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REVIEW

Cargo receptors and adaptors for selective autophagy in plant cells

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Plant selective (macro)autophagy is a highly regulated process where eukaryotic cells spatiotemporally degrade some of their constituents that have become superfluous or harmful. The identification and characterization of the factors determining this selectivity make it possible to integrate selective (macro)autophagy into plant cell physiology and homeostasis. The specific cargo receptors and/or scaffold proteins involved in this pathway are generally not structurally conserved, as are the biochemical mechanisms underlying recognition and integration of a given cargo into the autophagosome in different cell types. This review discusses the few specific cargo receptors described in plant cells to highlight key features of selective autophagy in the plant kingdom and its integration with plant physiology, aiming to identify evolutionary convergence and knowledge gaps to be filled by future research.

Keywords: chlorophagy; ER-phagy; mitophagy; nucleophagy; pexophagy; plant cell; plant physiology; selective autophagy; selective autophagy receptor/adaptor; xenophagy

As an evolutionary conserved degradation pathway in eukaryotes, autophagy (self-eating) is a catabolic process by which cytoplasmic macromolecules and/or organelles are encapsulated and vehiculated in a double membrane vesicle called the autophagosome fusing with the lysosome in animal cells, or with the vacuole in plant and yeast cells, for the degradation of their content [1]. Different forms of autophagy

Abbreviations

AGO1, argonaute 1; AIM, Atg8-interacting motif; AP, autophagosome; ATG, autophagy-related (protein); ATI1/2, ATG8-interacting protein 1/2; AtTSPO, Arabidopsis TSPO; BES1, BRI1-EMS suppressor 1; BR, brassinosteroid; BRI1, brassinosterioid insensitive 1; CaMV, cauliflower mosaic virus; DDRGK1, Asp-Asp-Arg-Gly-Lys domain-containing protein 1; DSK2A, dominant suppressor of Kar 2; ER, endoplasmic reticulum; ESCRT, endosomal sorting complexes required for transport; FIP200, FAK-family interacting protein of 200 kDa; FMT, friendly; FUNDC1, FUN14 domain-containing protein 1; GABARAP, GABA type A receptor-associated protein; GFP, green fluorescent protein; HOG1, high-osmolarity glycerol response 1; HR, hypersensitive response; HSP, heat shock protein; ICL, isocitrate lyase; IDL, individually darkened leave; LIR, LC3-iinteracting region; MLS, malate synthase; NBR1, neighbor of BRCA 1 gene 1; NDP52, nuclear domain protein 52; NLRs, leucine-rich repeat-containing proteins; NUFIP1, nuclear fragile X mental retardation interacting protein 1; PE, phosphatidylethanolamine; PEX, peroxin protein; PINK1, phosphatase and tensin homolog-induced putative kinase 1; PMN, piecemeal nucleophagy; PMP, peroxisomal membrane protein; PUB4, plant U-box protein 4; RCB, rubisco-containing bodies; ROF1, rotamase FKBP 1 (peptidyl-prolyl cis-trans isomerase FKBP62); ROS, reactive oxygen species; RPC, receptor protein complex; RPL26, ribosomal protein L26; RPN10, regulatory particle non-ATPase 10; Rtn1/2, reticulon protein 1/2; rubisco, ribulose 1,5-bisphosphate carboxylase/oxygenase; SAR, selective autophagy receptor; Sec62, secretory protein 62; SIRT1, sirtuin, silent mating type information regulation 2 homolog; SQSTM1, sequestosome-1; TM, tunicamycin; TOC, translocon of the outer membranes of the chloroplast; TOR, target of rapamycin; TSPO, translocator protein; TuMV, turnip mosaic virus; Ubp3, ubiquitin-specific processing protease; UFM1, ubiquitin-fold modifier 1; UIM, ubiquitin-interacting motif; UPR, unfolded protein response; UPS, ubiquitin–proteasome system; UVB, ultraviolet B; VIPP1, vesicle inducing protein in plastid 1; VPS, vacuolar protein sorting; XPO1, exportin 1.

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have been described in the literature (Box 1), with some specific to a given cell type such as chaperone-mediated autophagy only reported in animal cells [2]. However, plants essentially share two types of autophagy with other eukaryotes: microautophagy and macroautophagy [3]. In microautophagy, the vacuole/lysosome itself engulfs small portions of the cytoplasm by invagination of the vacuolar/lysosomal membrane [4]. The hallmark of macroautophagy is the *de novo* formation of autophagosome, required to enclose and deliver cytoplasmic components to the vacuole/lysosome for degradation and recycling [5]. A specific autophagy pathway known as mega-autophagy is considered to be involved in cell death and is characterized by the lysis of the lytic vacuole triggering the release of vacuolar hydrolases into the cytoplasm and degradation of the whole cell content [6]. Irrespective of the cell type, macroautophagy (hereinafter autophagy) is the most studied and the best characterized form of autophagy.

Box 1. Autophagy key components

Phagophore, a cup-shaped, double membrane structure that elongates and expands to sequester cytoplasmic components.

Autophagosome, a double membrane-bound vesicle resulting from the closure of the phagophore and delivering its content to the vacuole for degradation.

Autophagic body, the single membrane-bound vesicle released in the vacuolar lumen or the multivesicular body after autophagosome fusion with the prevacuolar compartment or the tonoplast. Pre-autophagosomal structure (PAS), autophagosome initiation complex structure made of biological membranes and autophagy initiation machinery.

Autophagy-related 8 (ATG8), a ubiquitin-fold protein acting as a modifier and docking platform for autophagic receptors and adaptors.

Phosphatidyl-ethanolamine (PE), a lipid added post-translationally to ATG8 through ubiquitylation-like conjugation.

ATG8-interacting motif (AIM), a consensus amino acid sequence on interacting partners of ATG8 including cargo receptors and autophagy adaptors.

LC3-interacting region (LIR) other name of AIM in the animal field.

Ubiquitin-interacting motif (UIM)-like, a sequence used by some selective autophagy receptors to interact with ATG8/LC3. Selective autophagy degradation of mitochondria (**mitophagy**), chloroplasts (**chlorophagy**), peroxisomes (**pexophagy**), endoplasmic reticulum (**reticulophagy**), nuclei (**nucleophagy**), proteasomes (**proteaphagy**), ribosomes (**ribophagy**), aggregated proteins (**aggrephagy**) and pathogens (**xenophagy**).

Initiation and formation of the autophagosome

The autophagosome (AP) formation is a hallmark of autophagy, and this highly regulated and stepwise process is well conserved in yeast, animal and plant cells [3,5,7,8]. Upon induction of autophagy, an isolation membrane structure is initiated and assembled (a) as a pre-autophagosomal structure. This structure, also known as phagophore, elongates and expands to sequester cytoplasmic components (b). The phagophore then seals to form a complete double membrane–bound AP (c), followed by a maturation step (d). Subsequently, the AP fuses with the tonoplast to release the internal vesicle (termed an autophagic body) into the vacuolar lumen (e), where its cargo is finally broken down by vacuolar hydrolases, and the resulting products can either be stored in the vacuole or transported back to the cytosol for metabolic reuse. Alternatively, the AP merges with an endocytic compartment (most likely the multivesicular body also known as the prevacuolar compartment in the plant cell) to generate an amphisome, which then fuses with the lytic compartment. A recent study suggests that this may also be the case in plants [9,10].

Core autophagy-related (ATG) proteins organized in cognate complexes regulate AP biogenesis. In yeast, ATG1–10, ATG12–14 and ATG16–ATG18 are essential to this process [11]. In Arabidopsis, ATG1, ATG13 [12], ATG14 [13] and ATG18 [14] have been characterized to some extent. The coordinated action of several ATG protein complexes governs AP formation. The ATG1 complex including ATG1, ATG13 and ATG101, and possibly ATG11, regulates the initiation step [12,15]. In parallel, the phosphoinositide 3-kinase complex containing the functional subunits vacuolar protein sorting (VPS)34 and VPS38, and the scaffold subunits VPS15 and ATG6, enriches the initiation membrane with phosphatidylinositol 3-phosphate, which is crucial for the nucleation process [16,17]. A cycling vesicular complex containing the transmembrane protein ATG9 acts in concert with ATG2 and ATG18 to provide lipids to the initiation membrane and expanding phagophore [16,18]. The phagophore membranes are decorated with lipidated ATG8, as a result of a conjugation system involving ATG12-ATG16-ATG5 [7].

How autophagosomes are transported to and fuse with the tonoplast in plants remains mostly unknown. Interestingly, an autophagy adaptor named CFS1 (i.e. cell death-related endosomal FYVE/SYLF protein 1) was reported as being involved in autophagic flux in the liverwort *Marchantia polymorpha* by connecting autophagosomes with the ESCRT-I component VPS23, leading to the formation of amphisome [19]. The hybrid organelle (amphisome) in this case is formed by the fusion of APs with the multivesicular body before fusing with the plant vacuole [19]. AP size can vary greatly ranging from 0.5 to 1.5 μm in diameter, depending on the autophagy-inducing signal, the cargo and the cell type [20]. AP can be initiated from the endoplasmic reticulum (ER) [18,21] in ER subdomain enriched in phosphatidylinositol 3-phosphate [22]. However, the molecular mechanism of AP biogenesis remains unclear, and mostly so in plants. Studies in animal and plant cells indicated that ER-derived coat protein complex II vesicles also play a role in generating autophagosome [23,24]. In plants, a recent study reported that Sar1D and RabD2a are involved in autophagosome formation [25]. The initiation of the AP may be determined by the cargo to be degraded. It is assumed that AP are likely initiated at the vicinity of the cargo and their selection involves specific cargo receptors and scaffold factors, both interacting with membrane-bound ATG8 to target the cargo to the growing phagophore. Although bulk autophagy has been described as a general response to nutrient starvation in eukaryotic cells, selective autophagy can target defined organelles or macromolecules in the cell is response to biotic and abiotic stresses [26–28].

Selective autophagy

The first studies reporting on selective degradation of a cellular organelle were conducted almost two decades ago and reported the selective degradation of peroxisomes (pexophagy) in the yeast *Saccharomyces cerevisiae* [29] and the selective degradation of mitochondria (mitophagy) in mice [30]. In 2006, selective autophagic degradation of cytosolic protein aggregate (aggrephagy) was reported in plants [31]. The naming of the different types of selective autophagy is dictated by the type of cargo that is specifically degraded. It remains to be determined whether the content of the resulting autophagosomes is exclusively or only predominantly composed of the specific corresponding cargo. A constancy all the same, any type of selective autophagy requires a specific receptor that interacts with the cargo on the one hand, and ATG8 anchored to the phagophore on the other hand [32]. Thus, the selective cargo receptor is involved in specific cargo recognition and enrichment of the phagophore and later the autophagosome with this cargo. The concept of selective autophagy receptors (SARs) was initially highlighted by the discovery of Atg19, involved in targeting aminopeptidase I to the vacuole in the yeast biosynthetic cytoplasm-to-vacuole pathway [33–35]. The characterization of human p62/sequestosome-1 (SQSTM1) [36,37] set a milestone of mammalian SARs studies. SARs, can be soluble or membrane bound [38]. Arguably, the first characterized SARs in plants were Arabidopsis neighbor of BRCA 1 gene 1 (NBR1) (AtNBR1) and a stress-induced membrane protein, translocator protein (TSPO) [39,40]. AtNBR1 and its ortholog in tobacco Joka2/NBR1 [41] appeared to be similar to p62 but possess hybrid properties of mammalian NBR1 and p62 [39]. The characteristics of SARs were further defined by structural and functional features including protein-specific binding domains and/or ubiquitin-specific binding domains, and/or transmembrane domains [42,43].

Not all proteins interacting with ATG8 are autophagy receptors. It was shown that some core ATG proteins involved in autophagosome biogenesis and numerous autophagy adaptors can interact with members of the ATG8/LC3/GABA type A receptor-associated protein (GABARAP) family [44]. Autophagy cargo adaptors can bridge a given cargo with the autophagy machinery and/or with LC3/ATG8 [44].

