Biochemical Society Transactions (2018) **46** 699–706
https://doi.org/10.1042/BST20170354

Review Article

Eat it right: ER-phagy and recovER-phagy

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The endoplasmic reticulum (ER) is the site of protein, lipid, phospholipid, steroid and oligosaccharide synthesis and modification, calcium ion storage, and detoxification of endogenous and exogenous products. Its volume (and activity) must be maintained under normal growth conditions, must be expanded in a controlled manner on activation of ER stress programs and must be reduced to pre-stress size during the recovery phase that follows ER stress termination. ER-phagy is the constitutive or regulated fragmentation and delivery of ER fragments to lysosomal compartments for clearance. It gives essential contribution to the maintenance of cellular homeostasis, proteostasis, lipidostasis and oligosaccharidostasis (i.e. the capacity to produce the proteome, lipidome and oligosaccharidome in appropriate quality and quantity). ER turnover is activated on ER stress, nutrient deprivation, accumulation of misfolded polypeptides, pathogen attack and by activators of macroautophagy. The selectivity of these poorly characterized catabolic pathways is ensured by proteins displayed at the limiting membrane of the ER subdomain to be removed from cells. These proteins are defined as ER-phagy receptors and engage the cytosolic macroautophagy machinery via specific modules that associate with ubiquitin-like, cytosolic proteins of the Atg8/LC3/GABARAP family. In this review, we give an overview on selective ER turnover and on the yeast and mammalian ER-phagy receptors identified so far.

Autophagy, the discovery

The term autophagy, literally 'self-eating', was first used in 1963 by Christian de Duve, during the CIBA Foundation Symposium on Lysosomes [1]. It now defines constitutive and regulated catabolic processes characterized by delivery of cytosolic material and organelles within the lysosomal compartment for clearance [2]. It was soon established that these self-eating pathways are enhanced by glucagon treatment or nutrient deprivation [3,4]. Initially, autophagy was merely studied in mammalian cells at morphological level. Transient intermediate autophagic structures (i.e. double membranes surrounding the cytosolic material that eventually fuse with lysosomes for degradation) were described [5]. The molecular mechanisms regulating autophagy were uncovered in the 1990s, when the process was first reported to exist also in the yeast *Saccharomyces cerevisiae* [6] and when genetic screens in this organism identified the first autophagy gene *APG1* (now *ATG1*) [7]. To date, ~40 autophagy-related (ATG) genes have been discovered. ATG genes are highly conserved from yeast to mammals to the point that yeast orthologs may functionally replace mammalian genes and *vice versa* [8].

Selective autophagy of organelles

From the very beginning, besides the observation of a bulk 'self-eating' process, the idea of selective degradation of intracellular components emerged. In fact, early morphological studies revealed the presence of whole organelles and organelle portions such as endoplasmic reticulum (ER), mitochondria and peroxisomes in lysosomes (or in the yeast vacuole) [9–11]. These selective degradative mechanisms may reflect the cellular need to control the size of organelles, to eliminate damaged organelles or to remove organelle subdomains containing toxic material. Based on the cargo delivered to

Received: 11 April 2018
Revised: 28 April 2018
Accepted: 2 May 2018

Version of Record published:
25 May 2018

Biochemical Society Transactions (2018) **46** 699–706
https://doi.org/10.1042/BST20170354

lysosomal compartments for clearance, these processes have been named aggrephagy for cytosolic protein aggregates, ER-phagy or reticulophagy for ER, mitophagy for mitochondria, pexophagy for peroxisomes, ribophagy for ribosomes and xenophagy for intracellular pathogens [12].

