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New advances in autophagy in plants: regulation, selectivity and function

Ping Wang^{a,b,1}, Yosia Mugume^{a,1}, and Diane C. Bassham^{a,*}

^aDepartment of Genetics, Development and Cell Biology, Iowa State University, Ames, IA 50011, USA

^bState Key Laboratory of Crop Stress Biology for Arid Areas, College of Horticulture, Northwest A&F University, Yangling, Shaanxi 712100, China

Abstract

Autophagy is a major and conserved pathway for delivering unwanted proteins or damaged organelles to the vacuole for degradation and recycling. In plants, it functions as a housekeeping process to maintain cellular homeostasis under normal conditions and is induced by stress and senescence; it thus plays important roles in development, stress tolerance and metabolism. Autophagy can both execute bulk degradation and be highly selective in targeting cargos under specific environmental conditions or during certain developmental processes. Here, we review recent research on autophagy in plants, and discuss new insights into its core mechanism, regulation, selectivity and physiological roles. Potential future directions are also highlighted.

Keywords

Autophagy; TOR; regulation; selective degradation; stress responses; plants

1. Introduction

Autophagy is a vacuolar degradation pathway by which cells recycle their components, including macromolecules and organelles. It is continuously maintained at a basal level for homeostasis, and upregulated under stress to aid plant survival [1]. Macroautophagy, more generally referred to simply as autophagy, is the best studied form of autophagy in plants and is enacted upon environmental stresses such as nitrogen and carbon starvation [2]. Starvation-induced autophagy is characterized by bulk degradation of macromolecules and organelles in the vacuole [3–5], whereas autophagy may also selectively target specific proteins, protein aggregates, or organelles for recycling [3, 6, 7].

*Corresponding author: bassham@iastate.edu.

¹Ping Wang and Yosia Mugume contributed equally to this work

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Autophagy is marked by the formation of a double-membrane vesicle, the autophagosome, at the phagophore assembly site, which engulfs cargo and targets it to the vacuole/lysosome for degradation [8, 9]. A subset of genes, termed AuTophagy-related genes (*ATG* genes), encode corresponding core ATG proteins. These proteins function in the biogenesis of autophagosomes and control of autophagy. From analysis based primarily on yeast (*Saccharomyces cerevisiae*), 36 ATG proteins that drive the autophagic process have been described [10]. Most of the ATG proteins that are required for autophagosome formation have also been identified in plants [4], but our understanding of the molecular mechanisms by which autophagy is regulated in plants is still in its infancy. Proteins that are essential for the autophagic process have been grouped into four core functional groups [11, 12]; the ATG1/ATG13 kinase complex initiates autophagosome formation in response to upstream nutrient demands, the class III phosphatidylinositol (PI) 3-kinase complex mediates vesicle nucleation, ATG9 may promote phagophore expansion by shuttling membrane components from different sources, and the ATG8/ATG12 ubiquitin-like conjugation systems aid in phagophore expansion and maturation [12]. Conjugation results in an ATG8-phosphatidylethanolamine (PE) conjugate via two parallel pathways. In the first, ATG5 is covalently linked to ATG12 to form an adduct that further interacts with ATG16 to produce an ATG5-ATG12/ATG16 tetrameric complex. This complex functions as an E3 ligase which transfers PE to ATG8 *in vitro* [13] to produce the autophagosome-localized lipidated form ATG8-PE [2, 14], which is commonly used as a marker for autophagosomes. Most *ATG* genes have been identified in *Arabidopsis thaliana* based on sequence similarity to the yeast genes, and have been shown to be essential for autophagy [15, 16].

Here we will review and discuss recent advances in plant autophagy, including its regulation, selectivity, and physiological functions in plant development and stress responses (Figure 1).

2. Regulation of autophagy by TOR

Target of rapamycin (TOR) is a phosphatidylinositol-3-kinase-related kinase that functions as a Ser/Thr protein kinase and is a negative regulator of autophagy in many organisms [17–19]. It also regulates growth and protein synthesis, dependent on nutrient and growth factor availability [17, 18, 20].

