeast is a droplet (Fujioka et al. 2020). In the Cvt (cytoplasm-to-vacuole-targeting) pathway, the ability of Ape1 to form semiliquid droplets, which the SAR Atg19 can float and condense on, is—together with the interaction with lipidated Atg8—required for the selective membrane sequestration of the Ape1 droplets (Yamasaki et al. 2020).

Pioneering studies in *Caenorhabditis elegans* revealed that the germline PGL granules are liquid droplets (Brangwynne et al. 2009). The H. Zhang lab (2009, 2018) then showed that the SAR SEPA-1 is required for the LLPS-mediated formation and degradation of PGL granules containing the RNA-binding proteins PGL-1 and PGL-3. SEPA-1 binds to PGL-3 and to the Atg8 protein LGG-1. The formation of PGL granules (droplets) is regulated by PRMT1-mediated arginine methylation and mTORC1 phosphorylation of PGL1 and 3. The scaffold protein EPG-2 coats the droplet surface and is required for the degradation of the PGL granules, which it also facilitates by inducing the transition from a more liquid to a more gel-like state.

Recent studies (Sun et al. 2018, Zaffagnini et al. 2018) have shown that p62 bodies are actually liquid droplets formed by LLPS when polymeric p62 interacts with ubiquitin. These liquid droplets are formed both in vivo and in vitro. In vitro, p62 and ubiquitin are sufficient to form droplets. The stress-induced p62 bodies formed in cells are more complex droplets that contain additional material, but the assembly of cellular droplets similarly depends on the binding of polymeric p62 to polyubiquitin. In vitro, the PB1 domain–mediated polymerization of p62 results in helical structures with a diameter of 15 nm (Ciuffa et al. 2015). The interaction of these flexible filaments with polyubiquitin causes the phase separation of p62 (Sun et al. 2018, Turco et al. 2019, Zaffagnini et al. 2018). Electron microscopy studies (Jakobi et al. 2020) show that p62 droplets in cells contain a dense meshwork of 15-nm-diameter filaments with an average length of 50 nm.

The UBA domain of p62 has a low affinity for ubiquitin (Kirkin et al. 2009), and factors that increase ubiquitin binding increase p62 droplet formation (Zaffagnini et al. 2018). TBK1 phosphorylates Ser403 in the ubiquitin-binding surface of the UBA domain (Pilli et al. 2012). This strongly increases ubiquitin binding of p62 (Matsumoto et al. 2011). Ubiquitin binding is also increased by the posttranslational modification of residues Lys420 and Lys435, which is needed to prevent an inhibitory self-interaction of the UBA domain (Lee et al. 2017, Peng et al. 2017). p62 droplets are efficiently induced by TIP60-mediated acetylation of these two sites (You et al. 2019), but the ubiquitination of p62 by the E2 ligase UBE2D2/3 is also essential for p62 droplet formation (Peng et al. 2017). Droplets formed by p62 are degraded, depending on their size, either as whole units or in a piecemeal fashion (Agudo-Canalejo et al. 2021). Droplets may have an intrinsic ability to induce wetting and phagophore formation even in the absence of a specific protein interaction mediating the docking of the droplet to the phagophore. Hence, dynamics may play an essential role in selective autophagy. Without the LIR-ATG8 interaction, p62 droplets promote the formation of empty autophagosomes, and the process becomes a type of bulk autophagy (Agudo-Canalejo et al. 2021, Kageyama et al. 2021). An important question is if other SLRs such as NDP52 or OPTN similarly accumulate in droplets when functioning in selective autophagy.

The Degradation of Soluble Selective Autophagy Receptors by Endosomal Microautophagy

p62 displays a predominantly diffuse localization pattern under basal conditions that is continuously degraded by autophagy in a LIR- and ATG8-dependent manner. This degradation is seemingly independent of ubiquitin binding or droplet formation. In yeast, ESCRT-dependent vacuolar uptake via microautophagy acts in concert with macroautophagy and is responsible for the selective degradation of many types of intracellular structures (Schuck 2020). In mammals, abrupt starvation triggers a rapid, mTOR-independent degradation of all the SLRs (except for OPTN) via an endosomal microautophagy pathway (Mejlvang et al. 2018). This degradation of p62 and NDP52 depends on ATG5 and ATG8s (Mejlvang et al. 2018). Hence, the initial docking to the endosome is likely mediated by the binding of p62 or NDP52 to ATG8s lipidated to the endosomal membrane. This model is supported by a recent study (Leidal et al. 2020) of a

secretory pathway for cytoplasmic LIR-containing proteins. Intraluminal budding into late endosomes was shown to depend on a LIR interaction with LC3-II on late endosomes. Proteins with KFERQ motifs can be degraded by Hsc70-dependent selective mechanisms such as chaperone-mediated autophagy (Cuervo & Wong 2014) or endosomal microautophagy (Sahu et al. 2011). In ATG7-knockout (KO) cells, NBR1 and TAX1BP1 are degraded by an unconventional ATG7- and ubiquitin-independent autophagy pathway under basal conditions (Ohnstad et al. 2020).