Selective autophagy of the ER

The ER is a dynamic organelle, whose volume is adapted to fluctuations in the protein and lipid biosynthetic demand, to changes of developmental and environmental conditions, to pharmacologic intervention or chemical insult and to attack by pathogens. First evidences of lysosomal degradation of the ER were observed in insect's fat body during the formation of storage granules [13] and in rat hepatocytes upon cessation of phenobarbital treatment [9]. *Constitutive* ER clearance maintains the volume of the organelle under normal growth conditions [14]. *Regulated* ER turnover is activated on nutrient deprivation [14–16], prevents excessive ER expansion in cells exposed to physiologic or pathologic stresses that elicit transcriptional and translational programs named unfolded protein responses (UPRs) [16,17] or terminates such ER stresses to re-establish pre-stress ER volume, content and activity [18]. ER-phagy may also be induced to remove subdomains containing faulty proteins and lipids [19] and by pathogen attack [20]. ER turnover requires ER vesiculation and capture of ER-derived vesicles by double-membrane autophagosomes that eventually fuse with lysosomes to clear their content. Alternatively, ER-derived vesicles may directly fuse with lysosomal compartments to deliver their luminal content for destruction. Most of these events eventually leading to ER clearance are mechanistically poorly understood. Paradoxically, the term 'ER-phagy' was coined by the group of Peter Walter to define the selective delivery of ER to the vacuole in yeast cells experiencing a dithiothreitol (DTT)-induced ER stress [17,21]. However, DTT-induced, yeast 'ER-phagy' cannot be considered representative for the catabolic processes regulating lysosomal ER turnover as described in this review. In fact, it results in the formation of ER whorls that are engulfed by the vacuolar membrane in a process that is topologically equivalent to microautophagy and does not require intervention of autophagy genes. Moreover, and significantly, the ER whorls are not degraded and accumulate in the vacuolar lumen. DTT-induced yeast ER-phagy has subsequently been defined as 'micro-ER-phagy' to distinguish it from another type of selective ER delivery to the yeast vacuole that has been defined as 'macro-ER-phagy'. The latter is triggered by the overexpression of membrane proteins, requires conventional autophagy genes, small GTPases and results in *de facto* ER degradation [19]. The autophagy gene Atg9 plays a role in the exit of macro-ER-phagy cargo from the ER, being required for the formation of ER-to-autophagy membranes (ERAM). The small GTPase Ypt1 is involved in the assembly of ERAM with pre-autophagosomal proteins Atg1, Atg8 and Atg11. The small GTPase Ypt51 mediates the delivery of autophagosomes to the vacuole. Atg2 plays an uncharacterized role in this process as its deletion impairs the removal of the membrane-bound cargo proteins. It is likely that macro-ER-phagy as defined in ref. [19] involves ER-phagy receptors that regulate the selective clearance of ER subdomains containing excess membrane proteins. However, these receptors remain to be characterized.

Autophagy receptors

Selectivity in autophagic processes implies the involvement of receptors bridging the cargo or the organelle to be degraded and the autophagic machinery. Autophagy receptors are defined by their capability (1) to recognize the cargo and/or to define the organelle or organelle portion to be degraded and (2) to interact with the autophagy modifier proteins of the Atg8/LC3 (light chain 3)/GABARAP (γ-aminobutyric acid receptor-associated protein) family via an Atg8-interacting motif (AIM) in yeast and via a LC3-interacting region LC3-interacting region (LIR) in mammals [22,23]. In the following sections, we will summarize the current knowledge on ER-resident, Atg8/LC3-binding proteins that ensure constitutive and regulated clearance of the ER by acting as ER-phagy receptors.

ER-phagy receptors in yeast

Atg39 and Atg40

In the budding yeast, ER-phagy is triggered by overexpression of integral membrane proteins (macro-ER-phagy) [19], by target of rapamaycin (TOR) inhibition on nitrogen deprivation or on incubation with the macrolide compound rapamycin [24,25]. As written above, receptors that regulate delivery of ER portions containing excess membrane proteins to the yeast vacuole (i.e. macro-ER-phagy receptors) have not been identified [19].