ATG8 proteins family and interacting motifs

ATG8 proteins are crucial for both autophagosome formation and selective cargo recruitment. These are small ubiquitin-like proteins with two extra N-terminal α-helices [35]. Vertebrates possess six ATG8-like proteins grouped into the microtubule-associated protein 1 light chain 3 and GABARAP subfamilies [38]. ATG8 proteins are processed at a specific C-terminal Gly residue by ATG4 proteins and conjugated to phosphatidylethanolamine (PE) by two conjugation systems involving ATG7, ATG10, ATG3, ATG5, ATG12 and ATG16 [5,35]. ATG8-PE moieties decorate the inner and outer membranes of the phagophore and the autophagosome, and can interact with cargo receptor or adaptor proteins containing GABARAP or LC3-interacting region (LIR) in animals and ATG8-interacting motif (AIM) in yeast and plants, but also through newly identified motifs [7,20,38]. For example, regulatory particle non-ATPase 10 (RPN10), a cargo receptor, interacts with ATG8 through a ubiquitin-interacting motif (UIM)-like sequence and binds to an

alternative ATG8 interaction site called the UIM-docking site [45,46]. ATG8 lipidation is reversible and the hydrolysis of ATG8-PE to recycle ATG8 protein is also catalyzed by ATG4 [47]. Unlike yeast expressing a single copy of ATG8, this family is more diversified in plants, with nine isoforms in Arabidopsis (AtATG8a–i), five in maize, seven in rice and potato, 11 in soybean and up to 22 ATG8 isoforms in *Brassica napus* [48,49]. This expansion and diversity can be explained by multiple whole-genome duplications, possibly to adapt to different environmental conditions. Additionally, the set of ATG8 isoforms in each plant family has been kept over millions of years of evolution [49], suggesting a key role of ATG8 proteins in autophagy.

Under various physiological conditions, part or whole organelle such as the ER or mitochondria, macromolecular complexes such as proteins aggregates, specific proteins and even invading pathogens can be selectively degraded through the autophagic pathway. We hereafter discuss our current knowledge of each of these pathways involving the degradation of mitochondria (mitophagy), chloroplasts (chlorophagy), peroxisomes (pexophagy), ER (reticulophagy or ER-phagy), nuclei (nucleophagy), proteasome (proteaphagy), ribosomes (ribophagy), aggregated proteins (aggrephagy) and pathogens (xenophagy), with an emphasis on the SARs and cargo adaptors involved in plants compared to other systems.

Mitophagy

Mitochondria are the cellular powerhouse that produces energy in the form of ATP, through oxidative respiration reactions in eukaryote cells [50]. In plants, during the night, when photosynthesis is inactive, mitochondria mediate energy production [51]. Plants store a portion of starch produced by photosynthesis in chloroplasts during day time, then gradually consume this energy source at night to release fructose and glucose, which drive respiratory energy machinery in mitochondria [52].

When plants are under shade, the output of photosynthesis is affected. The decrease of photosynthesis efficiency can cause early senescence of shaded leaves to facilitate nutrient restoration and recycling in younger tissues [53], which activates the autophagy degradation of mitochondria [54–56]. When Arabidopsis plants are subjected to a long period of darkness, the number of mitochondria decreases substantially [57], suggesting that mitochondria are likely degraded under long-term carbon starvation. Mitophagy also possibly take place in stressed roots under nitrogen starvation [15,56,58]. Interestingly, ultraviolet B (UVB) damage can promote the association between ATG8 and mitochondria as described in the cytoplasm and in the lytic vacuole [59], suggesting that UVB damage can initiate mitophagy in plants [56]. However, it was reported recently that carbon starvation because of prolonged darkness, natural age-related senescence and specific mitochondrial stress, but not nitrogen starvation or other general abiotic stresses (heat, hypoxia, UVB and H_2O_2), are key triggers of mitophagy in Arabidopsis [60].

Nutrient homeostasis of the cell and the respiratory status of mitochondria are likely to be important into determining whether bulk autophagy or mitophagy is the preferred means of mitochondrial degradation [61]. The autophagic turnover of mitochondria is well-described in yeast and mammals. Rising oxidative stress within mammalian mitochondria can cause the disposal of oxidized proteins. For example, phosphatase and tensin homolog-induced putative kinase 1 (PINK1) becomes stabilized on the surface of dysfunctional mitochondria, where it facilitates the recruitment of an E3 ubiquitin ligase, parkin, resulting in phosphorylation of various targets. Parkin enhances the mitophagy signal by ubiquitylating mitochondrial proteins on the membrane surface [62]. Alternatively, PINK1 can also recruit the mitophagy receptors nuclear domain protein 52 (NDP52) and optineurin on mitochondria and directly activate mitophagy independently of parkin [63].

Selective degradation of damaged mitochondria in yeast is activated by the high-osmolarity glycerol response 1 (HOG1) signaling pathways. Downstream of HOG1, CK2 phosphorylates Atg32, which is a mitochondrial outer membrane protein [64]. The pseudo-receiver domain of Atg32 regulates its activation and the initiation of mitophagy [65]. At the phagophore assembly site, Atg32 subsequently interacts with the phosphorylated form of the coiled-coil domain-containing adaptor Atg11 and with Atg8 [66]. Both Atg11 and Atg32 can interact with Atg8 through their respective AIM motif. It is still not clear whether Atg32/Atg11 interact with membrane-bound Atg8-PE or soluble Atg8 [67].

There is no Atg32 homolog in animal cells, but a growing number of mitochondria-localized SARs have been identified. In addition to the ubiquitin-dependent mitophagy pathway, defined outer mitochondrial membrane mitophagy receptors containing consensus LIR, such as FUN14 domain-containing protein 1 (FUNDC1) [68], BCL2 interacting protein 1 [69], NIX [70], Bcl2L13 [71] and FKBP8 [72] have been characterized. The functions of NIX, BNIP3, and FUNDC1 are mechanistically best understood. Each of these

mitophagy SARs is activated by phosphorylation and upon mitochondrial damage to recruit LC3. Unlike NIX or BNIP3, FUNDC1 binds to and recruits ULK1 to the mitochondria, a step essential for FUNDC1-induced mitophagy [73] (Fig. 1).

Although mitophagy has been described as a plant response to different physiological conditions, we know very little on the SARs or adaptors involved. Neither Atg32, nor the other mammalian mitophagy receptors have homologs in plants. However, in Arabidopsis, an Atg11-related protein (AtATG11, encoded by a single locus, At4g30790) was identified as playing a key role in senescence-induced mitophagy [15]. Interestingly, AtATG11 structurally possesses both the characteristics of the mammalian RB1-inducible coiled-coil protein 1, also known as FAK-family interacting protein of 200 kDa (FIP200), with an Atg17 functional domain at the N-terminus, and an Atg11 functional domain at the C-terminus [67]. The recruitment of AtATG11 on the surface of mitochondria promotes starvation-induced phosphorylation of ATG1 and resulting autophagic degradation of ATG1 and ATG13 [15]. This study suggests that AtATG11 (and possibly ATG101) may act as important adaptors connecting the ATG1/13 complex to both bulk autophagy and selective mitophagy. Moreover, FIP200 (animal) and Atg17 (yeast), interact with the Atg1-related kinases and the accessory protein C12orf44/Atg101 during autophagosome formation [74], suggesting that the functional composition of the ATG1 complex is conserved in plant, yeast and mammalian cells. Plant mitophagy was also shown recently to be controlled by ATG5 and ATG11 proteins in plants [60]. Furthermore, in Arabidopsis, a set of predicted ATG8-interacting mitochondria proteins includes 12 candidates, such as cytochrome *b* reductase, hexokinase 1, translocases of the outer mitochondrial membrane (TOM20 and TOM40) and the voltage-dependent anion

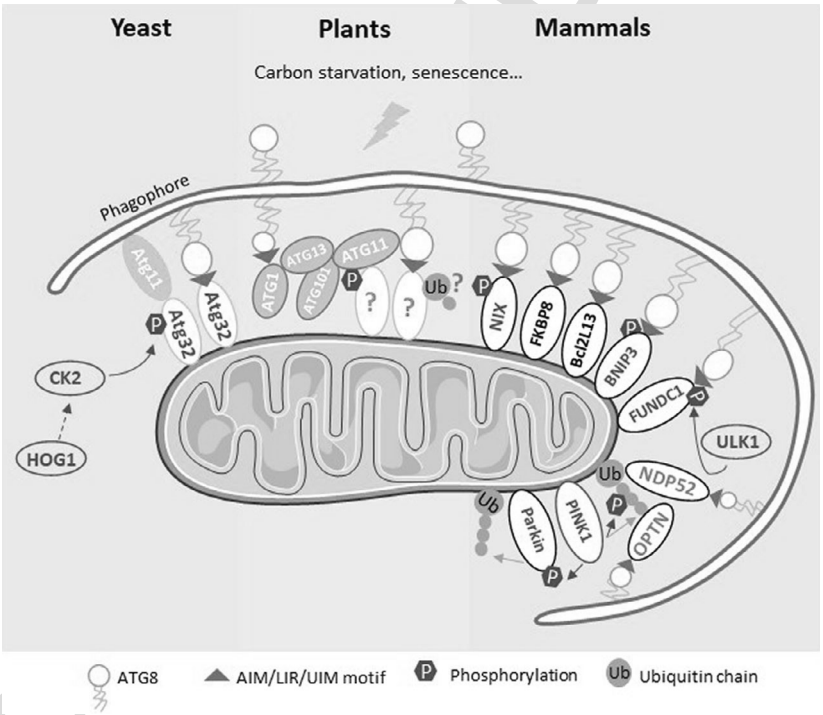

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Fig. 1. Selective autophagy receptors in mitophagy. In yeast (left), stress activation of the HOG1 (high osmolarity glycerol response 1) pathway induces CK2 (casein kinase 2)-mediated phosphorylation of Atg32. Atg11 interacts with phosphorylated Atg32, which targets mitochondria to the phagophore assembly site. Atg32 interacts with Atg8 through the Atg8-family interacting motif (AIM). In plants (centre), TOR kinase inhibition activates the ATG1/13 complex through regulatory dephosphorylation. Along with ATG11 and ATG101, the ATG1/ATG13 complex relocates to the surface of mitochondria. Although plant ATG11 binds to ATG8 directly in this context, defined plant mitophagy receptors are still missing (question marks). In mammalian cells (right), the kinase PINK1 phosphorylates its targets and facilitates the recruitment of PARKIN, which amplifies the signal by ubiquitylation of mitochondrial outer membrane proteins. Ubiquitylated mitochondria are recognized by the autophagic cargo receptor protein p62. ATG8/LC3 could also directly bind to other dedicated mitochondrial outer membrane autophagic receptors, such as FUN14 domain-containing protein 1 (FUNDC1), BCL2 interacting protein 1 (BNIP1), NIX, Bcl2L13 and FKBP8, through their AIM/LIR motif. FUNDC1 recruits ULK1/ATG1 complex to the mitochondria.

channel VDAC2, suggesting their possible function as mitophagy receptors/adaptors [61].

A recent study in Arabidopsis identified Friendly (FMT), a clustered mitochondria family protein, and showed that, upon damage, it is recruited on and required for mitochondrial dynamics [75]. Furthermore, FMT contributes to autophagosome assembly during mitophagy. Targeting of the cytosolic FMT on the mitochondria and the association of FMT with ATG8 in response to mitochondrial damage suggest that FMT may function as a mitophagy adaptor [75].

Chlorophagy

Chloroplasts are organelles proper to plants and other photosynthetic organisms and are the site of light energy conversion into chemical energy via photosynthesis. Light energy is captured by the chlorophyll pigments of photosystems I and II (PSI and PSII) and transferred to the photosynthetic electron chain located in the thylakoid membranes of the chloroplast. The resulting reducing equivalents and ATP are then used for carbon fixation and glucose production in the Calvin–Benson cycle, which takes place in the chloroplast stroma.

External physiological constraints can damage chloroplasts and/or render them superfluous for the plant cell. For example, an input of light energy superior to the photosynthetic capacity undeniably generates the production of toxic compounds such as reactive oxygen species (ROS), which will directly cause oxidative damage to the chloroplast and the cell [76]. On the other hand, a lack of light energy, such as a darkening of the leaf, results in a photosynthetic decrease and leads to carbon starvation. The combination of different stresses as well as their intensity can synergize to damage chloroplasts. For example, intense UV exposure combined with low temperature or drought aggravate ROS production by chloroplasts [77,78]. Given the metabolic importance of this organelle, the amount of chloroplast as well as its functionality must be finely controlled by the plant cell, which implies an efficient and adaptable renewal. Autophagy has already been described as a recycling process capable of turnover of organelles such as chloroplasts. Given the fact that chloroplasts are unique to plants, that they are not present in all cell types and that many stresses can lead to different damage to this organelle, it is important to take these considerations into account to understand how plant cell autophagy models this organelle. Indeed, the plant cell degrades chloroplasts in different autophagy-dependent manner: the so-called 'piecemeal' degradation pathway in which portions of the chloroplast are transported to the vacuole for degradation; alternatively, the entire organelle can be target for degradation in the vacuole (chlorophagy *per se*). As we discuss below, these different strategies of chloroplast degradation are to be put in a physiological context related to the cellular state and the stress encountered.