TOR is an upstream regulator that controls ATG1/ATG13-mediated autophagy [17]. In yeast, TOR negatively regulates autophagy by phosphorylating ATG13, increasing its affinity for ATG1 during nutrient-rich conditions and decreasing autophagy activity. During nutrient starvation TOR is inactivated, preventing phosphorylation of ATG13 and increasing binding between ATG13 and ATG1. Autophosphorylation of ATG1 follows, leading to stimulation of phagophore expansion and enclosure [21]. *Arabidopsis* TOR knock out mutants are lethal [16, 22], but RNAi-*AtTOR* plants with decreased expression of *AtTOR* are viable, allowing the demonstration that TOR is also a negative regulator of autophagy in plants [19]. In *Arabidopsis*, ATG1 and ATG13 are phosphoproteins that interact and localize to phagophore-related structures [23]. Unexpectedly, the levels of ATG1 and ATG13 decreased during nutrient starvation due to turnover by autophagy, indicating tight regulation of this kinase complex, possibly to prevent excess autophagy activity and cell death. Regulation of ATG1 by TOR has not yet been demonstrated in *Arabidopsis*; analysis of

ATG1/ATG13 phosphorylation and activity after blocking TOR activity should address this issue.

While TOR is usually considered to regulate autophagy in response to nutrient concentrations, in *Arabidopsis* a decrease in TOR activity is required for activation of autophagy by a range of stress conditions [24]. Overexpression of TOR blocks autophagy activation by salt and osmotic stress in addition to nutrient deficiency, but has no effect on autophagy activation by oxidative or endoplasmic reticulum (ER) stress, indicating that both TOR-dependent and -independent pathways exist for regulation of autophagy [24].

Recent research has revealed a relationship between TOR signaling and the growth-promoting hormone brassinosteroid (BR). TOR signaling activates the BR pathway by favoring the accumulation of active BZR1, a BR-regulated transcription factor that is important for growth induced by multiple hormonal and environmental signals [25]. TOR inhibition led to activation of autophagy, which in turn was suggested to degrade BZR1 in a PEST domain-dependent manner, leading to growth arrest during sugar starvation. The related transcription factor BES1 has also been shown to be degraded by selective autophagy, and the receptor responsible for this selectivity has been identified as DSK2 [26]. The phosphorylation of DSK2 by the GSK3-like kinase BIN2, a negative regulator of BR signaling, promotes an interaction between DSK2 and ATG8, thereby targeting BES1 for autophagic degradation [26].

3. Non-ATG proteins function in membrane trafficking and remodeling during autophagy

The actin cytoskeleton is involved in autophagosome formation [27] and the ARP2/3 actin nucleation complex, important for the formation of branched actin networks [28], functions in autophagosome biogenesis in mammalian cells [28]. In plants, ARP2/3 [29, 30] is activated by the suppressor of cyclic AMP receptor (SCAR)/WAVE complex [31, 32], whose disruption results in serious developmental defects [32, 33]. The *Arabidopsis* membrane-localized SCAR/WAVE complex component Nck-Associated Protein (NAP1) has been shown to be required for the formation of autophagosomes [34]. NAP1 localizes to autophagosomes under different stress conditions, notably mechanical stress imposed by a coverslip. NAP1 puncta formed much earlier than ATG8 puncta when the two fluorescently-tagged proteins were co-expressed in leaf epidermal cells, indicating that actin is involved in early stages of autophagosome formation [34]. It is hypothesized that NAP1 is recruited to the ER membrane to regulate actin polymerization and membrane deformation to form phagophores, followed by recruitment of ATG8 [34]. The exact mechanism by which actin influences autophagosome biogenesis remains unclear.

Arabidopsis SH3 DOMAIN CONTAINING PROTEIN2 (SH3P2) [35] has also been proposed to function in membrane remodeling during autophagosome biogenesis [36]. SH3P2 contains an N-terminal BAR domain, a membrane-binding module for membrane deformation [37], and localizes to autophagy-related structures/autophagosomes and to the ER. This dual localization indicates that the cup-shaped isolation membranes from which autophagosomes are derived most likely originate at the ER, as in mammalian cells [38, 39].

SH3P2 associates with the PI3K complex, and SH3P2 puncta are diminished upon PI3K inhibition by wortmannin [39, 40], suggesting that SH3P2 regulates autophagy through an effect on the PI3K complex [41, 42]. SH3P2 RNAi lines had reduced autophagic flux with accumulation of ATG8-PE and ATG8. This is interpreted to mean that the autophagosome maturation step may be compromised, whereby the ATG8-PE conjugate associated with the autophagosome membrane but was not delivered to the vacuole. SH3P2 is therefore hypothesized to function in autophagosome expansion and maturation [36].