The Recruitment of Core Autophagy Proteins

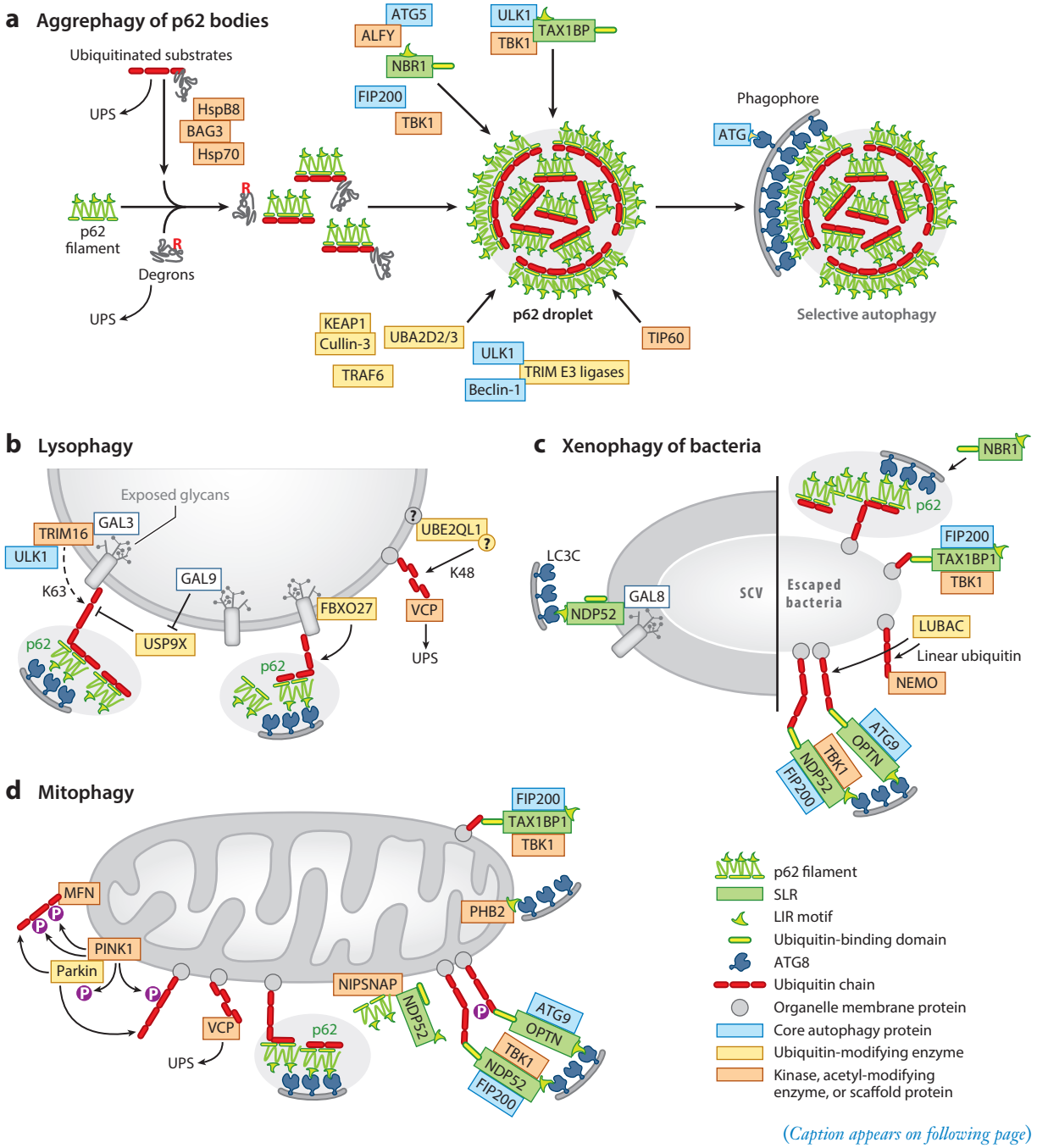
The soluble SAR must have a way of linking the cargo to the core autophagy machinery. Yeast Atg11 connects the SAR–cargo complex with the core autophagy machinery at the PAS by interacting with Atg1, Atg13, and Atg9 (Hollenstein & Kraft 2020). This results in the local activation of Atg1 (Kamber et al. 2015, Torggler et al. 2016). The 11-armadillo-repeat protein Vac8 is bound to the vacuolar membrane via myristoylation and palmitoylation and binds to Atg13 to tether the PAS to the vacuole. Vac8 is also required for selective autophagy (Hollenstein & Kraft 2020). In mammals, there is little evidence that the SAR–cargo complex is transported to preexisting mammalian PAS (mPAS). Instead, the core autophagy machinery is recruited directly by SARs to the SAR–cargo complex. This was first shown for TRIM family E3 ligases and SARs followed by studies of yeast Atg19 and Atg34, p62 in aggrephagy, and NDP52 in mitophagy (Fracchiolla et al. 2016; Kimura et al. 2015, 2016; Mandell et al. 2014; Ravenhill et al. 2019; Smith et al. 2018; Turco et al. 2019; Vargas et al. 2019). In this way, an mPAS is established in situ initiating phagophore expansion to encapsulate the SAR–cargo complex.

The prevailing model is that the specific recruitment of ULK1 and ATG9 is critical and possibly sufficient to recruit the rest of the core autophagy machinery except for the ATG8s. Selective autophagy mediated by the SLRs also depends on the serine-threonine kinase TBK1 (Tank-binding kinase 1). p62, NDP52, OPTN, and TAX1BP1 are phosphorylated by TBK1 (Richter et al. 2016). The function of OPTN in mitophagy, xenophagy, and aggrephagy strongly depends on TBK1. TBK1 phosphorylates Ser177 in the LIR motif and Ser473 in the UBAN domain of OPTN; this strongly increases its affinity for ATG8s and ubiquitin, respectively (Richter et al. 2016, Wild et al. 2011). Droplet formation of p62 depends on TBK1. How TBK1 is recruited to p62 bodies is as yet unknown. TBK1 binds to NDP52 via an interaction of its SKICH domain with the TBK1 adaptors SINTBAD and NAP1 (Thurston et al. 2016). The SKICH domain of NDP52 also binds to FIP200 and thereby recruits ULK1, but this involves a different surface of the SKICH domain and does not exclude a simultaneous recruitment of TBK1 (Ravenhill et al. 2019, Vargas et al. 2019). TBK1 facilitates the recruitment and activation of ULK1 at the cargo. In line with the self-activation of Atg1 in the yeast Cvt pathway (Kamber et al. 2015, Torggler et al. 2016), ULK1 activation is independent of AMPK or mTORC1, and a locally elevated concentration of ULK1 at the cargo appears to be sufficient to induce an autoactivation of the kinase (Vargas et al. 2019). The evolutionarily related TAX1BP1 also contains a SKICH domain that binds to FIP200 and SINTBAD (Ravenhill et al. 2019, Thurston et al. 2016). In a recent study (Yamano et al. 2020), OPTN was shown to bind directly to ATG9, an interaction that is essential for the role of OPTN in selective autophagy. In cases in which NDP52 and OPTN colocalize, these two SLRs are therefore likely to collaborate in recruiting the core autophagy machinery.