Our current knowledge suggests that there are two chloroplast piecemeal autophagy pathways: Autophagic degradation of ribulose 1,5-bisphosphate carboxylase/oxygenase (rubisco)-containing bodies (RCB) and the ATG8-interacting protein 1 (ATI1) body-mediated chloroplast degradation [79]. Ribulose-1,5-bisphosphate carboxylase/oxygenase (rubisco) is the key enzyme for carbon fixation during the dark phase of photosynthesis. Rubisco is present only in the stroma of chloroplasts and can represent up to 30% of total leaf protein in C3 species [80]. During natural or dark-induced leaf senescence, the decrease of rubisco content is much faster than the decrease in the number of chloroplasts in leaves [81,82]. These observations suggest that entire chloroplast degradation alone cannot explain the decrease in rubisco, suggesting that there is another independent mechanism for stromal degradation.

Using immunoelectron microscopy, Chiba et al. [83] showed that, in naturally senescing wheat (*Triticum aestivum*) leaves, rubisco is released from chloroplasts into the cytoplasm and transported to the vacuole for subsequent degradation in small spherical bodies, named RCBs. These RCBs were detected in the cytoplasm as well as in the vacuole. With a size of 0.4–1.2 μm in diameter, these vesicles do not contain a thylakoid membrane. RCBs are double-membraned as chloroplasts and different membrane-bound organelles (autophagosome) engulfing these RCBs as well as cytoplasm were described. Subsequently, it was shown that the formation of RCBs is dependent on autophagy because RCB production was abolished in *atg5* and *atg4* autophagy-deficient mutants [84]. Excised mature Arabidopsis leaves incubated in the dark for 20 h resulted in autophagy-dependent degradation of RCBs but not whole chloroplasts. Chloroplast protrusions, most likely stromules, were also decorated with ATG8 as confirmed by Spitzer et al. [85]. Moreover, in Arabidopsis *atg5* and *atg7* mutants, RCBs remained attached to these stromule-like structures and are not released into the cytoplasm [85]. Stromules consist of thin tubular stoma-enriched extensions of the chloroplast double membrane [83]. It has been proposed that stromules can be formed in response to different stresses such as drought, salt stress, viral infection, darkness and high temperature [87,88]. However, carbon starvation triggers the production of RCBs, as

reported by Izumi et al. [89]. Indeed, the number of RCBs in the cell increases drastically when an excised mature leaf of Arabidopsis is exposed to light, in the absence of exogenous sugar, and treated with 3-(3,4-dichlorophenyl)-1,1-dimethylurea, an inhibitor of photosynthetic electron transport. This observation suggests that the production of RCB is indeed associated with the carbon status of the tissues. Starch content also appears to be a key factor in RCB production as the appearance of RCBs tends to be higher in leaves of starchless mutants and lower in starch-excess mutants compared to the wild-type in both continuous light and day/night conditions [89]. It was postulated that RCB production is primarily mediated by carbohydrate accumulation rather than nitrogen limitation in individual leaves because significantly fewer RCBs were observed in leaves of nitrogen-limited plants compared to nitrogen-sufficient plants. However, the data also indicate that, in leaves of nitrogen-limited plants, the levels of chlorophyll, nitrogen, soluble protein and rubisco decreased rapidly, indicating that a mechanism other than the RCB pathway mediated the degradation of rubisco [89]. It may be that the RCB pathway is a form of selective autophagy of the chloroplast stroma (Fig. 2).

From a physiological point of view, the RCB pathway can be seen as a faster way of providing respiratory carbon rapidly. When the leaf is subjected to a prolonged darkness, photosynthesis is compromised, soluble sugar and starch reserves are depleted, autophagy is triggered, and the production of RCBs allows the recycling of the huge amount of carbon/nitrogen available in the form of rubisco and other stromal proteins as well as chloroplast envelope proteins. The recycling of the stroma without degrading the chloroplast entirely would allow to keep a basal

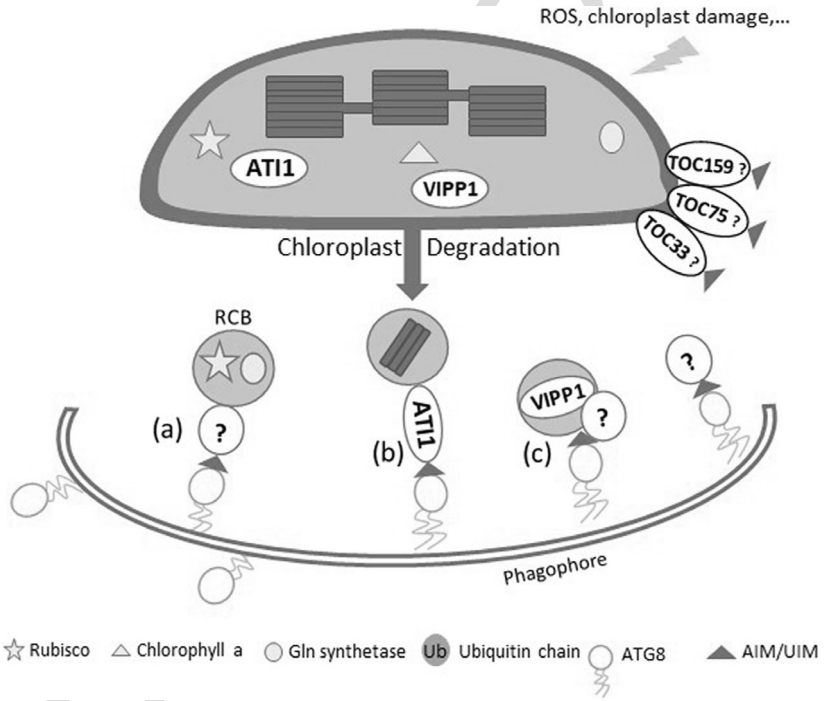

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Fig. 2. Chlorophagy pathways and putative selective autophagy receptors. Under stress conditions or during senescence, partial or whole chloroplast content are sequestered into various types of membrane-bound compartments for degradation in the vacuole. The different described types or routes for chlorophagy are presented schematically. (a) Through piecemeal-type degradation of stromal portions, chloroplast content is degraded as rubisco-containing bodies (RCBs) during senescence or nutrient starvation. The mechanism of cargo selection for RCBs is still unknown (question mark). (b) The ATG8-interacting protein ATI1 interacts with chloroplast proteins to generate ATI1 plastid-associated body (ATI-PS body). ATI1/2 has been reported as plant-specific receptor in chlorophagy, and can bind ATG8 in response to sugar starvation. How ATI1/2 are targeted to the chloroplast is not yet clear. (c) Vesicle inducing protein in plastid 1 (VIPP1) is a protein regulating chloroplast envelope integrity. Overexpression of VIPP1 reduces chloroplast swelling and mesophyll cells in a vipp1-deficient mutant display swollen chloroplast, which can be recognized by an ATG8-containing membrane structure. Additionally, TOC159, TOC75 and TOC33 are predicted AIM-containing proteins in *Arabidopsis*. By extrapolating what is known about the possible involvement of mitochondrial outer membrane proteins in the process of mitophagy, one can speculate that, in parallel, these AIM-containing chloroplast outer membrane proteins could play a role of receptor or scaffold protein in chlorophagy. Future research could confirm or refute this hypothesis.

photosynthetic capacity in case of return to light. By contrast, Wada et al. [54] observed simultaneous transport of RCBs as well as whole chloroplasts to the vacuole when the leaves were individually darkened (IDL). These differences in chloroplast autophagy can be explained by the fact that IDL leaves were treated for 1, 3 or 5 days, which is more intense than the 20 h treatment in most other studies including that of Ono et al. [81], and also by the fact that IDL treatment may not mimic natural senescence. When the plant is completely subjected to darkness, older leaves senesce, the decrease of chloroplasts (in size and number) is less rapid and degradation of chloroplasts is mainly accomplished through RCBs. This may reflect a strategy in which, when an individual leaf is suddenly subjected to unfavorable conditions compared to the rest of the plant, it is preferable to recycle the available nutrients in the affected organ before shedding it.

In addition, overexpression of vesicle inducing protein in plastid 1 (VIPP1), a protein that regulates chloroplast envelope integrity, reduces chloroplast swelling and protects chloroplasts against heat shock, whereas mesophyll cells in the *vipp1* mutant display swollen chloroplasts [90,91]. Swelling could be a mechanism by which the autophagy machinery may recognize damaged chloroplasts [92]. It has been suggested that swollen chloroplasts are initially recognized by ATG8-containing structures in an ATG8-mediated microautophagy [93], and that VIPP1 possibly plays a role in chlorophagy (Fig. 2). Moreover, VIPP1 regulates thylakoid biogenesis and maintenance [94].

From a molecular perspective, the consensus is that chloroplasts form stromules enriched in stroma, which facilitates their engulfment by a phagophore that may be initiated at the end of the stromule and evolve into an autophagosome. So far, no receptor is known to bind and connect the stromule to the expanding phagophore.

Two potential selective autophagy receptors of chloroplasts are the closely related proteins ATI1 and 2 [95] (Fig. 2). These proteins were identified using ATG8f as a bait in a yeast two-hybrid approach, and the interaction between ATG8f and ATI1/2 was subsequently confirmed *in planta* [96]. ATI1/2 possess two AIM motifs on either side of a predicted transmembrane domain. It was shown that in Arabidopsis hypocotyl epidermal cells, ATI1 and ATI2, are associated with the ER tubular network and occasionally form spherical structures called ATI1-ER. When seedlings are subjected to carbon starvation (germination on a sugar-free plate for 6 days and darkened for 24 h), ATI1 relocates from the tubular network to spherical structures, associated with ER tubules [96]. These spherical structures are highly dynamic along the ER network but do not contain ER luminal proteins. However, colocalization between ATI1-ER and ATG8f appeared to be a rare event, even under carbon starvation [96]. Parallel to ATI1-ER structures, and during carbon starvation, ATI1 forms ring-like structures delineating the chloroplast surface as well as small vesicles associated with chloroplasts called ATI1-PS [95]. In chloroplast-poor cells such as hypocotyl epidermal cells, ATI1-ER and ATI1-PS appear to co-exist upon darkening. By contrast, in cotyledon mesophyll cells (rich in chloroplast), ATI1 appears to form only ATI1-PS and the frequency of these structures increases with time during stress exposure [95], suggesting not only that ATI1 protein can generate two types of structures within the same cell, but also that its behavior changes depending on the cell type.

In mesophyll cells of mature Arabidopsis IDL (for 20 h) leaves, ATI1-green fluorescent protein (GFP) is only visible in senescing cells and the signal colocalizes with mRFP-ATG8f [95]. Chloroplasts in these senescing cells are depleted of stroma (visualized by chloroplast-targeted GFP) and the remaining small amount of stroma is enriched in vesicles formed by ATI1 on the surface of these chloroplasts, which will subsequently bud and detach from the organelle. The formation, budding and release of ATI-PS into the cytosol does not appear to be strictly dependent on functional autophagy as it occurs in *atg5* mutants. By contrast, the transport of ATI1 vesicles enriched in chloroplastic material into the vacuole is dependent on functional autophagy. By contrast to RCBs containing only stroma, intravacuolar structures containing either stroma (CT-GFP) or ATI1-GFP as well as plastid fractions containing stroma (CT-GFP) were described [95]. ATI1 was shown to interact with 13 chloroplastic proteins localized in the stroma, chloroplast envelopes and thylakoids, many of which are directly involved in photosynthesis and regulation of oxidative stress, such as the thylakoid protein NPQ4 (i.e. non-photochemical quenching 4), light harvesting complex a4, and APE1 (i.e. acclimation of photosynthesis to the environment). Biochemical and biophysical analyses showed that ATI1 and ATI2 are transmembrane proteins possessing long intrinsically disordered N-terminal regions that contain functional AIM [97]. Additionally, a set of predicted AIM-containing proteins in Arabidopsis chloroplast includes translocon of the outer membranes of the chloroplast (TOC)159, TOC75 and TOC33. These proteins are localized in the outer membrane of chloroplast, as components of the TOC complex involved in the import of chloroplast proteins [98] (Fig. 2).