In contrast, ER-phagy receptors have been characterized for starvation- and rapamycin-induced ER-phagy. Here, the Atg8-binding proteins Atg39 and Atg40 decorate the membrane of ER and nuclear envelope subdomains to be delivered to the vacuole for clearance [26]. Atg39 and a small fraction of Atg40 localize in (and regulate turnover of) the nuclear envelope, which in *S. cerevisiae* is equivalent to the mammalian perinuclear ER. Atg40 mainly localizes to (and regulates turnover of) the cytoplasmic and cortical ER. Both Atg39 and Atg40 are transcriptionally and translationally induced in response to nitrogen deprivation- or rapamycin-induced TOR inactivation. Atg40 (but not Atg39) contains a domain similar to the mammalian reticulon-homology domain (RHD; Figure 1) required for membrane shaping and probably facilitating ER fragmentation. Both Atg39 and Atg40 contain an AIM (Figure 1) that engages phagophore membrane-bound Atg8. They both also interact with Atg11, an autophagy mediator that recruits the autophagosome biogenesis machinery at the receptor–cargo complex [27], but only Atg39 displays a consensus Atg11-binding sequence (Atg11BR, Figure 1) [26]. So far, it has been established that Atg39- and Atg40-mediated ER-phagy require Atg1, Atg8, Atg11 and Atg17, the vacuolar peptidase Pep4 and the small GTPase Ypt7 (Table 1) [26].

ER-phagy receptors in mammalian cells

FAM134B

FAM134B [family with sequence similarity 134; also known as RETREG1 (reticulophagy regulator 1)] is a member of the FAM134 reticulon protein family [14,28,29]. It harbors a RHD, which promotes curvature of ER membranes, and a LIR at the cytosolic C-terminus (Figure 1) that engages LC3 and/or GABARAP displayed at the limiting membrane of growing phagophores. This hints at a role of FAM134B as an ER-phagy receptor. Consistently, the RHD and the LIR are required for ER fragmentation, capture of ER fragments

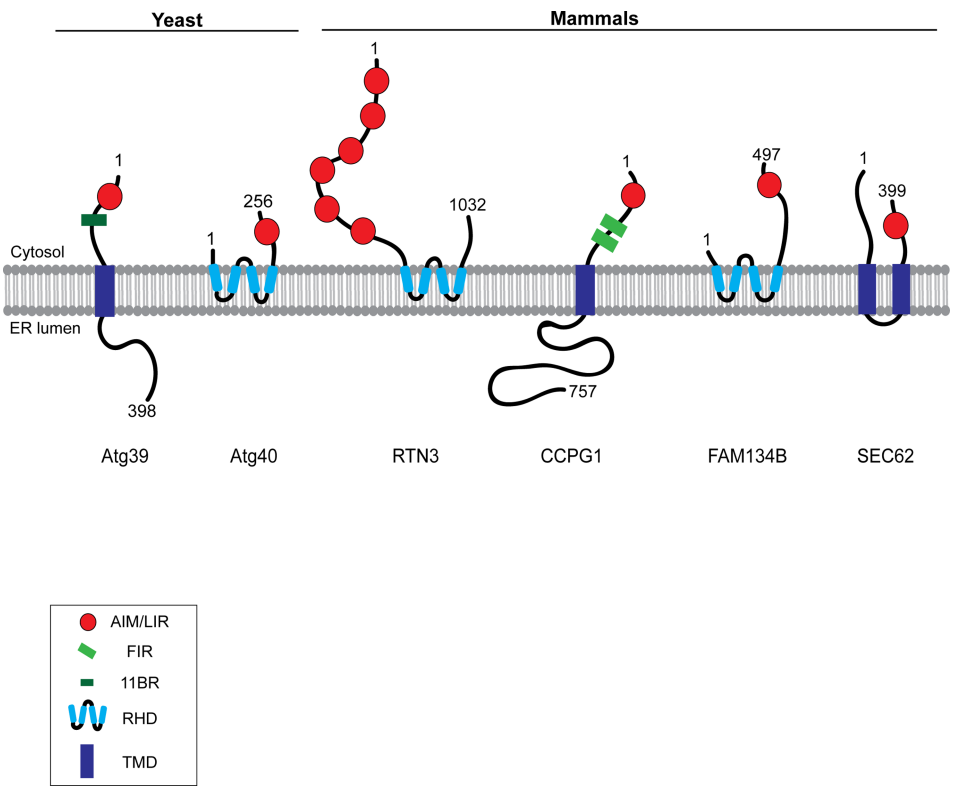

Figure 1. ER-phagy receptors in yeast and mammals.