Aggrephagy

Aggrephagy denotes the autophagic degradation of individual proteins and protein aggregates, and involves individual proteins being ubiquitinated and sequestered into droplets or aggregates

before their degradation by autophagy. We focus here on p62 bodies because this is the dominant aggrephagy substrate in mammals and is used as a model to study the role of LLPS in selective autophagy. The formation of p62 bodies represents a major aggrephagy pathway in mammals used for the degradation of misfolded or damaged proteins, usually tagged with ubiquitin (**Figure 1*a***). p62 bodies are dynamic, transient structures that accumulate in different cell types



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Ubiquitin-dependent selective autophagy pathways. (*a*) Aggrephagy of misfolded and damaged proteins via p62 bodies. Important proteins recruited to the p62 body are listed above or below the droplet. Red Rs indicate arginylated degrons. (*b*) Damage-induced lysophagy depends on the recruitment of GALs and the ubiquitin-mediated recruitment of SLRs (p62 shown) and VCP. (*c*) Xenophagy of (*left*) *Salmonella*-containing vacuoles and (*right*) intracellular bacteria. (*d*) Mitophagy induced by PINK1 and Parkin. Activation of PINK1 and Parkin at the OMM induces fission of the mitochondria (not shown), ubiquitination of OMM proteins, recruitment of SLRs, and induction of mitophagy. Abbreviations: ATG, autophagy-related protein; GAL, Galectin; LIR, LC3-interacting region; MFN, mitofusin; OMM, outer mitochondrial membrane; P, phosphorylation; SCV, *Salmonella*-containing vacuole; SLR, Sequestosome-1-like receptors; TBK1, Tank-binding protein 1; UBA, ubiquitin-associated domain; UPS, ubiquitin-proteasome system.

and under different stress conditions. Their contents therefore vary. Several types of cancer are associated with a constitutive accumulation of p62 bodies (Sánchez-Martin et al. 2018), but the formation of such bodies is normally kept at a low level, balancing the need for protein quality control. Among the proteins degraded via p62 bodies are also functional proteins. One important example is the NRF2 regulator KEAP1. A KIR motif in p62 interacts directly with KEAP1, and the formation of p62 bodies correlates with the sequestration and autophagic degradation of KEAP1 (Jain et al. 2010, Komatsu et al. 2010). In tumors in which p62 bodies accumulate, this may lead to a constitutive activation of the NRF2 pathway (Sánchez-Martin et al. 2018).

How the core autophagy apparatus is initially recruited to stress-induced p62 bodies is still unknown. p62 interacts directly with FIP200 via a FIR motif that overlaps with the LIR motif. However, this interaction is not needed for the recruitment of ULK1 (Turco et al. 2019). Here we discuss three proteins that are strongly implicated in the degradation of p62 bodies: NBR1, TAX1BP1, and ALFY. NBR1 is evolutionarily related to and collaborates with p62 in several autophagy processes. There are no p62 or Nbr1 orthologues in yeast, but other nonmetazoan lineages express Nbr1. Early in the metazoan lineage, gene duplication of Nbr1 gave rise to the current p62 and Nbr1 in metazoans (Svenning et al. 2011), in which only p62 has a polymeric PB1 domain needed to form droplets. Nonmetazoan orthologues are named Nbr1 based on sequence and domain architecture, but nonmetazoan Nbr1 resembles p62 by having a polymeric PB1 domain that can form helical filaments in vitro as well as ubiquitin-positive droplets in cells resembling those formed by p62 in metazoans (Jakobi et al. 2020, Svenning et al. 2011). p62 in metazoan species and Nbr1 in nonmetazoan species therefore most likely form similar types of droplets. NBR1 binds to the PB1 domain of p62 and is recruited to p62 bodies via this interaction. The translational inhibitor puromycin increases the formation of defective ribosomal products (DRiPs) that accumulate in p62 bodies and are degraded by selective autophagy (Pankiv et al. 2007). DRiPs also accumulate in p62 bodies upon activation of dendritic cells (Argüello et al. 2016). NBR1 is only partially needed for the assembly of DRiPs in p62 bodies, but it is required for their autophagic degradation (Argüello et al. 2016, Kirkin et al. 2009). The critical function of NBR1 in p62 bodies is not yet known, but it facilitates LLPS (Kirkin et al. 2009, Zaffagnini et al. 2018) and binds to membranes (Deosaran et al. 2013). Another potentially important function of NBR1 may be to recruit TAX1BP1. In HeLa cells lacking TAX1BP1, p62 bodies are efficiently formed in response to puromycin treatment, but they persist upon the subsequent removal of puromycin (Sarraf et al. 2020). Hence, TAX1BP1 may have a direct role in the degradation of p62 bodies. A recent study (Ohnstad et al. 2020) revealed that TAX1BP1 binds directly to NBR1. TAX1BP1 also has a SKICH domain binding to FIP200 and TBK1 (Ravenhill et al. 2019, Thurston et al. 2016). The LIR-independent degradation of NBR1 by nonconventional macroautophagy in ATG7-KO cells depends on the interaction of TAX1BP1 with NBR1, FIP200, and TBK1 (Ohnstad et al. 2020). A similar role for TAX1BP1 in recruiting TBK1 and FIP200 to p62 bodies is clearly possible. A third protein consistently recruited to p62 bodies is the 400-kDa scaffold protein ALFY. ALFY interacts with ATG5, GABARAP, and PI3P, suggesting a role for ALFY in phagophore

formation. ALFY is observed in all cellular structures containing p62 and NBR1, and ALFY is required for the degradation of both p62 bodies and aggregation-prone proteins in mammals and flies (Knaevelsrud & Simonsen 2010).