It has been proposed that autophagosomes with an average diameter of 1 μm were sufficiently not large to engulf an entire chloroplast (average diameter of 5–7 μm). The hypothesis was therefore that piecemeal autophagy of chloroplast was the first step and that once the size of the chloroplast was trimmed, a phagophore could engulf what remained of the chloroplast. ATG8-enriched tubular structures capable of engulfing photodamaged chloroplasts has been described, suggesting that whole chloroplast removal by an autophagosome is possible, and termed chlorophagy. In Arabidopsis leaves treated with UVB (1200 $\mu mol \cdot m^{-2} \cdot s^{-1}$ for 3 h), a subset of chloroplasts is photodamaged in mesophyll cells. These chloroplasts show a discontinuous damaged envelope, and the stroma is missing [78]. The number of photodamaged chloroplasts increases with the length of UVB exposure. The damaged chloroplasts are subsequently selectively targeted to the vacuole, in contrast to that observed in autophagy-deficient mutants in which the number of chloroplasts lacking stroma does not decrease. These observations indicate that autophagy is capable of selectively recycle a photodamaged chloroplast from an unaffected chloroplast population. To test whether there is synergy between the RCB and chlorophagy pathways during UVB treatment, the number of RCBs and the percentage of cells showing chlorophagy after light stress treatment were calculated. It was found that the RCB pathway does not occur prior to chlorophagy. Accordingly, the hypothesis of a chloroplast thinned via RCB before being degraded through selective autophagy could be ruled out. Physiologically, it is hard to conceive that both RCB degradation and chlorophagy could act simultaneously. Alternatively, these two degradation pathways could affect two distinct populations of chloroplasts.

An unanswered fundamental question is how the cell can differentiate between damaged and healthy chloroplasts?

In mammals and yeast, damaged mitochondria are labeled with polyubiquitin chains prior to mitophagy. The modification of mitochondrial outer membrane proteins is facilitated by, among others, an E3 ligase.

In Arabidopsis, mutations in plastid ferrochelatases 2, an enzyme involved in heme biosynthesis, lead to an increased production of ROS and degradation of damaged chloroplasts, with a reduction in the number of chloroplasts in mesophyll cells. This degradative process involves plant U-box protein 4 (PUB4), an E3 ubiquitin ligase, which ubiquitylate the chloroplast surface [99]. Therefore, it has been postulated that PUB4 can directly (or indirectly) ubiquitylate photodamaged chloroplasts to mark them for removal. Recently, it has been shown that PUB4 is dispensable for the induction of both chlorophagy and RCB-mediated autophagy [100,101]. However, these results do not confirm that chloroplasts are not ubiquitylated similar to mitochondria before being selectively degraded by autophagy.

The degradation of chloroplasts by autophagy, although essential for plant survival, is still largely not well characterized. It is crucial to determine the selective autophagy receptors, if any, that allow targeting of the whole chloroplast as well as fragments of the organelle to phagophore. Also, because chloroplast degradation can be triggered by several stresses and/or plant developmental cues, it would be important to check whether any given chlorophagy SAR is also stress-dependent.

Pexophagy

Peroxisomes house enzymes both producing and degrading hydrogen peroxide, and are found in almost all eukaryotes with the exception of some protozoans [102,103]. Peroxisomes were first isolated from rat liver by Christian de Duve and Pierre Baudhuin in 1966 [104] and were later shown to physically and metabolically interact with other organelles such as chloroplasts, mitochondria and oil bodies [105,106]. In plants, glyoxysomes in germinating embryo are developmentally evolved into peroxisomes in the seedling [107]. For example, Graham [108] showed that germinating oilseed initially require fatty acid β-oxidation and the glyoxylate cycle for the conversion of stored lipids into carbohydrates. Glyoxysomes possess two glyoxylate cycle enzymes, isocitrate lyase (ICL) and malate synthase (MLS) [109,110]. The acetyl-CoA resulting from fatty acid β-oxidation in the glyoxylate cycle is consumed to produce sugars. When photosynthesis is established in mature seedlings, the glyoxylate cycle becomes antiquated, with the degradation of ICL and MLS [111,112].

Peroxisomes can be remodeled during early seedling development in three modes: the two-population model, the one-population model and the continuous turnover model [107]. In the two-population model, peroxisomes containing glyoxylate cycle enzymes are degraded in the vacuole via autophagy, and peroxisomes accommodating photorespiration enzymes are generated *de novo* from the ER. Nonetheless, the levels of ICL and MLS are not stabilized in autophagy mutants [109,113], in conflict with the basic prediction of the two-population model. In the one-population model, peroxisomes include both glyoxylate cycle and photorespiration enzymes [110,114,115], and ICL and

MLS are downregulated as seedlings transition to autotrophic mode [107]. Immunolabeling experiments using greening cucurbit cotyledons supported the one-population model [112,116]. Alternatively, it was suggested that peroxisomal proteins might be retrotranslocated out of the peroxisome and degraded by the proteasome but not by resident peroxisomal proteases [107,111,112,117]. However, this interpretation remains questionable [107]. In the continuous turnover model, peroxisomes are *de novo* generated from the ER and degraded via autophagy. This hypothesis was put forward following the observation that peroxisomes associate with lipid bodies during germination, with lipid bodies and plastids during the transition period, and with plastids following the consumption of lipid bodies [40]. Although this model has attracted less attention as compared to the others, it appears to be consistent with recent findings [107].

The maintenance and turnover of peroxisomes are essential for plant development and growth under normal conditions but more so under stressful conditions, both biotic and abiotic [67]. There is a physiological requirement for the cell to get rid of damaged peroxisomes to avoid excessive ROS accumulation and ensure that cellular redox homeostasis is maintained. The increased turnover of peroxisomal proteins relative to other organellar proteins suggests that pexophagy possibly occurs at a higher basal rate than other categories of selective autophagy [107]. Basal pexophagy rates also differ among various plant tissues [107]. For example, Arabidopsis *atg* mutants have relatively more peroxisomes and increased peroxisomal protein levels in hypocotyls and leaves but not in roots [109,118]. Also, heightened oxidative damage possibly causes the prevalence of pexophagy in aerial tissue [107].

Furthermore, in Arabidopsis, ATG8 was shown to be associated with peroxisome aggregates, clearly indicating that damaged peroxisomes are degraded by pexophagy [116]. The peroxisomal protease LON2 that is involved in the degradation of obsolete or damaged peroxisomal proteins also provided additional evidence for the existence of pexophagy in plants. Indeed, peroxisome turnover via autophagy is enhanced in LON2 non-functional background [113]. Intriguingly, Arabidopsis LON2 plays a role in plant peroxisomes similar to that which Drosophila Lon, a mitochondrial LON ortholog, plays in mitochondria by degrading pexophagy-promoting factors in peroxisomes [107,119].

Recent research has begun to uncover the mechanism of pexophagy through identifying the selective receptors involved in this pathway. In yeast, pexophagy can be triggered by a shift in nutrient conditions [120,121]. Atg30 and Atg36 were identified as SAR for pexophagy in *Pichia pastoris* and *S. cerevisiae*, respectively [120,121]. Both SARs interact with Atg8 and Atg11 acts as an adaptor factor in pexophagy [122]. Atg30 and Atg36 can be phosphorylated by the kinase Hrr25, a prerequisite for the recruitment of Atg11 [123,124]. In addition, Atg30 can interact with the peroxins Pex3 and Pex14 to generate a receptor protein complex (RPC), and binds the integral peroxisomal membrane protein Atg37, an acylCoA-binding protein interacting with palmitoyl-CoA [125]. In *Hansenula polymorpha*, Pex3 is removed from the peroxisomal surface by the ubiquitin–proteasome system (UPS) prior to sequestration and degradation of the organelle by pexophagy [126] (Fig. 3).

In mammals, several stress conditions can stimulate pexophagy including hypoxia, oxidative stress, nutrient deprivation, and peroxisomal dysfunctions (AAA-complex defects). However, only the ubiquitin-binding autophagy receptors NBR1 and SQSTM1/p62 have been shown to facilitate peroxisomes association with the phagophore. Ubiquitylation of peroxin protein (PEX)5 and other peroxisomal membrane proteins may initiate pexophagy. PEX14 has been reported to link peroxisomes to the phagophore either by directly binding LC3 family members or TNKS1/TNKS2 [127]. In humans, the counterpart of Atg37, ACBD5, localizes to peroxisomes and is specifically required for pexophagy. ACBD5/ATG37 may be involved in the assembly of the pexophagic RPC [125]. Under amino acid starvation, PEX2 proteins are stabilized upon mTORC1 inhibition. Upregulation of PEX2 leads to the ubiquitylation of peroxisomal proteins [PEX5, peroxisomal membrane protein (PMP)70, and others unspecified], signaling NBR1 and p62-mediated pexophagy [128]. Activation of ATM (i.e. ataxia-telangiectasia mutated) by ROS phosphorylates PEX5, which facilitates PEX5 monoubiquitylation by the PEX2, PEX10 and PEX12 complex (E3 ligase complex) [129]. The autophagy receptor p62 recognizes ubiquitylated PEX5 and recruits the core autophagy machinery to eliminate damaged peroxisomes under oxidative stress [130]. In humans, noise-induced hearing loss is a strongly prevalent sensorineural hearing impairment affecting individuals of all ages. Pejvakin-mediated pexophagy can protect auditory hair cells against noise-induced damage [131] (Fig. 3).

Although pexophagy has been long postulated to be active in plants, no clear evidence of a selective receptor/adaptor has been reported for this pathway. To date, no related counterparts of Atg36 or Atg30 have been described in plants. However, circumstantial

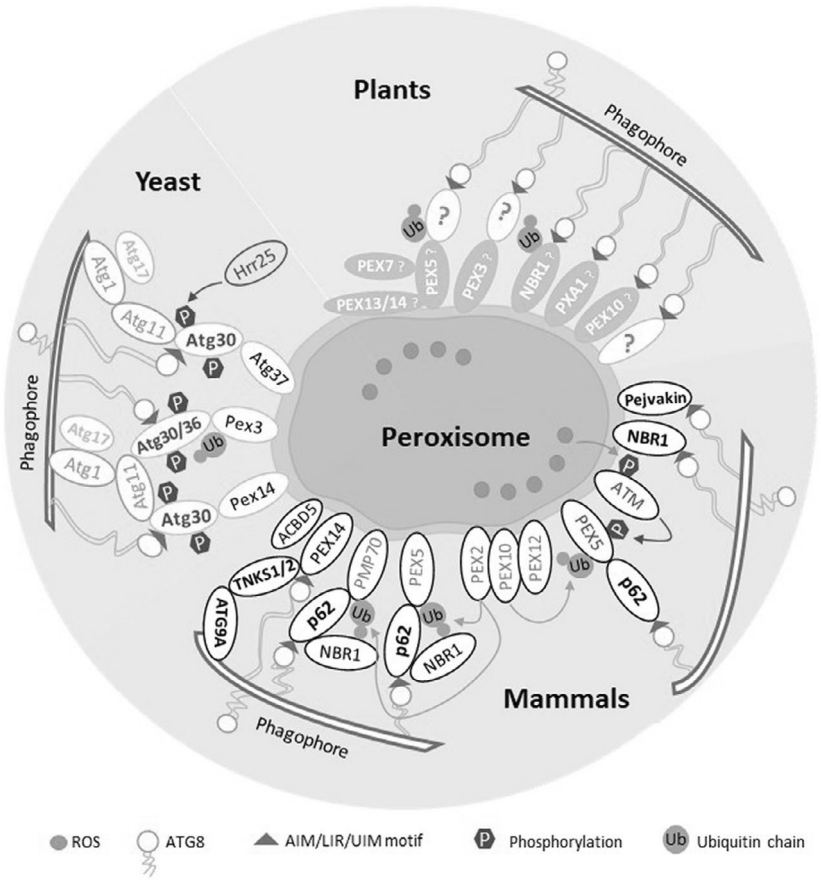

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Fig. 3. Selective autophagy receptors in pexophagy. In yeast, a shift in nutrient status triggers pexophagy. Atg30 and Atg36 are reported as pexophagy receptors in *P. pastoris* and *S. cerevisiae*, respectively. These receptors link peroxisomes to the phagophore by binding to Atg8. Atg11 plays a key role as a scaffold protein for both *P. pastoris* and *S. cerevisiae* mitophagy. Atg30 and Atg36 are phosphorylated by the kinase Hrr25 to allow recruitment of Atg11. Atg11 homooligomer interacts with the selective autophagy receptors, the scaffold protein Atg17 and the Atg1 kinase complex. In addition, Atg30 could interact with the peroxins Pex3 and Pex14 to form a RPC. Atg30 also binds to the integral peroxisomal membrane protein Atg37, an acylCoA-binding protein interacting with palmitoyl-CoA. The proteins working along Pex14 in linking the peroxisome to the phagophore are yet to be identified. In *H. polymorpha*, Pex3 is removed from the peroxisomal surface by the UPS prior to sequestration and degradation of the organelle by pexophagy. In mammals, pexophagy is induced by several stresses including hypoxia, nutrient deprivation and peroxisomal dysfunction. The ubiquitin-binding autophagy receptors NBR1 and SQSTM1/p62 have been shown to facilitate pexophagy. Other pexophagy receptors include PEX14, which targets peroxisomes to the growing phagophore via physical interaction with LC3 proteins or with TNKS1/TNKS2 (tankyrases1/2). Human ACBD5 (Atg37 ortholog) is also involved in pexophagy by regulating the PEX14-containing receptor protein complex. PEX2 can ubiquitylate peroxisomal proteins (such as PEX5, PMP70) under amino acid starvation, initiating NBR1 and p62-dependent pexophagy. Under oxidative stress, ATM (ataxia-telangiectasia mutated protein kinase) phosphorylates PEX5, leading to its mono-ubiquitination by an E3 ligase complex (PEX2, PEX10 and PEX12). Additionally, ubiquitylated PEX5 can subsequently recruit the autophagy machinery on the damaged peroxisome. Oxidized Pejvakin protein by noise stress interacts with LC3 and activate pexophagy to protect auditory hair cells against noise-induced damage. In plants, there are several potential candidates for selective receptors in pexophagy, such as PEX5, PMPs, PEX3 and PEX14 (question mark). However, plants do not have obvious orthologs of either Atg30 or Atg36, and there is no clear evidence for plant NBR1 involvement in pexophagy. The peroxisomal proteins PXA1 and PEX10 were recently showed to interact with ATG8 via an AIM motif, suggesting that they could act as putative pexophagy receptors.

evidence suggests that plant NBR1 may be involve in plant pexophagy. In mammals and plants, it has been reported that the peroxisome receptor proteins PEX5 and PEX7 recognize and bind to newly synthesized peroxisome matrix proteins in the cytosol before the receptor-cargo complex is anchored on the membrane at the docking complex formed by PEX13 and PEX14 (peroxisomal membrane proteins) [132]. Moreover, the ubiquitylation of PEXs, such as PEX3, PEX5 and PEX14, may trigger pexophagy in plants [107]. The

peroxisome proteins PXA1 and PEX10 were recently shown to bind ATG8 via an AIM, suggesting that they could be pexophagy receptors [133,134].