In addition to originating at the ER, the membrane required for phagophore elongation may be delivered by vesicle trafficking pathways via a mechanism involving ATG9 [43] and its recycling system [44]. Several studies have shown a link between autophagy and other trafficking mechanisms in the cell. The exocyst complex, initially identified in yeast [45] and mammals [46] as required for exocytosis, is conserved in plants [47], and the exocyst component EXO70B1 is essential for autophagosome formation and transport to the vacuole in *Arabidopsis* [48]. *exo70B1* mutants are hypersensitive to nitrogen starvation and have defects in vesicular transport of anthocyanins [49], suggesting that this exocyst component is important for autophagy-related transport. All *Arabidopsis* EXO70 homologs have an ATG8 interaction motif (AIM) [50], and indeed, YFP-EXO70B1 colocalized with the autophagosome marker ATG8 inside the vacuole [48]. However, unlike other autophagy mutants, *exo70B1* showed no hypersensitivity to carbon starvation, leading to the hypothesis that EXO70B1 could be involved in autophagy induced only by specific stresses [48].

The plant-specific endosomal sorting complex required for transport (ESCRT) component FYVE domain protein required for endosomal sorting 1 (FREE1) has recently been shown to be required for vacuolar protein transport and control of autophagic degradation [51, 52]. Disruption of *FREE1* led to accumulation of autophagosomes and ATG8-PE, but not free ATG8 [51], suggesting that *free1* mutants are defective in membrane fusion between autophagosomes and the vacuole, but not in the induction of autophagy. Consistent with this, FREE1 was shown to facilitate the fusion of autophagosomes with the vacuole. FREE1 also functions in vacuole formation [51–53] and in the endocytic delivery of the PYL4 ABA receptor to the vacuole for degradation [54], indicating a role in multiple transport pathways to the vacuole.

4. Characterization of selective autophagy in plants

Selective autophagy involves engulfment of specific proteins or organelles into autophagosomes. It is mediated by receptors or adaptor proteins that bind the cargo and also interact with ATG8 via AIMs [55], leading to recruitment of the cargo into autophagosomes. Such AIMs can be predicted and identified based on defined degenerate consensus F/W/Y-XX-L/I/V sequences by bioinformatics approaches [56, 57]. Selective autophagy contributes to cellular homeostasis and quality control of proteins and organelles [58]. This section will focus on recent discoveries characterizing selective autophagy in plants (Figure 2).

4.1 Chlorophagy

Chloroplasts are specialized organelles in green plant and algal cells that conduct photosynthesis and carry out a variety of metabolic and signaling functions [59]. Dedicated

quality control of chloroplasts is necessary for maintaining their function, especially under adverse environmental conditions. Chloroplast degradation is an important means for such quality control and for recycling nutrients from chloroplast proteins such as Rubisco. Whole chloroplasts are transported to the vacuole for recycling through an autophagy-dependent process in individually darkened leaves under starvation or senescence [60]. A recent report demonstrates that autophagy is responsible for the elimination of entire damaged chloroplasts induced by strong light or ultraviolet-B (UVB) radiation. This stress-induced chlorophagy is impaired in *atg5* and *atg7* mutants, leading to increased UVB-induced cell death and reactive oxygen species (ROS) accumulation. These findings indicate that chlorophagy can function as a photoprotective mechanism in response to sunlight-induced damage in plants [61].

Small double-membrane spherical structures called Rubisco-containing bodies (RCBs) bud from chloroplasts during senescence and contain stromal proteins but not thylakoid proteins; these RCBs were suggested to be involved in chloroplast degradation [62]. Autophagy transports RCBs to the vacuole during leaf senescence [60, 63]. RCB production is suppressed by accumulated leaf carbohydrates, while it is less responsive to nitrogen limitation, suggesting that the RCB-mediated process is linked to leaf carbon status but not nitrogen status [64]. RCBs are also observed during infection by avirulent *Pst* DC3000 (*AvrRps4*) in *Arabidopsis*, by which plants might mobilize needed nitrogen, trigger an ROS burst, and induce the defense response [65]. The ESCRT machinery typically sorts ubiquitylated plasma membrane proteins into intraluminal vesicles for degradation in the vacuole, but, unexpectedly, plants deficient in the ESCRT component Charged Multivesicular Body 1 (CHMP1) accumulate plastid components and cytoplasmic bodies containing plastid proteins. This suggests that ESCRT components may be involved in the RCB pathway, possibly by promoting efficient delivery of RCBs to the vacuole [66]. CHMP1 assists phagophore maturation/closure and sequesters autophagic plastid cargo into autophagosomes for degradation [66]. Since a *chmp1* mutant also hyperaccumulates peroxisomal and mitochondrial proteins, it is possible that the ESCRT machinery functions in selective autophagy of other organelles as well and a potential function in the autophagy-dependent turnover of organelles during development or under stress warrants further investigation.