Lysophagy

Quality control of lysosomes is essential for cellular homeostasis. GALs, i.e., GAL1, GAL3, GAL8, and GAL9, are recruited to damaged lysosomes and act as sensors for lysosomal damage (Papadopoulos et al. 2020). Each GAL binds to a distinct set of effector proteins to coordinate the lysosomal damage response. GAL3 is important both for the ESCRT complex–mediated repair of ruptured lysosomes and for their clearance by lysophagy if the repair process fails (Papadopoulos et al. 2020) (**Figure 1*b***). The efficient recruitment and activation of the ESCRT complex depends on two sequential events. First, a release of Ca^{2+} from the lysosome activates the lipid-binding activity of the ESCRT component ALIX, and second, GAL3 directly binds to ALIX and other ESCRT components to facilitate their recruitment and assembly at the site of lysosomal damage (Jia et al. 2020b). LLOMe (L-leucyl-L-leucine methyl ester) is commonly used to permeabilize late endosomal and lysosomal membranes. ESCRT components are recruited within minutes after lysosomal damage, while the ubiquitination of damaged lysosomes and the induction of the lysophagy pathway occurs much later (Jia et al. 2020b). The induction of the lysophagy pathway correlates with a change in GAL3-interaction partner from ALIX to TRIM16 (Chauhan et al. 2016, Jia et al. 2020b). TRIM16 binds to ULK1, Beclin-1, and ATG16L1 and needs to be in a complex with ULK1 before interacting with GAL3. Importantly, this suggests a mechanism in which the core autophagy apparatus is recruited independently of any recruited SAR. TRIM16 also contributes to the ubiquitination of the damaged lysosome and the recruitment of p62. However, ubiquitination of the lysosome is also induced by other recruited proteins such as GAL9, FBXO27, and UBE2QL1 (**Figure 1*b***). GAL9 acts by activating TAK1 and AMPK, and this results in inhibition of the DUB USP9X that under normal conditions removes ubiquitin from lysosomes (Jia et al. 2020a). FBXO27 is a receptor for substrates of the SCF (SKP1-CUL1-F-box) ubiquitin ligase complex; if it is expressed, it is rapidly myristoylated upon lysosomal damage and ubiquitinates LAMP1 and LAMP2 even before GAL3 is recruited (Papadopoulos et al. 2020). FBXO27 then contributes to p62 recruitment and increases the efficiency of the lysophagy process. UBE2QL1 is an E2 ubiquitin ligase that modifies proteins with K48-linked ubiquitin chains, and it is essential for the recruitment of VCP to damaged lysosomes (Koerver et al. 2019). How UBE2QL1 is recruited to lysosomes is not yet known, but while K63-linked ubiquitin chains are detected within 30 min, which correlates with the recruitment of p62, UBE2QL1 peaks at 2 h after damage. No specific lysophagy receptor has yet been identified, and lysophagy depends on the recruitment of SLRs. Studies in which LLOMe is used to damage lysosomes (Papadopoulos et al. 2020) indicate that p62 plays an important role but also that TAX1BP1 is recruited. In lysophagy induced by α-synuclein fibrils, TBK1 and OPTN are needed. After bacteria-induced endomembrane damage, a ubiquitin-independent recruitment of NDP52 occurs that is mediated via a direct interaction with Gal8 (Papadopoulos et al. 2020).

Xenophagy

Xenophagy is collectively used to describe the degradation of bacteria, viruses, or fungi by autophagy. Specialized pathogens have evolved advanced mechanisms to escape the autophagy machinery, but the exact strategies vary extensively between different pathogens. Nonpathogenic bacteria entering the cell are ubiquitinated and efficiently cleared by selective autophagy, unless

they have developed a strategy to avoid this. *Salmonella typhimurium* can proliferate in specialized *Salmonella*-containing vacuoles (SCVs). Before the bacteria enter the cytosol, GALs are transiently recruited to damage on SCV membranes produced by the bacteria. In an early response, NDP52 binds to GAL8 and initiates autophagy of the SCV (Thurston et al. 2012) (**Figure 1*c***). In this xenophagy pathway, docking of the SCV to the phagophore depends on a specific interaction of the atypical LIR motif in NDP52 with LC3C (von Muhlinen et al. 2012). After escaping from the vacuole, bacteria are rapidly ubiquitinated, and different SLRs are then recruited to induce xenophagy (Thurston et al. 2009, Zheng et al. 2009). Studies of xenophagy have revealed that the ubiquitin linkage type is potentially important when recruiting the SLRs. Linear ubiquitin formed by LUBAC (linear ubiquitin assembly complex) specifically recruits OPTN and NEMO to induce xenophagy and NF-κB activation but not p62 or NDP52 (Noad et al. 2017). LUBAC is recruited to ubiquitin-positive bacterial surfaces that are no longer covered by host membranes, and the ubiquitin coat is remodeled by the addition of linear ubiquitin. Bacteria are relatively large structures, and their degradation depends on the formation of multiple phagophores. Interestingly, while p62 and NBR1 colocalize in patches on the surface of the bacteria, NDP52 and OPTN colocalize in patches that are separate from those containing p62 (Wild et al. 2011). This may reflect a difference in their preference for ubiquitin linkages present on the bacteria, but there may also be structural reasons for the lack of colocalization. Xenophagy represents an essential part of the immune response, and the constant interplay with various pathogens may explain the seemingly overlapping functions of SLRs in the xenophagy of bacteria, and on a broader scale also the occurring evolution of SLRs and TRIM proteins. Several of the signaling or autophagy roles of SLRs are related to immunity responses, and p62-mediated xenophagy substrates include bacteria (Zheng et al. 2009), viral particles (Orvedahl et al. 2010), and inflammasomes (Zhong et al. 2016). The connection to immunity is even more evident for the autophagy roles displayed by the different TRIM proteins (see section titled Ubiquitin-Dependent Soluble Selective Autophagy Receptors).