ER-phagy/reticulophagy

The ER is one of the organelles occupying the most cell volume and its structures explore almost every nook and cranny of the cytoplasm not occupied by the vacuole in the plant cell. The ER also act as a multitasking cellular factory involved in correct folding and maturation of almost 40% of the proteome [135]. However, protein folding can fail leading to misfolded/unfolded proteins that accumulate in the lumen of the ER triggering ER stress and impairing its function, which can ultimately lead to cell death. Several environmental and cellular factors can severely increase the frequency of ER stress, such as saline and drought stress, heat, nutrient deficiencies, and pathogens, at different growth and developmental stages, including when the demand for secreted proteins is higher [136,137]. ER stress can also be induced experimentally by pharmacological treatments such as tunicamycin (TM) and dithiothreitol treatments, which are known to affect protein folding in the ER [137,138]. TM induces ER stress by blocking oligosaccharide (N-glycosylation) transfer to nascent polypeptides and preventing their proper folding, whereas dithiothreitol disrupts the redox conditions required for the formation of disulfide bridges in proteins.

Eukaryotes have evolved to protect themselves from ER stress. The unfolded protein response (UPR) is the set of pathways implemented to decrease ER stress via transcriptional and translational responses. As a result of UPR signaling, the ER-associated degradation pathway and ER autophagy (ER-phagy) are triggered. In Arabidopsis, there are two main pathways conducive to UPR: the basic-leucine zipper transcription factor family protein 28 pathway and the inositol-requiring enzyme 1 pathway [139]. More mechanistic information on the UPR response is available elsewhere [137,140]. The UPR involves increasing the synthesis of chaperones that stabilize protein conformation and improve the folding capacity of the ER, in addition to other components of the ER-associated degradation system, which allows the export of aberrant peptides to the cytosol for degradation via the 26S proteasome [141]. Although the link between the UPR and ER-phagy is still largely unclear, some evidence is emerging. For example, autophagy can be activated by the accumulation of misfolded protein in the ER lumen [142]. It was also shown that in Arabidopsis, autophagy is involved in the degradation of ER components in response to TM or dithiothreitol in an inositol-requiring enzyme 1b-dependent manner [143]. Moreover, recent studies have identified different receptors involved in the selective degradation of the ER and in relatively specific physiological conditions.

In plants, four types of ER-phagy receptors have been identified, namely secretory protein 62 (Sec62), ATI1/2, C53 and Rtn1/2 [144–147] (Fig. 4). Meanwhile, in yeast, Atg39 and Atg40 in *S. cerevisiae* bind both Atg8 and Atg11. Atg40 is a RHD-containing ER-phagy receptor more likely acting as FAM134B, a mammalian ER-phagy receptor [148]. A soluble ER-phagy receptor, Epr1, has been reported in *Schizosaccharomyces pombe*. Epr1 acts as a linker between Atg8 and VAPs, with VAPs mediating the formation of ER-plasma membrane contact, also important for ER-phagy [149]. Additionally, an ER membrane protein, Lnp1, was also described to be involved in yeast ER-phagy [150]. In mammals, several mammalian ER-phagy receptors have been identified: FAM134B [151], SEC62 [151], RTN3 [152], CCPG1 [153], ATL3 [154], TEX264 [155], TRIM13 [156], CALCOCO1 [157] and C53 [146,158].

Sec62 is a component of the Sec translocation complex, along with Sec61 and Sec63 proteins, allowing the integration of newly synthesized peptides into the ER lumen. Arabidopsis Sec62 (AtSec62) is structurally different from its yeast and mammalian counterparts in that it has three transmembrane domains and two AIMs facing the cytosol, with the C-terminal portion in the lumen of the ER [144]. Upon ER stress (induced by TM or dithiothreitol), Sec62 is enriched in ATG8-positive ring-like structures in root cells of 5-day-old transgenic plant [144]. This observation is strictly related to ER stress because similar structures containing AtSec62 are not observed after carbon/nitrogen deprivation or benzo-(1,2,3)-thiadiazole-7-carbothioic acid *S*-methyl ester (a salicylic acid agonist which can induce autophagy) treatment. It is also dependent on fully functional autophagy because similar structures were not found in autophagy-deficient mutants (Arabidopsis *atg5*/*7* mutants). AtSec62 interacts with ATG8 via its two AIMs, is degraded in the vacuole, and AtSec62-deficient seedlings are more sensitive to ER and salt stress than the wild-type plant. By contrast, over-expression of AtSec62 increases tolerance to both forms of stress. However, the relationship between UPR and AtSec62-mediated ER-phagy is still unclear. It is worth stressing that both *atsec62* and UPR mutants are phenotypically similar, with decreased fertility and inhibited vegetative growth, although it can be argued that such phenotypic manifestation could also result from a malfunction of the

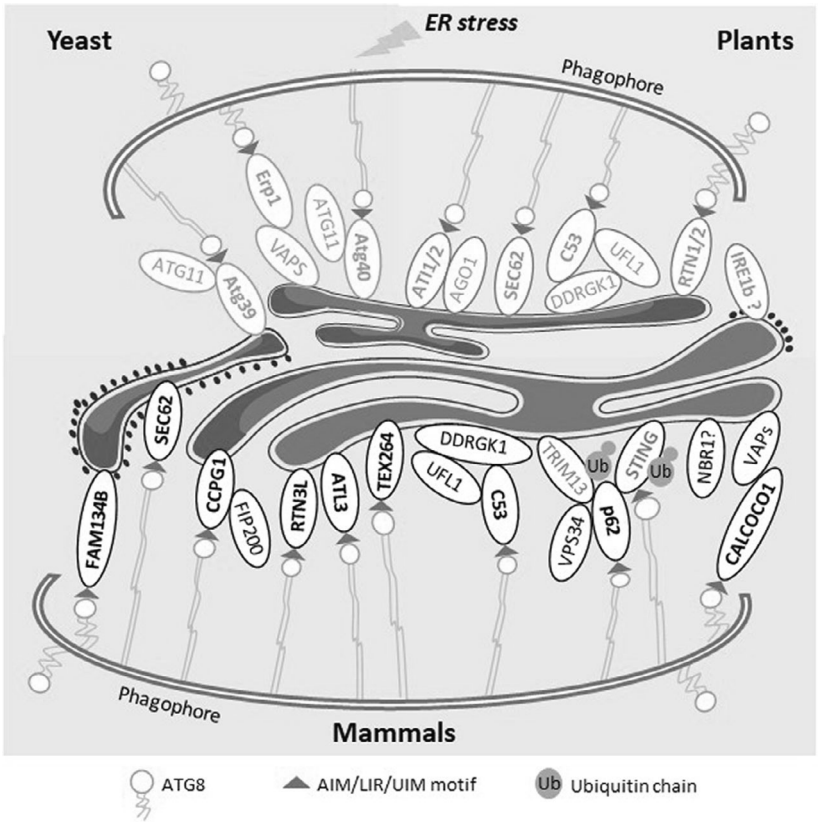

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Fig. 4. Selective autophagy receptors in reticulophagy. In yeast, Atg39 and Atg40 bind both Atg8 and Atg11. Atg40 is a RHD-containing ER-phagy receptor, and more likely an ortholog of mammalian ER-phagy receptor FAM134B. A soluble ER-phagy receptor, Epr1, has been reported in *S. pombe*. Epr1 link Atg8 and VAPs, with VAP mediating ER-plasma membrane contact. ER-phagy receptors are well studied in mammals. Some of these receptors are mentioned (FAM134B, SEC62, RTN3, CCPG1, ATL3, TEX264, TRIM13, CALCOCO1 and C53). FAM134B and Sec62 are localized to curved ends of ER sheets, whereas RTN3 and ATL3 work at ER tubules. The ER subdomain containing high insoluble proteins are directed to ER-phagy by CCPG1 protein. TEX264 have a C-terminal LIR motif that interacts with ATG8 throughout the ER network. TRIM13 works as selective receptor for p62 and promotes its degradation through ER-phagy. CALCOCO1 also has LIR/UIR domain to bind with LC3 and initiate VAP-mediated degradation of tubular ER. Cytosolic protein C53 interacts with ATG8 in complex with UFL1 and DDRGK1 to work as receptor in animal and plant cells during ER stress. STING protein has several LIR domains for LC3 binding and it directs p62 to ER-phagy. The involvement of NBR1 in reticulophagy is still debatable. ATI1 and ATI2 were shown to act as AIM motif-containing reticulophagy receptors in *A. thaliana*. These plant-specific proteins are localized in the ER membrane under stress conditions and have no known homologs in yeast or mammals. ATI1 or ATI2 can form functional complex with AGO1 (argonaute 1) on the ER and in the autophagosome. The family of ER-phagy receptors in plants also consists of AtSec62, the reticulon homology domain (RHD)-containing proteins Rtn1 and Rtn2 (from *Zea mays*), and the soluble protein AtC53, a cross-kingdom conserved selective autophagy receptor.

ER translocon. Indeed, *atsec62* mutants show a defective phenotype in growth stages that require high protein biosynthesis, which has been shown to be a risk factor for ER stress [144].

It is not yet clear which signal allows AtSec62 to functionally switch from a translocon component to an ER autophagy receptor. It may be that the C-terminus of AtSec62 could play a role in detecting unfolded/misfolded proteins. AtSec62 may then congregate at the vicinity of these polypeptides determining the portion of the ER to be degraded. It may be that unfolded/misfolded proteins could also obstruct the translocon, a potential source of ER stress [159], which could trigger a functional modification of AtSec62, additionally acting as a receptor determining the location and extent of the ER fragment to be targeted by the autophagy pathway. It would be interesting to check whether Sec62-mediated ER-phagy is possibly linked to the Sec translocon functional defect.

Accumulation of unfolded/misfolded proteins in the endoplasmic reticulum is not the only pathway triggering ER-phagy. It was proposed that ATI1 and ATI2 may act as receptors for ER-phagy under carbon starvation [145]. When Arabidopsis mature leaves are

darkened for 24 h, ER marker-enriched ATI1 vesicles are observed in the vacuole of epidermal cells and colocalize with ATG8f. This observation is dependent on the key sensor kinase target of rapamycin (TOR), as well as on a functional autophagy pathway, but is independent of ER stress. Complementary biochemical and genetic approaches were used to identify the ER-localized membrane steroid binding protein 1, a member of the membrane associated progesterone receptor family, as well as MAPR4 as interactors of ATI1 [145]. Autophagic turnover of membrane steroid binding protein 1 depends on ATI proteins, suggesting a role for the ATI proteins in selective ER-phagy. ATI1 also colocalizes and interacts with ER-localized argonaute 1 (AGO1) suggesting a role in AGO1 degradation [145].

It is not clear whether the described ATI1-mediated ER-phagy is a mechanism of ER degradation to recycle nutrients upon darkening or whether bits of ER are degraded as collateral damage of the ATI1-mediated selective degradation of proteins such as MSPB1 or AGO1 localized on these organelles upon darkening. Similarly, activation of autophagy in plants starved for phosphate might be the consequence of the ER stress response in the root tip, rather than as a mean for the recycling of phosphate [160].