The figure illustrates the yeast ER-phagy receptors Atg39 and Atg40 and the mammalian ER-phagy receptors FAM134B, SEC62, RTN3 and CCPG1. Number of residues in protein topology is shown. AIM: Atg8-interacting motif; LIR: LC3-interacting region; FIR: FIP200-interacting region; 11BR: Atg11-binding region; RHD: Reticulon-homology domain; TMD: transmembrane domain.

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https://doi.org/10.1042/BST20170354

Table 1 ER-phagy receptors in yeast and mammals: cargos and requirements

The table shows a list of the yeast and mammalian ER-phagy receptors reported so far in the literature, the ER subdomain and the ER-resident proteins cleared on their intervention and the gene products reported to be involved in the given ER-phagy pathway.

Receptors	Cargo degraded	Cargo excluded	Gene products required	Gene products not required
Yeast				
Atg39	Perinuclear ER Hmg1, Kar2, Src1, Nop1, Sec63	Rtn1	Atg1, Atg8, Atg11, Atg17, Ypt7, Pep4	ND
Atg40	Cytosolic/cortical ER Rtn1, Sec63	Kar2	Atg1, Atg8, Atg11, Atg17, Ypt7, Pep4	ND
Mammals				
FAM134B	ER sheets SEC61B, CLIMP63, TRAP-α, RTN4	RTN3, RTN1, Reep5	LC3/GABARAP ATG5, Beclin1, FIP200	RTN3
SEC62	ER chaperones (e.g. CNX, CRT, BiP,…) Folding enzymes (e.g. ERp72, ERp57,…)	ERAD factors	LC3 ATG5, ATG7	ND
RTN3L	ER tubuli (RTN1, RTN4, Reep5)	CLIMP63, TRAP-α FAM134B	LC3/GABARAP ATG5, ATG7, FIP200	FAM134B
CCPG1	Peripheral/tubular ER (RTN3)	FAM134B	LC3/GABARAP, ATG5, FIP200	ND

Abbreviation: ND: not determined.

within autophagosomes and their subsequent delivery to lysosomal compartments for clearance. Ablation of FAM134B or sensory neuropathy-causing loss-of-function FAM134B mutations cause ER expansion as a consequence of defective ER clearance [14,28]. This reveals a constitutive role of FAM134B in the maintenance of mammalian ER size [14]. FAM134B-mediated ER clearance is enhanced in cells subjected to nutrient deprivation. FAM134B co-localizes with SEC61B, CLIMP-63, TRAP-α (translocon-associated protein subunit alpha) and to a lesser extent with reticulon (RTN)4 to the edge of ER sheets, which are the ER subdomains found to be selectively cleared by FAM134B-regulated ER-phagy. This requires the autophagy gene products LC3/GABARAP, ATG5, Beclin1 and FIP200 (FAK family kinase-interacting protein of 200 kDa) (Table 1) [14,15].