Ubiquitin-Dependent Mitophagy

Mitophagy describes the degradation of excess or damaged mitochondria by selective autophagy. The best understood mitophagy pathway is the ubiquitin-dependent PINK1-Parkin pathway that degrades heavily depolarized mitochondria (**Figure 1*d***). Normally PINK1 is imported into the mitochondria and is cleaved by proteases. A loss of membrane potential prevents PINK1 import; instead it is stabilized and activated at the outer mitochondrial membrane (OMM) (Narendra et al. 2010). PINK1 then phosphorylates many substrates, including the E3 ligase Parkin (Kondapalli et al. 2012) and ubiquitin (Kane et al. 2014, Kazlauskaite et al. 2014, Koyano et al. 2014). The activation of Parkin results in the further ubiquitination of OMM proteins, which are subsequently extracted by VCP and degraded by the UPS facilitating fission of the mitochondria (Chan et al. 2011, Xu et al. 2011, Yoshii et al. 2011). Ubiquitination also induces the formation of a tight and stable association of the mitochondria with ER membranes, and an early and essential response to the ubiquitination is also the recruitment of SLRs, TBK1, and FIP200 (Heo et al. 2015, Zachari et al. 2019). Studies of HeLa cells revealed that NDP52 and OPTN are essential for mitophagy induced by PINK1 and Parkin, while other recruited SLRs such as p62 and TAX1BP1 are less important (Heo et al. 2015, Lazarou et al. 2015). The reason may be that NDP52 and OPTN are needed for the efficient recruitment of the core autophagy machinery (Vargas et al. 2019, Yamano et al. 2020). The binding of OPTN to ubiquitin depends on the phosphorylation of ubiquitin by PINK1 (Lazarou et al. 2015). The use of SLRs in ubiquitin-dependent mitophagy may be context dependent. p62 is essential for Parkin-dependent autophagy in macrophages treated

with inflammasome NLRP3 agonists (Zhong et al. 2016). The matrix proteins NIPSNAP1 and NIPSNAP2 act as "eat-me" signals in the mitophagy of depolarized mitochondria via the PINK1-Parkin pathway (Abudu et al. 2019). Similar to KEAP1, the NIPSNAPs accumulate on the OMM upon depolarization. They interact directly with p62 and NDP52, and this interaction is essential for a sustained recruitment of SLRs and a robust mitophagy induction (Abudu et al. 2019). The inner mitochondrial membrane (IMM) protein Prohibitin-2 (PHB2) also facilitates PINK1-Parkin-dependent mitophagy by acting as a SAR binding to LC3 when the OMM is ruptured (Wei et al. 2017).

The importance of the PINK1-Parkin pathway as an inducer of mitophagy under physiological conditions is unclear. Some mammalian cell types do not express PINK1 or Parkin, and there is a need to clarify if other OMM-resident or SLR-associated E3 ligases can participate in the induction of ubiquitin-dependent mitophagy. Ubiquitin-dependent mitophagy induced by the lactone ivermectin is PINK1-Parkin independent. In this case, the ubiquitination of OMM proteins depends on E3 ligases such as CIAP1, TRAF2, and CIAP2 (Zachari et al. 2019).

UBIQUITIN-INDEPENDENT SOLUBLE SELECTIVE AUTOPHAGY RECEPTORS

In *Saccharomyces cerevisiae*, the biosynthetic Cvt pathway uses the SARs Atg19 and Atg34 to deliver the prApe1 enzyme as well as Ams1 and Ape4 to the vacuole via small autophagosomes called Cvt vesicles. This ubiquitin-independent pathway has been studied extensively as a yeast model for selective autophagy (Lynch-Day & Klionsky 2010, Nakatogawa et al. 2009). Examples of mammalian ubiquitin-independent SARs are the ferritinophagy receptor NCOA4 (Dowdle et al. 2014, Mancias et al. 2014), the glycophagy receptor Stbd1 (Jiang et al. 2011), and the ribophagy receptor NUFIP1 (Wyant et al. 2018). For NUFIP1, it is not yet known if an "eat-me" signal is involved. Stbd1 possesses a carbohydrate-binding domain for cargo recognition and interacts with GABARAPs (Jiang et al. 2011). NCOA4 binds directly to the FTH1 subunit of ferritin via a conserved NCOA4 C-terminal domain. NCOA4 also interacts with ATG8s, but the mechanisms of degradation are unclear, as both ATG7-dependent macroautophagy and a nonclassical ESCRT-mediated degradation involving TAX1BP1, VPS34, ATG9A, and ULK1/2-FIP200 occur (Goodwin et al. 2017, Mancias et al. 2014).

MEMBRANE-ASSOCIATED AUTOPHAGY RECEPTORS

By definition, an organelle-resident SAR sits in the membrane of a specific organelle, interacts with ATG8s, and is essential for the autophagy of that organelle. In general, organelle-resident SARs seem to act independently of the SLRs. However, SLRs may play a role in the degradation of organelles, suggesting potential cross talk between SLRs and organelle-resident SARs. Many organelle-resident SARs have other autophagy-independent roles. Because organelle-resident SARs sit on the cargo all the time, their functions in selective autophagy need to be tightly controlled. The majority of identified organelle-resident SARs in mammals are present on the ER or mitochondria. Here we discuss ubiquitin-independent mitophagy and ER-phagy as processes involving membrane-bound SARs.

Ubiquitin-Independent Mitophagy

In yeast, mitophagy is induced by nitrogen starvation (Onishi et al. 2021). The yeast mitophagy receptor Atg32 is an OMM-resident protein that links stressed mitochondria to the core machinery via interaction with Atg11 (Kanki et al. 2009, Okamoto et al. 2009) (**Figure 2**). Atg32 also binds to Atg8 to dock mitochondria to the phagophore (Kondo-Okamoto et al. 2012). The induction of