Another physiological inducer of ER-phagy is the blockage of ribosomes on the surface of the rough ER. During translation–translocation of a nascent peptide via an ER-associated ribosome, the ribosome may become stalled. This phenomenon can occur when mRNAs lack a stop codon or are prematurely adenylated causing ribosomes to be stalled on polyadenylation chains [141]. It can also occur on free ribosomes in the cytoplasm, in which case the ribosome-associated protein quality control response machinery rescues the ribosome, with the peptide and the defective mRNA cleared via ubiquitylation. Stalling of ER translocon-associated ribosomes appears to require a special pathway, involving ufmylation of the large ribosome subunit protein ribosomal protein L26 (RPL26) [161,162]. This addition of ubiquitin-fold modifier 1 (UFM1) on RPL26 requires the E3 enzyme ligase UFL1 as well as its ER membrane adaptor Asp-Asp-Arg-Gly-Lys domain-containing protein 1 (DDRGK1) [163] (Fig. 4). Although related to ER homeostasis, it is still unknown how ribosome ufmylation can alter its function and clearance. A recent interesting work identified C53 as a cytosolic protein likely capable of linking stalled ribosome at the ER surface and ER-phagy [146]. The current model of C53 function is that, under non-stressful conditions, C53 is bound to UFL1 and DDRGK1 at the ER surface, with UFM1 preventing the interaction between the tripartite complex and ATG8. During ribosome stalling, UFM1 is transferred from the C53 receptor complex to the tail of RPL26, exposing a non-canonical shuffled AIM on the intrinsically disordered region of C53, for ATG8 binding and subsequent recruitment to the autophagosome [146]. However, it was not possible to confirm C53-dependent degradation of small and large ribosomal subunits, highlighting a highly selective, yet unknown cargo selection mechanism of C53.

Reticulons (Rtns) are a family of proteins that adjust the size, shape and dynamics of the endoplasmic reticulum tubule and cisternae network [164,165]. A critical role for Rtn proteins in ER homeostasis, turnover and autophagy has been discovered in maize endosperm aleurone cells [147]. In a study of endosperm-expressed and ER-localized maize Rtn1 and Rtn2, it was suggested that these proteins do function as autophagic receptors for ER autophagy under ER stress. Rtn1 and 2 are membrane proteins that localize in the ER membrane and, more precisely, in the three-way tubular ER junctions. Although Rtn2 does not relocalize during ER stress, the affinity between ATG8 and Rtn2 increases when cells are treated with dithiothreitol, and Rtn2 positive autophagosomes can be observed [147]. This affinity between Rtn2 and ATG8 is mediated by four AIMs. Dithiothreitol treatment also increased the affinity between Rtn2 and calnexin, a transmembrane chaperone involved in the protein folding machinery, as well as two additional ER lumenal proteins, the chaperone binding immunoglobulin protein and the protein disulfide isomerase. This differential affinity of Rtn1 and 2 for ATG8, their numerous functional AIMs and their role in ER autophagy under ER stress led to the hypothesis that these proteins act as ER-selective autophagy receptors.

Nucleophagy

Nuclear integrity and maintenance are essential to all eukaryotic cells. Autophagy degrades nuclear components essentially in two ways: micronucleophagy and macronucleophagy. Micronucleophagy is the prerogative of certain unicellular (such as baker's yeast) or filamentous (such as *Aspergillus* and *Magnaporthe oryzae*) fungi, or certain protozoa [166]. This degradation pathway is almost independent of core autophagy regulators and operates at the site of contact between the nucleus and the vacuole. The main players are the membrane proteins Vac8 (vacuole protein 8) and Nvj1 (nucleus vacuole junction), which interact with each

other at the contact site and facilitate the respective invagination and vesiculation of the two organelles (Fig. 5) [167]. Micronucleophagy involves membranes interactions and rearrangements with distinct molecular mechanisms. We will not develop this pathway further here, which has not yet been described in plants. Alongside micronucleophagy or piecemeal nucleophagy (PMN) (Fig. 5), a form of selective microautophagy hitherto exclusively described in certain fungi, there is macronucleophagy characterized by the degradation by autophagosomes of nucleus-derived vesicles, targeting specific component such as the nuclear pore complex, heterochromatin, individual nuclear protein or the entire nucleus [168].

In yeast, the protein Atg39 was identified as a macronucleophagy receptor, although it may also be involved in micronucleophagy [148]. Atg39 is induced by nitrogen starvation or ER stress and is localized in the nuclear membranes. Atg39 binds to both the outer and the inner nuclear membrane via its N-terminal transmembrane domain and its C-terminal amphipathic helices are in the perinuclear space. The cytoplasmic region of Atg39 interacts with Atg11, which recruits the autophagy machinery, and Atg8 to allow autophagosome formation on the surface of the nuclear envelope [148]. Vesiculation of the nuclear envelope entrapping intranuclear material is then targeted to a phagophore. The resulting autophagosome with the intranuclear material surrounded by four layers of membrane fuses with the vacuole and the intralumenal vesicle is surrounded by three membranes as in the case of micronucleophagy-derived lumenal vesicles.

There is no Atg39 counterpart in mammalian or plant cells. However, in response to a specific insult, defined mammalian proteins [e.g. lamins and sirtuin,

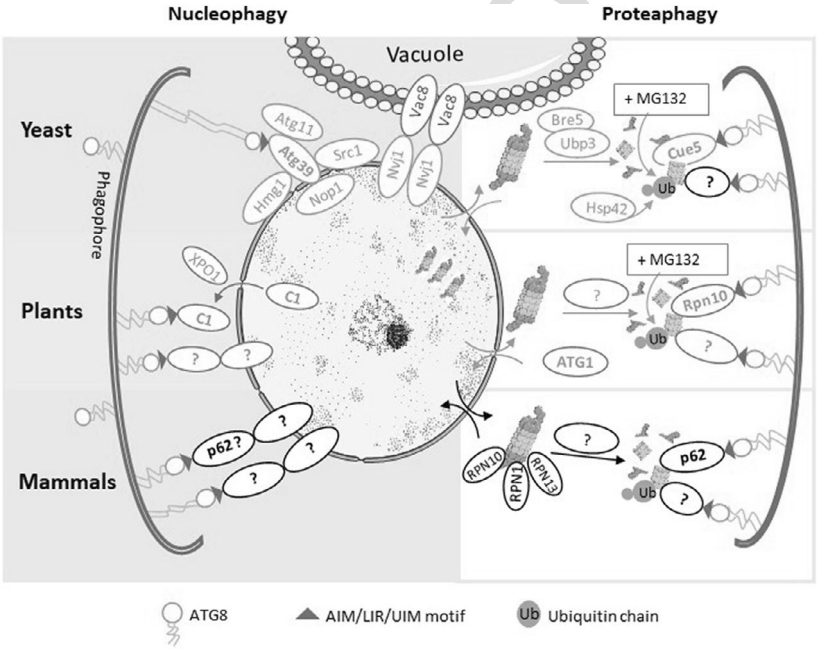

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Fig. 5. Selective autophagy receptors in nucleophagy (left) and proteaphagy (right). In yeast, PMN takes place under nutrient-rich and early nitrogen starvation conditions. PMN is initiated by the formation of nucleus-vacuole (NV) junctions involving Nvj1 (nucleus) and Vac8 (vacuole) proteins. Another yeast protein involved in nucleophagy is Atg39, which localizes to the nuclear envelope and interacts with Atg11. Atg39 also interacts with the nuclear envelope proteins Hmg1 and Src1 and the nucleolar protein Nop1 and acts as a macronucleophagy receptor. In mammals, p62 is the only known selective nucleophagy receptor; other speculative components are still to be identified (question mark). In plants, an abundance of C1 geminivirus nuclear proteins triggers autophagy through a nuclear export-dependent process mediated by XPO1. C1 interacts with ATG8 in the nucleus and the complex is transported to the cytoplasm as a result of XPO1. The degradation of proteasome through autophagy is known as proteaphagy. The proteasome inhibitor MG132 was instrumental in understanding the mechanism of proteaphagy. In yeast, the 26S proteasome can be ubiquitinated in an Hsp42-dependent manner and targeted to autophagosome membranes by the selective proteaphagy receptors Cue50. Ubiquitin carboxyl-terminal hydrolase 3 (Ubp3) regulates proteaphagy along with Bre5 by ubiquitination of Cue5 and its binding to Atg8. In Arabidopsis, inactivation of proteasome degradation causes ubiquitylation of RPN10, which is recognized by ATG8 via its C-terminal ubiquitin-interacting motif (UIM) and acts as a proteaphagy receptor. In mammals, the proteasome subunits RPN1, RPN10 and RPN13 have been identified as major ubiquitylated targets, and are poly-ubiquitinated upon amino acid starvation, before being recognized by p62.

silent mating type information regulation 2 homolog (SIRT1)] and plant virus protein (e.g. geminivirus protein C1) can be targeted for degradation by autophagy [169,170]. Upon oncogenic insults, lamins associated with heterochromatin domains interact with LC3 and the DNA–protein complexes are exposed to the phagophore as a nucleus-derived vesicle. How the vesicle is recognized by the autophagy machinery is still unclear. Mammalian SIRT1 binds to LC3 in the nucleoplasm during nuclear senescence and the protein complex is exported through the nuclear pore complex to the cytosol where it is engulfed by a growing phagophore [170]. It is not clear whether the interacting LC3 is later lipidated or not, or whether the recognition of the complexed SIRT1 to LC3 by the autophagy machinery involves other molecular mechanisms.

A similar targeting mechanism as described for SIRT1 of a pathogenic virus protein for autophagy degradation from the plant nucleus was recently reported [169]. C1 is a conserved pathogenic protein among geminivirus species [169]. As a plant defense mechanism, C1 is complexed to Atg8 in the host nucleoplasm, and the complex exportation to the cytosol is mediated by exportin 1 (XPO1) which interacts with ATG8 [169]. In the cytoplasm, XPO1 is released and the C1-Atg8 dimer is engulfed by a phagophore. Intriguingly, the commonality in the autophagic degradation of mammalian SIRT1 and viral C1 by the plant cell suggests a functional localization of LC3/Atg8 proteins in the nucleus and that lipidation of LC3/Atg8 is not required for their interaction with at least some autophagic cargo.

Proteaphagy

The two main pathways of protein degradation in eukaryotic cells are the autophagy pathway and the UPS. Although the functional connections between these two systems are known, work in Arabidopsis has shown that the proteasome can be selectively degraded by autophagy (coined proteaphagy) [46]. Other work subsequently validated this discovery by reporting that the autophagic degradation of the proteasome by eukaryotic cells is, beside a few mechanistic peculiarities, active in all eukaryotic cells [171]. The 26S proteasome is a 2.5-MDa protein complex, located in the cytosol and the nucleus [172,173]. It consists of two functionally distinct sub-particles: the 20S core protease and the 19S regulatory particle. In Arabidopsis, bulk autophagy degradation of the proteasome is induced by nitrogen starvation and is regulated by the ATG1 kinase [174]. In addition, inactivation of the proteasome can target the complex for selective degradation by autophagy. Genetic and pharmacological inactivation of the proteasome revealed that its selective autophagic degradation is independent of the ATG1 kinase in Arabidopsis [174]. Inactivation of the Arabidopsis proteasome triggers ubiquitylation of its subunit RPN10, which then can interact with ATG8 via a novel interacting motif termed UIM at its C-terminus. Therefore, ubiquitylated RPN10 can target the inactive proteasome to the phagophore for autophagic degradation [46,174,175]. The RPN10 ubiquitylation pathway and its regulation have not yet been clarified in plants.

In yeast, the 26S proteasome can be ubiquitylated in an Hsp42-dependent manner and shepherded to expanding autophagosome membranes by the selective proteaphagy receptors Cue5 [176]. Ubiquitin carboxyl-terminal hydrolase 3 (Ubp3) has been reported to play a role in proteaphagy along with Bre5, which supports the ubiquitylation of Cue5 and its binding to Atg8 [176]. In mammals, the proteasome subunits RPN1, RPN10 and RPN13 have been identified as major ubiquitylation targets, and are poly-ubiquitylated upon amino acid starvation, then recognized by the selective autophagy receptor p62 [177,178].