SEC62

SEC62 (translocation protein SEC62) is an ER-resident transmembrane component of the SEC61/SEC62/SEC63 translocation machinery involved in the import of newly synthesized proteins into the ER lumen [30–32]. SEC62 was identified as the ER-phagy receptor that regulates ER turnover after conclusion of a transient ER stress. SEC62-regulated catabolic processes re-establish pre-stress ER volume and ER content and have been defined as recovER-phagy [18]. Bioinformatics analysis revealed a LIR at the C-terminus of SEC62 (Figure 1), which is conserved in Metazoa, not in yeast. This functional region is required for the function of SEC62 in recovER-phagy, but is dispensable for its role in protein translocation. The LIR-mediated interaction of SEC62 with LC3 was validated *in vitro* (surface plasmon resonance, nuclear magnetic resonance spectroscopy and peptide array analyses) and *in cellulo* [18]. SEC62-mediated recovER-phagy is activated on resolution of a transient ER stress to ensure the clearance of specific ER subdomains and restore ER homeostasis. Mass spectrometry analyses confirmed the selectivity of this process. In fact, recovER-phagy clears ER fragments, leaving unaffected mitochondria. More important, the catabolic activity targets ER subdomains containing molecular chaperones and folding enzymes [e.g. calnexin, calreticulin, BiP, PDI (protein disulfide isomerase), ERp72 and ERp57], but not factors that regulate ER-associated degradation (ERAD) [18]. This finding supports the notion

that different luminal activities (in this case, protein folding and selection for protein disposal) are compartmentalized in distinct ER subdomains. Interestingly, tumors expressing increased levels of SEC62 show a higher ER stress tolerance and drug resistance, which directly correlate with higher malignancy [33–36]. This new identified role of SEC62 in clearance of excess and damaged ER may explain why cancer cells with increased levels of SEC62 better tolerate ER stresses [37]. So far, it has been reported that SEC62-mediated recovER-phagy relies on the autophagy proteins LC3, ATG5 and ATG7 (Table 1) [18].

Reticulon3

RTN3 belongs to the RHD-containing proteins (RTN1–4), which are curving-membrane proteins highly enriched in tubular ER [38]. Among the numerous splice variants, only the longest (RTN3L) functions as the ER-phagy receptor [15]. It contains six LIRs in the N-terminal cytosolic domain of the protein (Figure 1), which interact with LC3 and GABARAP. Like FAM134B, the role of RTN3L in ER-phagy is activated on amino acid deprivation. However, in contrast with FAM134B that regulates turnover of ER sheets [14], RTN3L regulates the selective fragmentation and autophagic degradation of ER tubules containing RTN1, RTN4, REEP5 and RTN3 [15]. This process requires the oligomerization of RTN3L as well as the association of LC3/GABARAP and is abolished on disruption of all six LIRs. LC3/GABARAP, ATG5, ATG7 and FIP200 are required for starvation-induced ER tubules turnover (Table 1) [15].

CCPG1

Cell-cycle progression gene 1 (CCPG1) is a receptor for ER stress-induced ER-phagy [16]. CCPG1 localizes to perinuclear ER and in small foci at the ER periphery. It contains a LIR at the N-terminal cytosolic domain engaging LC3/GABARAP. However, it is defined as a non-canonical ER-phagy receptor because it also contains two FIP200-interacting regions, defined as FIRs (Figure 1). FIR shows similarity to the Atg11BR displayed by the yeast Atg39 protein, which facilitates the recruitment of the autophagic machinery. During ER stress, endogenous CCPG1 is induced and drives the autophagic degradation of peripheral ER. In cells lacking CCPG1, the starvation-induced degradation of the peripheral/tubular ER marker RTN3 was impaired, while degradation of a marker of ER sheets, FAM134B, was not affected. *In vivo*, CCPG1 plays an important role in maintaining the proteostasis of the pancreas protecting against aggregation of ER luminal proteins and consequent UPR activation, thus sustaining tissue health. CCPG1-mediated ER-phagy requires LC3/GABARAP, ATG5 and FIP200 (Table 1) [16].