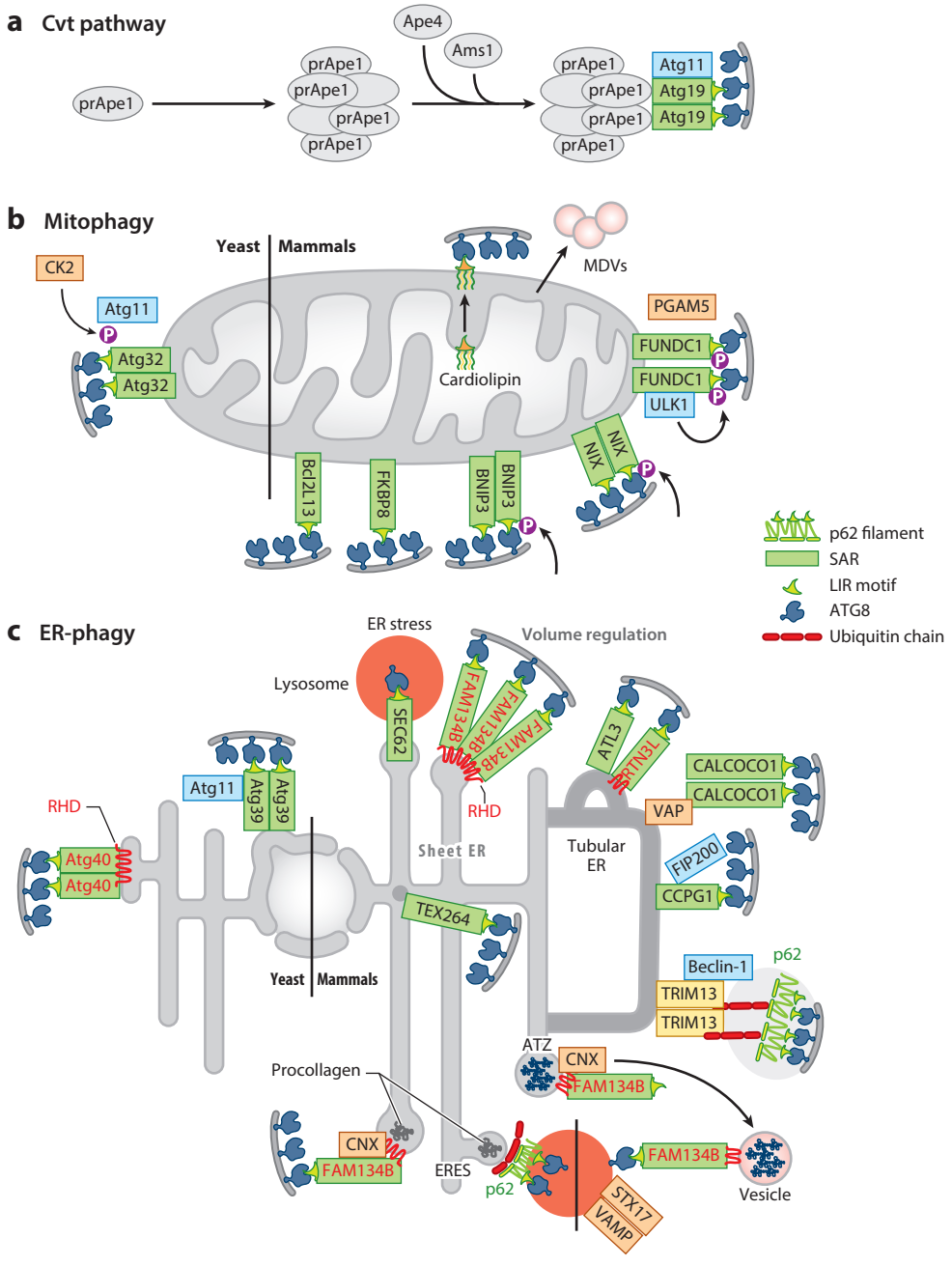


Figure 2

Ubiquitin-independent selective autophagy pathways in yeast and mammals. (*a*) The Cvt pathway in yeast, indicating essential interactions of the SAR Atg19 with the cargo: Atg11 links Atg19 to the phagophore-assembly site, and Atg8 is needed for docking the SAR–cargo complex with the phagophore. (*b*) Ubiquitin-independent mitophagy pathways in yeast and mammals, indicating the importance of posttranslational modifications for the binding of the SAR to Atg11 in yeast or ATG8s in mammals. (*c*) ER-phagy pathways in yeast and mammals. Shown are macroautophagy pathways (indicated by the presence of a phagophore) as well as microautophagy and vesicle pathways. Abbreviations: Atg, autophagy-related protein; ATZ, α1-antitrypsin Z; Cvt, cytoplasm-to-vacuole-targeting; ER, endoplasmic reticulum; ERES, endoplasmic reticulum exit site; LIR, LC3-interacting region; MDV, mitochondria-derived vesicle; P, phosphorylation; RHD, reticulon-homology domain; SAR, selective autophagy receptor; TRIM, tripartite motif.

mitophagy is associated with the increased transcription of Atg32. However, ectopic expression of Atg32 does not induce mitophagy, and the activation of Atg32 strongly depends on casein kinase 2 (CK2)-mediated posttranslational phosphorylation, which increases its affinity for Atg11 [reviewed in Onishi et al. (2021)]. CK2 is active under nutrient-rich conditions, but it is unclear how CK2 is regulated. The ability of Atg32 to function as a SAR is confirmed by studies in which the N-terminal part of Atg32 induces pexophagy if it is attached to peroxisomes (Kondo-Okamoto et al. 2012).