An additional pathway for plastid degradation involves ATG8-INTERACTING PROTEIN1 (ATI1), which localizes to both ER- and plastid-associated (PS) bodies [67, 68]. ATI1 interacts with plastid-localized proteins and with ATG8f, targeting the plastid bodies to the vacuole by a process that requires active autophagy. Upon carbon starvation or salt stress, ATI1-PS bodies recycle specific plastid proteins and contribute to quality control of chloroplasts [68]. Although both originate from plastids, RCBs and ATI1-PS bodies deliver different plastid proteins for degradation in the vacuole, representing two distinct pathways. The regulatory mechanisms of chloroplast quality control need to coordinate autophagy-dependent pathways such as RCBs and ATI1 with autophagy-independent pathways including senescence-associated vacuoles (SAVs) [69, 70] and chloroplast vesiculation (CV) [71] under different conditions. How different stimuli are recognized and converge to a physiological response remains to be investigated.

4.2 Pexophagy

Plant peroxisomes are ubiquitous organelles that play critical roles in several important metabolic pathways. Forward and reverse genetic studies have shown that pexophagy, the autophagic degradation of peroxisomes, participates in the functional transition of peroxisomes from heterotrophy to photoautotrophy, as well as in peroxisomal quality control both under normal growth conditions and during starvation [72–77]. Pexophagy seems to occur at a higher basal rate than other types of selective autophagy [76, 77] and to be tissue-dependent, active in hypocotyl and leaves but not roots in *Arabidopsis* [73, 77]. To date, four pexophagy-specific receptors have been identified: Atg30 in *Pichia pastoris* [78], Atg36 in *Saccharomyces cerevisiae* [79], and Neighbor of BRCA1 gene 1 (NBR1) and p62 in mammals [80]. NBR1 is the only characterized pexophagy receptor with a plant homolog [81], but there is no direct evidence connecting NBR1 to pexophagy in plants. Specific receptors may have evolved to fulfill distinct functions in different species, and identification of such receptor proteins is crucial for the future study of plant pexophagy.

4.3 Mitophagy

Selective degradation of mitochondria via autophagy, known as mitophagy, is an important mitochondrial quality control mechanism [82]. Li et al. [83] described mitophagy in *Arabidopsis* while characterizing ATG11 function. In yeast, Atg11 is an accessory protein of the Atg1-Atg13 complex, facilitating the scaffolding of the complex to the PAS and binding to selective autophagy adaptors [84, 85]. Likewise, *Arabidopsis* ATG11 interacts with ATG1, ATG13, ATG101 and binds to ATG8 through AIMs [83]. *Arabidopsis* ATG11-deficient plants displayed similar phenotypes to well-characterized *atg* mutants, and also had decreased turnover of mitochondrial proteins and decreased autophagic transport of mitochondria into vacuoles during dark-induced leaf senescence [83]. Co-localization of a mitochondrial marker with both ATG8a and ATG11 further confirmed their involvement in the clearance of plant mitochondria from the cytoplasm to the vacuole [83]. Currently it is not clear how ATG11 participates in plant mitophagy. In yeast, Atg11 recruits damaged mitochondria by directly binding to Atg32, a mitochondrial integral outer membrane protein [85]. However, Atg32 is not present in plants. The identification of ATG11-interacting proteins that recognize damaged or dysfunctional mitochondria for degradation by mitophagy in plants is an important direction for future research.

4.4 Reticulophagy

ER stress is defined as the accumulation of unfolded or misfolded proteins in the ER lumen, and is caused by certain environmental stresses [86]. Reticulophagy, autophagic degradation of the ER, functions when the unfolded protein response (UPR) fails to restore protein homeostasis within the ER [87, 88]. In *Arabidopsis*, autophagy is triggered by ER stress, correlating with the accumulation of unfolded or misfolded proteins in the ER lumen [89, 90], and delivers fragments of ER to the vacuole [4]. This ER stress-triggered autophagy requires the ER stress sensor INOSITOL-REQUIRING ENZYME-1b (IRE1b), but not its splicing target bZIP60 or another ER stress response factor bZIP28 [4, 89], which suggests the participation of other unidentified signaling pathways in reticulophagy. The factors downstream of IRE1 in activation of reticulophagy remain unknown; in animal cells the

kinase domain of IRE1 activates the c-Jun N-terminal kinase (JNK) signaling pathway, which in turn activates autophagy [91], but the JNK pathway is absent from plants.