Involvement of promiscuous LC3-binding proteins in ER turnover: BNIP3 and p62

BNIP3 (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3) and p62 regulate removal of the ER via autophagy [39,40]. BNIP3 is a transmembrane protein involved in apoptosis signaling, which contains a LIR at its N-terminal region. Endogenous BNIP3 localizes at the mitochondria, but during hypoxia, small amounts can relocate at the ER. Overexpression of BNIP3 enhances both mitophagy and reticulophagy via BNIP3-mediated engagement of autophagosome-localized LC3 [41]. However, disruption of BNIP3–LC3 interaction does not completely abolish autophagy of the ER, indicating the contribution of other ER-phagy receptors [39]. The autophagy receptor p62 has also been proposed to play a role in ER turnover [40]. p62 is a cytosolic, LIR-containing protein that regulates lysosomal clearance of polyubiquitylated polypeptides. Its involvement in ER clearance can be ascribed to the recognition of ER proteins polyubiquitylated at their cytosolic domains. After withdrawal of the xenobiotics 1,4-*bis*[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP), mouse liver cells lacking p62 fail to degrade excess ER, indicating the relevance of p62 in ER clearance [40].

Concluding remarks

ER misfunction causes severe disease conditions. For that reason, intense research has been devoted to characterize the pathways that maintain ER homeostasis. The transcriptional/translational ER stress responses [42], as well as the pathways delivering misfolded polypeptides from the ER to the cytosol for degradation by the ubiquitin proteasome system [43], have been elucidated in molecular details. Pharmacologic modulation of the UPR [44–46] and the ubiquitin proteasome system [47] are expected to affect on protein misfolding diseases, cognitive disorders and tumors to mention just a few pathologic states resulting from proteostasis impairment. In sharp contrast, only recently the characterization of the molecular mechanisms ensuring lysosomal clearance

Biochemical Society Transactions (2018) **46** 699–706
https://doi.org/10.1042/BST20170354

of ER fragments or subdomains has attracted the interest of cell biologists. The identification of ER-phagy receptors, both in yeast and in mammalian cells, paves the way to the characterization of constitutive and regulated ER turnover and clearly shows that ER subdomains can specifically be selected for disposal. A limitation of studies published so far is that ER turnover is activated on cells exposure to unspecific stimuli such as chemically induced ER stresses, nutrient deprivation or autophagy modulators. Such stimuli certainly led to the identification of few ER-phagy receptors both in yeast and in mammalian cells. However, they certainly have pleiotropic effects as shown by the fact that the same experimental conditions have been used to investigate conventional autophagic pathways as well as other types of organelle-specific macroautophagies, all of which are possibly simultaneously induced. More physiologic stimuli eliciting exclusive activation of clearance of select ER subdomains and leaving unaffected the turnover of other subdomains, other cargos or other organelles are actively sought after and must be the focus of future research. It is likely, in fact, that individual ER-phagy receptors are displayed in particular subdomains of the ER that sense the luminal and membrane environment and eventually send alert signals on accumulation of faulty proteins, lipids, otherwise toxic material or pathogens to the autophagy machineries located in the cytosolic space.

Abbreviations

AIM, Atg8-interacting motif; ATG, autophagy-related; BiP, binding immunoglobulin protein; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CCPG1, cell-cycle progression gene 1; DTT, dithiothreitol; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ERAM, ER-to-autophagy membranes; FAM134, family with sequence similarity 134; FIP200, FAK family kinase-interacting protein of 200 kDa; FIR, FIP200-interacting regions; GABARAP, γ-aminobutyric acid receptor-associated protein; LC3, light chain 3; LIR, LC3-interacting region; RHD, reticulon-homology domain; RTN, reticulon; SEC62, translocation protein SEC62; TOR, target of rapamaycin; TRAP-α, translocon-associated protein subunit alpha; UPR, unfolded protein response.

Funding

M.M. is supported by the SNF, Signora Alessandra, AlphaONE Foundation, Foundation for Research on Neurodegenerative Diseases, the Novartis Foundation, Swiss National Science Foundation (SNF), the Comel and Gelu Foundations.

Acknowledgements

We thank members of the M.M.'s laboratory for discussions and inputs during the preparation of this manuscript.

Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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