In mammals, basal mitophagy is essential for the maintenance of a healthy pool of mitochondria and depends on OMM-resident mitophagy receptors such as BNIP3L/NIX (Novak et al. 2010), BNIP3 (Hanna et al. 2012), FUNDC1 (Liu et al. 2012), Bcl2L13 (Murakawa et al. 2015), and FKBP8 (Bhujabal et al. 2017) (**Figure 2*b***). These receptors may have partially redundant functions and their interplay is unclear. We focus here on NIX, BNIP3, and FUNDC1, as these are mechanistically best understood. NIX and BNIP3 are homologous proteins related to the BH3-only family, and they function either as proapoptotic proteins or mitophagy receptors (Hanna et al. 2012, Novak et al. 2010). They are attached to the OMM via a single TM domain. Homodimerization is essential for mitophagy induced by these proteins, and the formation of a stable homodimer is probably regulated (Hanna et al. 2012). NIX and BNIP3 both contain a cytoplasmic LIR motif essential for their functions in mitophagy (Hanna et al. 2012, Novak et al. 2010). NIX was initially identified as a mitophagy receptor needed for programmed mitophagy under differentiation of reticulocytes (Sandoval et al. 2008), but NIX and BNIP also act in other types of mitophagy, including PINK1-Parkin-mediated mitophagy and reactive oxygen species–induced mitophagy (Onishi et al. 2021). NIX and BNIP3 are regulated at both the transcriptional and posttranslational levels, and an activating phosphorylation of the LIR motif at position X_{-1} relative to the core motif is essential for the induction of mitophagy by NIX (Rogov et al. 2017) or BNIP3 (Hamacher-Brady & Brady 2016). NIX may also act in mitophagy by inducing mitochondrial depolarization (Sandoval et al. 2008), and there is evidence that depolarization induced by NIX is needed for the damage-induced translocation of Parkin to the OMM (Ding et al. 2010). FUNDC1 acts as a receptor for hypoxia-induced mitophagy (Liu et al. 2012). Unlike NIX or BNIP3, FUNDC1 binds to and recruits ULK1 to the mitochondria, which is essential for mitophagy induced by FUNDC1 (Wu et al. 2014). The level of FUNDC1 is regulated by transcription or by MARCH5-induced proteasomal degradation (Onishi et al. 2021). FUNDC1 has an essential core LIR motif of the Y-type (Y^{18}EVL). Under normoxia, this LIR motif is blocked by the phosphorylation of Tyr18 by Src and Ser13 by CK2 (Chen et al. 2014). Hypoxia promotes the dephosphorylation of these sites by PGAM5, and the LIR motif is further activated by the phosphorylation of Ser17 by recruited ULK1 (Chen et al. 2014).

As an alternative to the use of proteins, cardiolipin is a diphosphatidylglycerol lipid that in mammals may act as an "eat-me" signal or mitophagy receptor (**Figure 2**). It is normally located only at the IMM, but the lipid translocates to the OMM upon mitochondrial damage to induce apoptosis or mitophagy. It binds to the N-terminus of LC3, and the translocation of cardiolipin is essential for mitophagy in cortical neurons (Chu et al. 2013). Mitochondrial proteins, lipids, and membrane may also be degraded via the formation of mitochondria-derived vesicles (Sugiura et al. 2014). A main challenge now is clearly to integrate the different mitophagy pathways into a unified model, and to increase our basic understanding of how the different processes are regulated.

ER-phagy

As it is the largest organelle of the cell, being involved in many fundamental functions such as protein folding, processing, and trafficking as well as lipid and steroid synthesis, detoxification, and

calcium storage, the ER is continuously turned over and renovated to maintain its integrity and function. This important quality control is executed by the UPS through ER-associated protein degradation (ERAD) (Wu & Rapoport 2018) and by selective autophagy processes called ER-phagy (Chino & Mizushima 2020, Hübner & Dikic 2020, Wilkinson 2019) (**Figure 2**). The ER is both a substrate for ER-phagy and a membrane scaffold for autophagosome biogenesis, making it sometimes challenging to separate these processes experimentally. Six mammalian membrane-bound ER-phagy receptors are known including FAM134B (Khaminets et al. 2015), RTN3L (a long isoform of RTN3) (Grumati et al. 2017), CCPG1 (Smith et al. 2018), SEC62 (Fumagalli et al. 2016), TEX264 (An et al. 2019, Chino et al. 2019), and ATL3 (Chen et al. 2019), whereas in *S. cerevisiae* Atg39 and Atg40 are the two known such receptors (Mochida et al. 2015) (**Table 1**). Except for ATL3, these are all ER-membrane proteins with one or more LIR motifs separated from the TM domain(s) by a long intrinsically disordered region (IDR). The IDRs provide the distance (about 20 nm) necessary to account for the space between the ribosome-coated ER membrane and the autophagosomal membrane (Chino et al. 2019). Some ER-phagy receptors are known to interact with core autophagy components, with CCPG1 binding to FIP200 (Smith et al. 2018) and yeast Atg39 binding to Atg11 (Mochida et al. 2015). Both Atg39 and CCPG1 are single-pass TM proteins with an N-terminal LIR facing the cytosol.

In addition, soluble SARs act in ER-phagy. CALCOCO1 is an evolutionarily conserved paralog of the established SARs NDP52 (CALCOCO2) and TAX1BP1 that has not previously been implicated in autophagy. CALCOCO1 acts as a soluble SAR in the nutrient stress–induced ER-phagy of tubular ER by binding on the one hand to VAPA and VAPB on the ER membranes via a conserved FFAT-like motif and on the other hand to ATG8 proteins via both LIR- and UDS-interacting region motifs acting codependently (Nthiga et al. 2020). During ER stress *Schizosaccharomyces pombe* Epr1 acts similarly to CALCOCO1 as a soluble ER-phagy receptor by engaging VAP on the ER via a FFAT motif and Atg8 via an AIM. Epr1 is upregulated upon ER stress by the unfolded protein response regulator Ire1 (Zhao et al. 2020). CALCOCO1 and Epr1 show no sequence homology but carry out the same function.

The archetypical SAR p62 also acts as a soluble ER-phagy receptor. Removal of misfolded aggregates in the ER lumen is mainly achieved by the proteasomal ERAD pathway, but some densely packed aggregates depend on ER-phagy for their removal (Chino & Mizushima 2020). The presence of ER-resident insoluble aggregates leads to the N-terminal arginylation of the chaperone BiP, forming an N-degron that p62 binds with its ZZ domain and oligomerizes (Cha-Molstad et al. 2017). Oligomeric p62 binds to the ER TM E3 ligase TRIM13, which also oligomerizes and auto-ubiquitinates itself with Lys63-linked ubiquitin chains that interact with the UBA domain of p62. TRIM13 also recruits core autophagy components of the PI3KC3-C1 complex, as indicated by the coimmunoprecipitation of VPS34 and Beclin-1. The result is macro-ER-phagy of the aggregated ER proteins (Ji et al. 2019).