4.5 Ribophagy

The process of ribophagy - degradation of ribosomes through selective autophagy - was first described in *Saccharomyces cerevisiae* upon nitrogen starvation. This degradation not only depends on the basal non-selective autophagy machinery, but is selective and requires other factors, such as the Ubp3p/Bre5p ubiquitin protease [92] and Rim15/Sch9 kinases [93]. Although ribophagy *per se* has not been demonstrated in plants, there is evidence for autophagy-dependent pathways of rRNA turnover in *Arabidopsis*. RNS2, a nonspecific endoribonuclease of the RNase T2 family, localizes to the vacuole [94] and is necessary for normal rRNA decay [95], raising the question of how the rRNA is transferred to the vacuole for degradation. Constitutive autophagy was observed in *rns2* mutants [95], and analysis of *rns2* and *atg* mutants indicated that both RNS2 and autophagy participate in rRNA turnover. Surprisingly, the autophagic turnover of rRNA is dependent on ATG5 but not ATG9 [96], suggesting alternative autophagy-related pathways such as microautophagy may function in rRNA degradation. One possibility is that the *atg5* mutant blocks both macro- and microautophagy (or other autophagic pathways) while *atg9* blocks only macroautophagy. The autophagic process that transports rRNA to the vacuole was suggested to play important roles in ribosome turnover and cellular homeostasis [96]. Whether other types of RNA can be selectively degraded by autophagy is as yet unclear, and current assays do not provide the sensitivity to address this question for less abundant RNA species. Since it is not clear how ribophagy affects the ribosome pool, protein synthesis and proteome composition of a cell, global analysis combining RNA-seq, protein mass-spectrometry and metabolome techniques might allow assessment of the mechanisms and consequences of turnover of ribosomal RNA and proteins more comprehensively in the mutants.

4.6 Proteaphagy

A new type of selective autophagy, proteaphagy, was discovered in *Arabidopsis* by Marshall et al. [97], in which inactive 26S proteasome complexes are degraded. Ubiquitylation is a universal signal for protein degradation via both the proteasome and autophagy [98], leading to the most obvious link between these two pathways. Marshall et al. [97] demonstrated that degradation of the proteasome by autophagy occurs either non-selectively upon nitrogen starvation or selectively upon exposure to a proteasome inhibitor. Inhibited proteasomes become extensively ubiquitylated, and subsequent proteaphagy is mediated by the ubiquitin receptor RPN10. The C-terminal domain of RPN10 contains three ubiquitin-interacting motifs (UIMs), with UIM1 necessary for binding ubiquitylated proteasome subunits and UIM2 for binding lipidated ATG8 [97]. Nitrogen starvation-induced non-selective proteaphagy is dependent on the ATG1 kinase, and thus might be regulated by upstream signaling components such as TOR [99]. Selective proteaphagy in response to the proteasome inhibitor is independent of ATG1 kinase, suggesting distinct pathways regulating proteaphagy in plants, although both mechanisms depend on the core autophagy machinery [97]. The E3 ligases responsible for proteasome ubiquitylation and the mechanisms by which they identify inactive proteasomes need further investigation.

The ability of RPN10 to bind both ubiquitin and ATG8, and high conservation of UIMs within plant species, make it a promising receptor for selective autophagy; however, the ATG8-UIM is absent in yeast and animal Rpn10 sequences, precluding this as a universal mechanism. However, a very recent study in yeast, also by Marshall et al. [100], solved this puzzle. They discovered that an extra-proteasomal ubiquitin receptor Cue5, evolutionarily unrelated to RPN10, binds ubiquitin and Atg8 and is required for clearance of impaired 26S particles. The intriguing discoveries in both *Arabidopsis* and yeast [97, 100] provide strong evidence for the interplay between proteasomes and autophagy, accelerating the elucidation of protein quality control in eukaryotic cells. The nature of the signal that regulates this interplay between the two degradation pathways, and how non-selective and selective proteaphagy respond to the signal, needs much more exploration.