Ribophagy

Quantitatively and qualitatively, the level of protein biosynthesis is an important aspect of the cellular response to stress and conditions the degree of adaptation to the resulting physiological insult. An anchor point for this regulation is the level of activity and quantity of active ribosomes in the cell [179]. Selective degradation of ribosomes and ribosomal RNA by autophagy (ribophagy) was first described in yeast. Indeed, in response to nutrient starvation, cells degrade and recycle ribosome components to reprogram and stabilize their metabolism [180]. The ribosomal 60S subunit is selectively degraded by ribophagy in response to amino acids starvation and this pathway requires the activity of Ubp3/Bre5 [181] (Fig. 6). Ubp3 can selectively de-ubiquitinylate Rpl25, whereas Ltn catalyzes the opposite reaction on Rpl25 under normal conditions [182]. Nuclear fragile X mental retardation interacting protein 1 (NUFIP1) was identified from lysosomal proteome under mTORC1 inhibitory condition as potential receptor for ribophagy in mammals [183]. A plant NUFIP1 relative from Arabidopsis, AtNUFIP1, shares limited sequence similarity with animal NUFIP1 and importantly, lacks the LIR/AIM motif present in mammalian NUFIP1. Thus a possible role of AtNUFIP1 as a receptor for ribophagy in plant is still questionable [184,185]. Interestingly, in

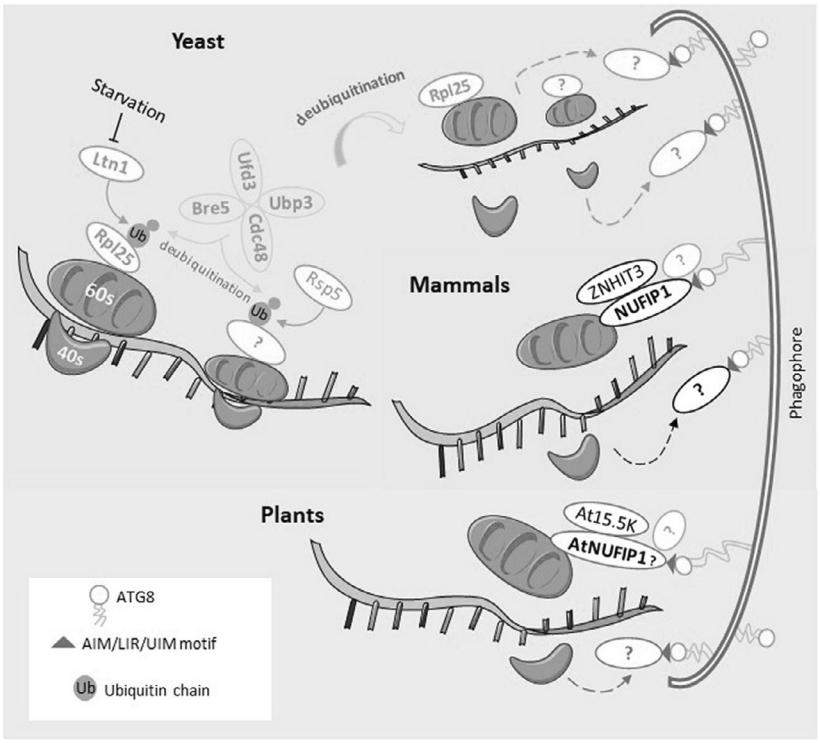

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Fig. 6. Selective autophagy receptors in ribophagy. Selective degradation of ribosomal and ribosomal RNA by autophagy is known as ribophagy. During nutrient starvation, yeast 60S ribosomal subunits are selectively degraded through a Ubp3/Bre5 ubiquitin protease-dependent pathway. Ubp3 can selectively deubiquitylate Rpl25, whereas Ltn catalyzes the opposite reaction on Rpl25 under normal conditions. Mammalian NUFIP1 (nuclear fragile X mental retardation interacting protein 1) and its partner ZNHIT3 redistribute from the nucleus to autophagosomes, lysosomes and ribosomes under nutrient deprivation conditions. NUFIP1 binds to LC3B and delivers ribosomes to autophagosomes, suggesting that NUFIP1 is a mammalian ribophagy receptor. Arabidopsis NUFIP protein contains the AIM domain. However, its role as plant ribophagy receptor is still questionable.

Arabidopsis autophagy deficient mutants such as *atg5*, the degradation of ribosome and rRNA is affected suggesting the implication of this pathway in regulating the levels of ribosomes in plants [186]. By contrast to starvation responses in yeast regulated by the TOR kinase, plant cells might undergo ribophagy when subjected to different environmental cues such as high temperature, limited water availability or immune response to pathogens. Thus, plant specific ribophagy is still uncharted territory and could be a valuable approach for identifying novel environmental stress adaptation mechanisms.

Aggrephagy

As described previously, physiological constraints such as heat, salinity or oxidative stresses can accelerate protein misfolding and lead to an accumulation of unfolded/misfolded proteins in the ER lumen leading to ER-phagy. However, upon these stresses, proteins present in the cytosol can also either misfold or be denatured. These aberrant polypeptides can be highly toxic because they can deleteriously interact with cellular essential components [187]. These denatured or unfolded proteins are likely to crosslink and, through hydrophobic interactions, generate protein aggregates inaccessible to the proteasome machinery [188]. Nevertheless, autophagy can degrade these protein aggregates in a mechanism called aggrephagy [187]. In mammalian cells, two structurally related proteins, p62 and NBR1, act as cargo receptors for selective autophagy degradation of aggregated proteins [189]. As mentioned previously, plant NBR1 proteins have a unique structural organization and are bifunctionally equivalent of the mammalian p62 and NBR1 proteins [39].

Plant NBR1 are the most studied plant selective autophagic receptors and play a major role in aggrephagy. Plant NBR1 are dispensable for normal growth [190]. However, it has been shown that plant NBR1 are essential for drought, oxidative stress and heat stress tolerance because *nbr1* mutants, just like autophagy-deficient mutants, are hypersensitive to

these physiological constraints [190]. In addition, the AIM motif-dependent binding of plant ATG8 by NBR1 is required for stress tolerance [190].

Plant NBR1 bind hydrophobic proteins aggregates in the cytoplasm prior to their degradation via autophagy. Consistent with this property, Zhou et al. [190] showed that, in contrast to wild-type plants grown at 22 °C or subjected to heat stress (45 °C) in which NBR1 is concentrated in the soluble fraction of proteins extract, NBR1 was found in protein aggregates in *atg7* mutant plants, suggesting an accumulation of aggregates in this autophagy deficient mutant when subjected to heat stress (45 °C for 3–9 h). NBR1-enriched insoluble aggregates were ubiquitylated [190]. Similarly, under heat stress, large aggregates of NBR1 and ATG8-containing proteins appear in the cytoplasm of Arabidopsis root cells as a result of their transfer from 22 °C to 37 °C for 4 h [191]. Furthermore, using an artificial aggregation-prone protein, GFP-FL2ΔSP, not only are autophagy and NBR1 essential for vacuolar degradation of cytosolic condensates, but also NBR1 coalesces with GFP-FL2ΔSP aggregates prior to aggregation [191]. This could be linked to the PB1 domain present in NBR1, allowing homo-oligomerization [190]. In addition to autophagy, these GFP-FL2ΔSP aggregates are also rapidly degraded through multiple protein quality control pathways, such as the UPS. This suggests that GFP-FL2ΔSP is ubiquitylated, which is consistent with the hypothesis that NBR1, through one of its ubiquitin-specific binding domains, would recognize its cargo via ubiquitylation [190]. Yet Jung et al. [191] could not highlight a form of GFP-FL2ΔSP carrying one or more ubiquitin. By contrast, evidence was provided of a polyubiquitylated form of NBR1 based on an additional 100-kDa band frequently observed by anti-NBR1 immunoblot in addition to the 70-kDa band corresponding to NBR1 [191]. The autophagy flux was not correlated with the intensity and duration of heat shock exposure. The data indicate that autophagy flux to the vacuole is increased by a short (1–8 h) exposure to 37 °C heat stress, whereas, when seedlings are either exposed to 37 °C heat stress for a longer period (12 h) or to 44 °C for a short period (2 h), autophagy was activated as monitored by the increase in the lipidated form of ATG8, although autophagy flux was impeded.

These observations agree with the recent model proposed by Thirumalaikumar et al. [192] involving NBR1-mediated autophagy during heat shock memory. When the plant cell is exposed to heat stress, HSFA2, a heat shock transcription factor, binds to the heat shock protein (HSP)90/rotamase FKBP 1 (ROF1) complex in the cytosol and the complex is translocated to the nucleus to activate the synthesis of heat shock proteins involved in heat stress response. This mechanism, called heat memory, allows the plant to be more responsive to an imminent recurrence of the heat shock. However, to return to a normal growth state when conditions become favorable again, the HSP90 and ROF1 proteins must be degraded. NBR1 was shown to be able to interact with HSP90 and ROF1 and mediate their degradation via autophagy and thus attenuate the heat memory response to return to a normal growth state [192]. It would be interesting to determine whether the reduced autophagy flux observed by [191] after a long exposure to heat stress (37 °C for 12 h) prevented the selective degradation of HSP90/ROF1 via NBR1, or whether the reduction of autophagy flux is linked to any damage to the autophagic machinery.

Xenophagy

Both the host plants and the encountered pathogens regulate autophagy for their own benefit [28]. For example, rice blast pathogen (*M. oryzae*) initiates an appressorium, a dome-shaped cellular structure, to enter the host cuticle, triggering the breach of the host cell wall to control the host cell metabolic pathways including autophagy [193]. Interestingly, during host colonization, the fungal pathogen *Botrytis cinerea* induces its BcATG1, whereas *Bcatg1* mutants failed to form the appressorium-dependent infection structure, resulting in limited penetration of the onion epidermis [194]. This observation suggests that autophagy is required for host cell penetration by some fungal pathogens. Additionally, mitophagy and pexophagy mutants showed no impact on host penetration and colonization of *M. oryzae*, whereas a pexophagy mutant of the anthracnose fungus *Colletotrichum orbiculare* displayed host penetration defects following appressoria maturation [28,195], indicating the role of some selective autophagy pathways during host invasion.

Currently, there is still a lack of information about the mechanisms involved in defense-related selective autophagy and the strategies employed by the pathogens to escape it. Xenophagy, with the prefix 'xeno', meaning 'stranger' or 'foreign', is defined as the selective autophagic degradation of intracellular pathogens, including viruses, bacteria and fungi. Xenophagy requires selective autophagy receptors (p62, NDP52, OPTN and NBR1) to selectively target the cargo to the autophagosomal membrane [167] (Fig. 7). In humans, NDP52 (also known as CALCOCO2) recognizes ubiquitin-coated *Salmonella enterica*, and recruits

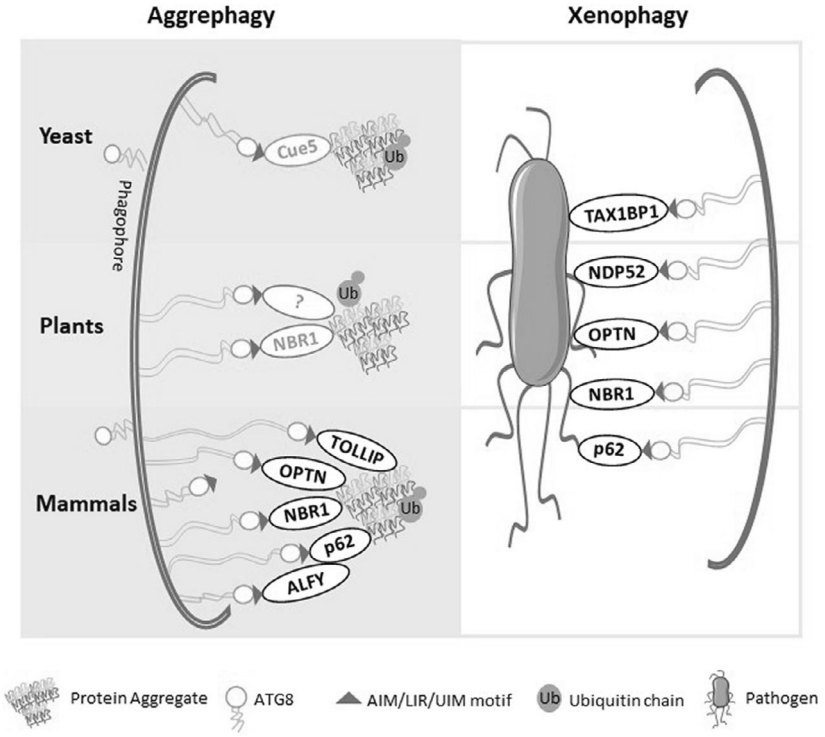

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Fig. 7. Selective autophagy receptors in aggrephagy (left) and xenophagy (right). Aggrephagy involves multiple E3 ligases participating in protein aggregate ubiquitylation. In yeast, Cue5 is a receptor for the clearance of aggregation-prone polyglutamine (polyQ)-containing proteins. Cue5 possesses a ubiquitin-binding CUE domain and an AIM, suggesting that Cue5 potentially facilitates the interaction between ubiquitylated aggregates and Atg8. TOLLIP is a Cue5 human homolog with a CUE domain, responsible for the degradation of polyQ protein aggregates in human cell lines. Three additional mammalian receptors, p62, NBR1 and OPTN, have LIRs and ubiquitin-binding domains. They act as ubiquitin-binding proteins and promote the interaction between ubiquitylated proteins and the core autophagy machinery. The nucleocytoplasmic shuttling protein ALFY works as a scaffold protein in aggrephagy. ALFY can bind to the core autophagy protein Atg5, the cargo receptor p62, GABARAP subfamily members and phosphatidylinositol 3-phosphate. In plants, the Arabidopsis homolog of human NBR1 (AtNBR1) was shown to act as an aggrephagy cargo-receptor. Its ability to homopolymerize suggests that AtNBR1 is a functional combination of the human NBR1 and p62. Xenophagy is the selective autophagic degradation of intracellular pathogens, including viruses, bacteria and fungi. Xenophagy receptors include p62, NDP52, OPTN and NBR1. NDP52 (also known as CALCOCO2) binds to invading bacteria. Human TAX1BP1, a paralogue of NDP52, acts as an autophagy receptor in a myosin VI-mediated xenophagy. In plants, the receptor NBR1 acts in xenophagic degradation of CaMV particles to restrict virus accumulation in *A. thaliana*.

tank-binding kinase through the adaptor proteins Nap1 and Sintbad. Moreover, NDP52 also interacts with LC3, and knockdown of NDP52 inhibits autophagic clearance of *Salmonella* [196]. Additionally, TAX1BP1, a paralogue of NDP52, acts as a novel autophagy receptor in myosin VI-mediated xenophagy. The lack of TAX1BP1 leads to an accumulation of ubiquitin-positive *Salmonella* [197].