Why are there so many ER-phagy receptors? One reason is that the ER is composed of regional subdomains including nuclear membrane, sheets, tubules, and ER exit sites (ERESs). In yeast, Atg40 degrades cortical ER and Atg39 perinuclear ER (Mochida et al. 2015). In mammals, RTN3L and ATL3 degrade tubular ER (Chen et al. 2019, Grumati et al. 2017), while FAM134B mostly degrades ER sheets (Khaminets et al. 2015). However, even sheets in the peripheral ER are often actually highly dynamic dense tubular matrices (Nixon-Abell et al. 2016). Some receptors are differently expressed, and some respond to different stress stimuli, while some are involved in the ER-phagy degradation of protein aggregates in the ER lumen. TEX264 is ubiquitously expressed, localizes to ER three-way junctions, and is responsible for more than 50% of ER-phagy upon nutrient starvation (Chino et al. 2019). CCPG1 is expressed predominantly in the pancreas and stomach and is induced during ER stress (Smith et al. 2018, Chino et al. 2019).

There are at least three different ER-phagy pathways including macro-ER-phagy, micro-ER-phagy, and the vesicular delivery pathway (Chino & Mizushima 2020). All known ER-phagy receptors are involved in macro-ER-phagy. In addition, SEC62 and FAM134B are involved in micro-ER-phagy and the vesicular delivery pathway, respectively (**Figure 2**). The mammalian translocon component SEC62 has an N-terminal LIR (not found in its yeast counterpart) that engages LC3 in a micro-ER-phagy pathway during recovery from ER stress (Fumagalli et al. 2016). LC3, ATG4B, ATG7, ATG16L1, and ESCRT-III components CHMP4B and VPS4A are essential. However, other core autophagy factors such as ULK1, ULK2, ATG13, and ATG14 are dispensable (Loi et al. 2019). In yeast, the ESCRT-dependent vacuolar uptake of ER whorls that arise from stacked ER sheets upon ER stress occur by micro-ER-phagy that does not require the core autophagy machinery (Schuck 2020). In mammalian cells, a subset of folded/misfolded procollagen molecules are directed toward lysosomal degradation through a micro-ER-phagy pathway initiated at ERESs. Misfolded procollagen accumulates at ERESs colocalized with ubiquitin, LC3, the SAR p62, and the core autophagy factors ATG14 and ATG9 (Omari et al. 2018). Another study (Forrester et al. 2019) shows that misfolded procollagen can be recognized by the ER luminal lectin chaperone Calnexin, which then interacts with FAM134B to mediate the macro-ER-phagy degradation of the affected part of the ER. A third study (Fregno et al. 2018) implicates a vesicular delivery pathway for the Calnexin- and FAM134B-mediated degradation of proteasome-resistant polymers of α1-antitrypsin Z (ATZ). Single-membrane, ER-derived, ATZ-containing vesicles fuse with endolysosomes dependent on LC3B interacting with the LIR of FAM134B. The fusion events require the ER-resident SNARE STX17 and the endolysosomal SNARE VAMP8.

ATG8-LIR interactions, clustering, and ER fragmentation are required for ER-phagy. In yeast, this is clearly illustrated by the Atg8-mediated assembly of reticulon-homology domain (RHD) protein Atg40 driving local ER deformation, which creates highly curved regions that are efficiently packaged into autophagosomes (Mochida et al. 2020). As observed previously for mammalian FAM134B (Li et al. 2018), the LIR of Atg40 contains a C-terminal helix that increases its binding affinity (Mochida et al. 2020). In mammals, the LIR-ATG8 interaction of FAM134B drives clustering, with the RHD-mediated membrane curvature acting with the GTPase activity of the Atlastins (ATL1–3) to induce the necessary fragmentation of ER sheets (Bhaskara et al. 2019, Khaminets et al. 2015, Liang et al. 2018). RTN3L employs six LIRs in its cytosolic N-terminal region for clustering combined with a C-terminal RHD to mediate the ER-phagy of tubular ER (Grumati et al. 2017). SEC62, CCPG1, and TEX264 have no intrinsic fragmentation activity and likely depend on a mechanism inducing molecular crowding at the site generating autophagosomes. Perhaps a more coherent network of interactions and cooperation of known mammalian ER-phagy receptors will emerge from future studies?

CONCLUSIONS AND FUTURE PERSPECTIVES

After 15 years of studies, we now have both a mechanistic and functional understanding of selective autophagy and its role in cellular homeostasis. A general mechanistic model for selective autophagy mediated by mammalian SLRs and organelle-resident SARs is evident. For SLRs, the initial and most important regulatory step is the binding of the SLR to a selected substrate. Recognition and binding depend on the presentation of "eat-me" signals such as ubiquitin or GALs. After the initial binding to the substrate, selective autophagy depends on three distinct roles displayed by the SLR. First, the SLR needs to coaggregate with the substrate in a way that enables phagophore formation. This involves the posttranslational modification of the SLR and, at least for p62, seems to depend on LLPS. Second, the SLRs need to recruit the core autophagy machinery, including ULK1 and ATG9, to induce phagophore formation. Third, the SLR strongly depends on the LIR

interaction for docking of the substrate to the phagophore. The SLR is then degraded together with the substrate. For organelle-resident SARs, the overall model is similar except that the SAR is already attached to the substrate. The most important regulatory step is therefore activation of the SAR; this often depends on the increased expression and phosphorylation of the LIR motif.

Despite a continuous flow of new data, important knowledge gaps remain in all of the selective autophagy pathways. A major task for further studies will be to integrate the knowledge we have into a unified model. For instance, in processes such as mitophagy and ER-phagy, the relative importance and interplay between the different SARs are poorly understood. In addition, the functional importance of noncanonical autophagy pathways is unclear. To fully understand the impact of selective autophagy in health and disease, we also need to study selective autophagy pathways in different cell types and tissues.

DISCLOSURE STATEMENT

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