5. Functions of autophagy in plants

5.1 Autophagy and plant development

A basal level of autophagy contributes to cell homeostasis under normal growth conditions. Most *Arabidopsis* autophagy-defective mutants can complete their life cycles under normal growth conditions, although their leaves senesce prematurely [15, 101–106], probably due to salicylic acid (SA) accumulation [107]. Senescence and seed germination require remobilization of nutrients on a large-scale; autophagy is involved in these important processes, in coordination with other degradation/hydrolysis pathways [4]. In maize, as seeds mature following pollination, ATG8 lipidation, an indication of autophagy pathway activity, increases in the starchy endosperm [108]. After seed germination, abundant lipidated ATG8 was detected, supporting a role for autophagy in mobilizing nutrients from the endosperm for early seedling development [108]. RNAseq data generated from different tissues of maize are consistent with the participation of autophagy in the maturation and programmed cell death (PCD) of endosperm during seed development [109].

Autophagy is important for root cell growth and root hair formation in *Arabidopsis* [1]. Autophagy is also activated during tracheary element (TE) differentiation, regulated by the RabG3b GTPase, and is proposed to participate in PCD during xylem formation [110, 111]. A TE-specific METACASPASE9 (MC9) was found to modulate autophagy to ensure confinement of cell death to the appropriate cells during TE differentiation [112]. Autophagy also has a role in metabolic regulation and nutrient supply within tapetum cells during anther development in rice [113, 114]. For example, *Osatg7* and *Osatg9* mutants failed to accumulate lipidic and starch components in pollen grains and showed complete male sterility, possibly because of their impairment of lipid metabolism during pollen maturation. However, *atg* mutants in *Arabidopsis* have no defects in male fertility, which might be due to the difference in the development of lipidic components in the pollen grains between monocots and dicots; unlike dicots, monocots do not form tapetosomes in tapetal cells for lipid transport [114].

5.2 The role of autophagy in plant nutrient availability and metabolism

Autophagy plays a crucial role in the response to nutrient starvation, as demonstrated in many autophagy-defective mutants and by the upregulation of *ATG* genes transcriptionally

upon carbon or nitrogen starvation [15, 101–103, 106, 115–118]. *Arabidopsis atg* mutants are hypersensitive to nitrogen starvation, have reduced seed production, and have lower nitrogen remobilization efficiency (NRE) at the whole-plant level than WT, suggesting that the autophagy core machinery is needed for nitrogen remobilization under both limiting and ample nitrate conditions [119]. Research in crop plants has also emphasized the importance of autophagy in nutrient remobilization. Nitrogen remobilization in the rice *Osatg7-1* mutant was suppressed during early leaf senescence, and the limited leaf growth in turn decreased the photosynthetic capacity of the plant, which directly affects biomass and nitrogen use efficiency (NUE) [120]. The ATG system in maize was characterized transcriptionally and genetically through *atg12* mutants. Under nutrient-rich conditions, *atg12* plants are phenotypically normal and fertile. However, under nitrogen starvation, they showed arrest of seedling growth, early leaf senescence, stunted ear development and impaired nitrogen remobilization, which severely reduced seed yield and productivity [109]. Therefore, the manipulation of autophagy might be an effective strategy to improve plant NRE or NUE in suboptimal agricultural conditions.

Autophagy participates in starch breakdown [121], and it contributes to carbon [122] and energy availability by maintenance of metabolites, further demonstrating a link between autophagy and plant metabolism [123]. Transcriptomics and metabolomics data give a global perspective on the impacts of autophagy on metabolism, development and stress responses [124]. Metabolomic analyses comparing autophagy mutants with wild type plants indicate the overaccumulation of several amino acids and related compounds such as glutamate, with depletion of hexoses, quercetins and anthocyanins. Transcriptomic data have revealed the perturbation in pathways for such metabolites. For example, anthocyanin depletion in *atg* mutants might be due to the downregulation of the genes in flavonoid biosynthesis and reduced preference of carbon skeletons for anthocyanin biosynthesis, instead being directed to SA biosynthesis. The amplified oxidative stress due to depletion of the antioxidant anthocyanin and SA accumulation together lead to hypersensitivity of *atg* mutants to stress, causing cell death [124]. Under carbon starvation, *atg* mutants have delayed growth and exhibit a reduction in amino acid levels, accumulation of proteins, increased respiration, and decreased flux to net protein synthesis. These results highlight the importance of autophagy in cellular metabolism and energy homeostasis in *Arabidopsis* seedlings [125].