The role of selective autophagy in plant–pathogen interactions has been reviewed extensively [198–200]. The accumulation of cauliflower mosaic virus (CaMV) P4 and viral DNA is suppressed by NBR1-mediated selective autophagy, indicating that the selective autophagy receptor NBR1 acts in xenophagic degradation of CaMV particles to restrict virus accumulation in *Arabidopsis thaliana* [201]. Infection caused by turnip mosaic virus (TuMV), a positive-stranded RNA potyvirus, was antagonized by NBR1-dependent autophagy. NBR1 acts as selective autophagy cargo receptor that specifically targets helper-component proteinase to suppress TuMV accumulation [202]. Furthermore, TuMV infection also upregulates ATG6 (i.e. plant ortholog of Beclin1). ATG6 then interacts specifically with Nib, the RNA-dependent RNA polymerase of TuMV, and targets Nib to autophagosomes via ATG8 for degradation, suggesting that ATG6/Beclin1 is required for xenophagy [203]. Further investigation of the precise mechanisms of selective autophagy will not only help us understand the pathogenesis of these infections, but also provide a weapon to fight against pathogens and improve crop adaptability to various biotic stress conditions.

Surface-localized recognition receptors detect pathogen-associated molecular patterns and activate the pathogen-associated molecular pattern/pattern-triggered immunity [28]. A set of intracellular immune receptors, nucleotide-binding domain and leucine-rich repeat-containing proteins (NLRs), can recognize effector proteins. Activation of NLRs produce effector-triggered immunity that often causes hypersensitive response (HR)-related cell death [28]. Autophagy is involved in the hypersensitive response and its local restriction [28]. Studies suggested silencing of autophagy genes including phosphoinositide 3-kinase/VPS34, ATG3 and ATG7, or expression of an ATG6/Beclin1 antisense transgene in tobacco and challenged with tobacco mosaic virus, can cause the uncontrolled spread of HR beyond primary virus infection sites [28]. Similarly, ATG6-deficient Arabidopsis is more sensitive to *Pseudomonas syringae* pv. tomato DC3000 (Pst DC3000). Autophagy Arabidopsis deficient mutants (*atg5, atg7, atg10* and *atg18a*) showed increased cell death when challenged by the necrotrophic fungi *Alternaria brassicicola* or *B. cinerea* [28,204]. However, it is still unclear whether autophagy is involved in NLR-mediated HR cell death. Autophagy cargo receptors or adaptors that specifically modulate these processes would be crucial for discovering the role of autophagy in HR-associated cell death.

Box 2. Open research questions

1 Why can there be so many receptors for the degradation of a specific organelle (example the ER)?
2 Can these different receptors involved in selective autophagy of the same organelle synergize or do their diversity reflect physiological or cell type or stress specification?
3 Are the physiological signals involved in selective degradation of the same cargo conserved during different growth/developmental stages, the same stress, or the same tissue?
4 Is there a link between a receptor otherwise function and its additional role in selective autophagy (e.g. Sec62 as a component of the ER translocon and Rtn1 as a reticulon involved in ER dynamics)?

Examples of other selective autophagic cargo and their cognate SAR in plants

Plant adaptation responses to abiotic stresses involve the phytohormones-dependent signaling cascade, including that of the stress hormone abscisic acid (a growth negative regulator) and that of brassinosteroid (BR) (a growth promoting regulator) to reprogram its metabolism [205]. When subjected to abiotic stress, plants have to balance between maintaining growth and competitiveness on the one hand, and ensuring survival on the other hand [206]. This delicate and vital process involves hormone-regulated master regulators, some of which have been characterized recently.

ABA insensitive 1 and protein phosphatase 2CA are negative regulators of ABA-dependent signaling, and the two phosphatases were shown to dephosphorylate and inactivate sucrose non-fermenting 1-related kinase 1, a kinase positively regulating the autophagy pathway [207]. ABA-dependent signaling results in the expression of effector proteins regulating different aspects of plant physiology. The plant translocator-related protein TSPO is a multi-stress regulator, transiently induced by water-related stress and ABA treatment in plants [208]. The expressed Arabidopsis TSPO (AtTSPO) is also rapidly (within 48 h after induction) degraded, suggesting a time-limited role for this protein during stress [40]. Expressed AtTSPO may temporally protect the cell from osmotic stress by physically interacting and preventing a highly expressed plasma membrane water channel, aquaporin PIP2;7, from reaching the plasma membrane during stressful conditions. The aquaporin–TSPO complex is targeted by autophagy for degradation in the vacuole [209]. However, constitutive expression of TSPO can be detrimental to plant growth and development [40,208]. The possible toxicity of the continuous presence of AtTSPO in the cell was ascribed to its intrinsic free heme binding capacity, and the consequence of this cytoplasmic heme titration on ROS scavenger enzymes activity [40,210]. The free heme/porphyrin detoxification function of TSPO may be required only transiently, when the plant cell needs to manage stress-induced ROS, and probably ROS-dependent signaling events [210]. The continuous presence of TSPO could indeed disrupt the channeling of heme to ROS scavengers and, paradoxically, trigger ROS accumulation as experimentally demonstrated in Arabidopsis [40]. It was shown that degradation of excess TSPO by the plant cell requires heme binding and a functional autophagy pathway [40], hence the suggestion that plant TSPO may act as an autophagy cargo receptor for a diverse set of cargo such as cytoplasmic free porphyrins and defined water channels [67].

BRs are a family of steroid phytohormones involved in cell division, and differentiation of specific cell types [211]. In addition, BRs are also involved in stress adaptation [212]. The brassinosterioid insensitive 1 (BRI1)-EMS suppressor 1 (BES1) is a transcription factor which positively regulates BR signaling. BES1 can be ubiquitylated, and interacts with dominant suppressor of Kar 2 (DSK2A), an autophagy adaptor that contains a ubiquitin-like domain, two AIM motifs, and a ubiquitin-associated domain. Forward genetic screening under differential environmental stimuli has revealed the regulatory components of BR signaling: BRI1 receptor kinase and the transcription factors BES1 and brassinazole resistant 1 [213]. In the absence of BR signaling, BES1 and brassinazole resistant 1 are retained by interacting with 14-3-3 family proteins and degraded in the cytoplasm [214].

DSK2A was shown to act as cargo receptor for selective autophagy degradation of BES1 [215]. DSK2A is a substrate of the kinase BIN2, and phosphorylation of DSK2A enhances its binding to ATG8, hence targeting BES1 for autophagic degradation. The tripartite interaction BES1-DSK2A-ATG8 and the subsequent degradation of BES1 modulates BR signaling and confers drought survival to plant by a favorable transcriptional reprogramming.

Conclusions and perspectives

We have highlighted our current understanding of selective autophagy with an emphasis on receptors and adapters and their functions in plant autophagy. Yet, our knowledge of the underlying molecular mechanisms and factors involved, which are as yet still unknown or uncharacterized, is fragmentary and limited in relation to the many demonstrated or potential selective autophagy pathways in plants. Even though the stimuli specifically inducing organelle autophagy are diverse, the core mechanisms by which these organelles are degraded appear to be similar in many cases. The mechanisms mediating selective recognition of cargos involve post-translational modifications, such as phosphorylation/ubiquitylation of the cargo or components of the cargo, occasional trafficking of the cargo and interaction with ATG8.

The molecular mechanisms of plant autophagy, including signaling modules, cargo selectivity, and the regulatory factors involved in autophagosome biogenesis and fusion with the vacuole and/or the multivesicular body, are not well understood, leaving a gap that prevents exploitation of this important pathway to enhance plant growth and development. We also do not know the signaling cascades triggering these different selective autophagy pathways. A detailed understanding of these pathways and their integration into plant physiology requires the identification of the molecular players involved.

The identification of the receptors and cargos implicated in each of the signaling pathways would require the ability to decipher the proteomes of the induced autophagosomes in a cell type-specific manner. However, methodological approaches remain to be designed and validated. A major limitation in the interpretation and integration of current data is the lack of spatiotemporal information, knowing that there would indeed be a cell type-specific response. A telling example in this field is that of chlorophagy, a complex pathway specific to certain plant cell types, which is studied mostly at the whole organ if not plant level. Selective autophagy in the plant is a fascinating subject with an enormous potential for salient discoveries (Box 2) and, in some cases, likely will lead or contribute to transformational applications in the way that we can imagine and design resilient plants.

Acknowledgements

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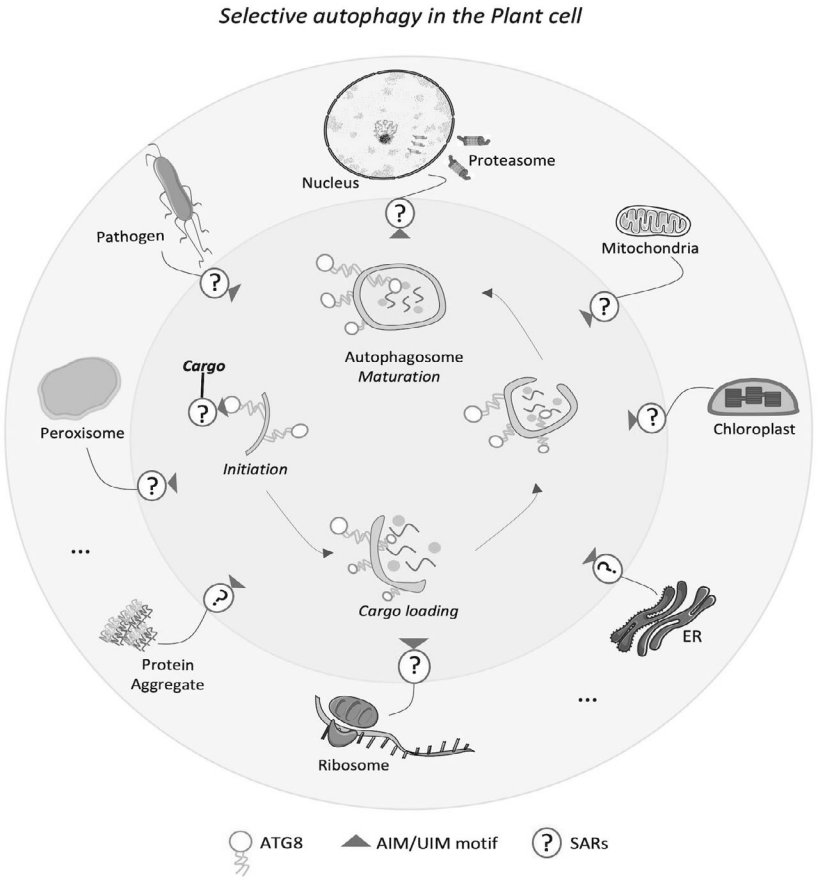

Selective autophagy is an essential metabolic pathway regulating growth and development of plants, particularly in response to environmental constraints. This review highlights the few selective cargo receptors and their cognate cargo so far identified in plants, and also emphasizes the specificities of selective autophagy in the plant kingdom and the gaps in our understanding of this vital process warranting future research.