5.3 The role of autophagy in abiotic stress responses

Autophagy can be induced by various abiotic stresses, including nutrient starvation, oxidative, salt, drought and heat stress, and autophagy-defective mutants are hypersensitive to these stress conditions [115, 126–130]. When plants are exposed to these conditions, ROS production, at least partially through NADPH oxidase, acts as a common signal to activate stress responses, including autophagy. Both NADPH oxidase dependent and -independent pathways exist to regulate autophagy [127, 131]. Autophagy is stimulated as a cell survival response during hypoxia in mammals [132], and *Arabidopsis atg* mutants are hypersensitive to submergence-induced hypoxia, via a pathway dependent on SA signaling. ROS production by NADPH oxidase is necessary for plant tolerance to submergence and activation of autophagy [131].

Heat stress can cause misfolding and denaturation of proteins, as well as trigger ER degradation to balance cellular homeostasis [133]. Autophagy is reported to target those protein aggregates derived from denaturation through NBR1-mediated degradation under heat stress [128], and to participate in ER degradation upon ER stress [4, 89, 90]. Heat stress induced the expression of *ATG* genes and the accumulation of autophagosomes, and autophagy is proposed to contribute to heat tolerance [90, 134]. A heat-shock transcription factor *A1a* (*HsfA1a*) from tomato was shown to regulate autophagy under drought stress. *HsfA1a* binds to the promoters of *ATG10* and *ATG18f* and activates autophagy, which leads to improvements in drought tolerance in *HsfA1a* overexpressing tomato plants [135]. This not only suggests a role for autophagy in promoting plant survival under drought stress, but also demonstrates the transcriptional regulation of autophagy. Identifying more stress-related autophagy regulators, e.g. transcription factors, and uncovering the underlying molecular mechanisms will be an interesting challenge for this field in the near future.

5.4 The role of autophagy in immune responses

Autophagy has been reported to have both pro-survival and pro-death roles in the regulation of hypersensitive response PCD (HR-PCD) and plant immune responses to biotic stresses [136–138]. Autophagy has a positive function in preventing infection and restricting the spread of cell death from necrotrophic pathogen infection [139, 140]. However, conflicting observations have been made on the role of autophagy during biotrophic pathogen infection [41, 105, 107, 141–143], probably relating to SA signaling and leaf age. Induction of autophagy by pathogens requires the SA signaling pathway, which is age-dependent. Young leaves contain low levels of SA and have no significant differences in cell death between WT plants and *atg* mutants. In older leaves, which accumulate high SA levels, cell death induced by pathogens is restricted in WT plants but not in *atg* mutants [107].

Some regulators participate in plant defense responses via autophagy. For example, RabG3b, a small GTP-binding protein, promotes HR-PCD by activation of autophagy in response to avirulent bacterial pathogens in *Arabidopsis*, playing a positive role in plant immunity [111]. Tobacco cytosolic glyceraldehyde-3-phosphate dehydrogenases (GAPCs) were found to negatively regulate autophagy and immunity by interacting with ATG3; interestingly, this interaction is regulated by ROS [144]. Likewise, *Arabidopsis* GAPCs regulate ROS accumulation and cell death in response to the bacterial pathogen *P. syringae* [145]. Autophagy confers resistance to the necrotrophic fungal pathogen *B. cinerea*, which is triggered by cleavage of BAG6, a member of the Bcl-2-associated athanogene (BAG) family, which are core regulators of PCD [146]. A recent study shows that PexRD54, an effector from the Irish potato pathogen *Phytophthora infestans*, can bind the host autophagy protein ATG8CL and stimulate autophagosome formation. By outcompeting the autophagy cargo receptor Joka2 from the ATG8CL complex, PexRD54 makes the plant more susceptible to infection by *P. infestans* [147]. The structural basis of this interaction is also newly defined [148]. These interesting studies offers new insights into structure/function relationships of the effector and host autophagy machinery during infection.

In animals, autophagy is a key mechanism in the fight against a wide range of viruses, with both anti- and proviral roles [149, 150], and a role in plant viral responses has recently been

demonstrated. Autophagy was found to play an important role in the RNA silencing suppression pathway and geminivirus infection in *N. benthamiana* by degrading a Suppressor of Gene Silencing 3 (SGS3) [151]. Haxim et al. [152] showed that autophagy functions as an antiviral mechanism against three types of geminiviruses in plants, through targeting and degrading the virulence factor via interaction with the key autophagy protein ATG8. Hafren et al. [153] have proposed a model for the roles of autophagy in the cauliflower mosaic virus (CaMV) infection cycle. NBR1-dependent selective autophagy plays antiviral roles in CaMV infection during transmission, whereas NBR1-independent bulk autophagy has proviral roles by preventing the death of infected plants, thus extending the timespan of virus production and possible viral transmission [153]. Given the importance of autophagy in plant-virus interactions, future research will most likely provide more evidence of virus-induced selective or bulk autophagy.

6. Conclusions and perspectives

Autophagy research in plants has made great progress in the past 15 years, including the identification of the core machinery of autophagy and elucidation of its role in various environmental stress responses and developmental events. In addition, some non-ATG proteins that participate in autophagy have been characterized. Progress continues to be made in the analysis of the regulation of autophagy, and the TOR kinase complex appears to be a major regulator. Identification of transcriptional or post-transcriptional factors that target the core autophagy machinery would be beneficial for the elucidation of mechanisms of autophagic degradation or of interactions between the autophagy network and other pathways such as hormone- and stress-related signaling. In recent years, selective autophagy has received substantial attention, and functions during specific conditions to degrade specific proteins or organelles. It is essential to identify and characterize the adapters/receptors or other new components that mediated selective autophagy pathways, as well as signals that act in cargo recruitment. Autophagy is important in nitrogen remobilization and responses to abiotic or biotic stresses, so the study of autophagy in crop plants is likely to be of great value. Manipulation of autophagy might be an effective strategy to improve NUE or stress tolerance, potentially leading to enhanced yield.

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Abbreviations

AIM	ATG8 interaction motif
ATG	AuTophagy-related
ATI1	ATG8-interacting protein 1
BAR	Bin-amphiphysin
BR	Brassinosteroid

CHMP1	Charged multivesicular body 1
CV	Chloroplast vesiculation
EM	Electron microscopy
ER	Endoplasmic reticulum
ESCRT	Endosomal sorting complex required for transport
FREE1	FYVE domain protein required for endosomal sorting 1
GAPCs	Glyceraldehyde-3-phosphate dehydrogenases
HR-PCD	Hypersensitive response PCD
IRE1b	Inositol-requiring enzyme-1b
JNK	c-Jun N-terminal kinase
NAP1	Nck-associated protein
NBR1	Neighbor of BRCA1 gene 1
NRE	Nitrogen remobilization efficiency
NUE	Nitrogen use efficiency
PCD	Programmed cell death
PE	Phosphatidylethanolamine
PtdIns3K	Phosphatidylinositol-3-kinase
RCBs	Rubisco-containing bodies
ROS	Reactive oxygen species
SA	Salicylic acid
SAVs	Senescence-associated vacuoles
SH3P2	SH3 domain containing protein 2
TE	Tracheary element
TOR	Target of rapamycin
UIMs	Ubiquitin-interacting motifs
UPR	Unfolded protein response
UVB	ultraviolet-B

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Figure 1.

Summary of the induction, process and functions of autophagy in plants. Autophagy can be induced by various developmental or environmental factors as indicated. Upon induction, a cup-shaped double-membrane phagophore forms around the cargo. The membrane elongates and closes to form a double-membrane vesicle, the autophagosome. The red dots on the autophagosome membrane represent ATG8-PE adducts. The outer membrane of the autophagosome fuses with the vacuole, and its contents are broken down by vacuolar hydrolases. Autophagy functions in a range of quality control, developmental and stress response pathways.

Figure 2.

Schematic diagram of pathways for selective autophagy in plants. Five types of organelle-specific autophagy have been identified: degradation of entire chloroplasts and Rubisco-containing bodies (RCB) (chlorophagy), degradation of ER (reticulophagy), degradation of mitochondria (mitophagy), degradation of peroxisomes (pexophagy) and degradation of proteasomes (proteaphagy). ATI bodies participate in both the degradation of plastids and ER. Proteaphagy is mediated by the ubiquitin-binding receptor RPN10. Degradation of ribosomes (ribophagy) is not fully elucidated in plants, but autophagy is involved in rRNA turnover. Key genes for each type of selective autophagy are listed.