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REVIEW ARTICLE

Interactions between autophagy and phytohormone signaling pathways in plants

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Autophagy is a conserved recycling process with important functions in plant growth, development, and stress responses. Phytohormones also play key roles in the regulation of some of the same processes. Increasing evidence indicates that a close relationship exists between autophagy and phytohormone signaling pathways, and the mechanisms of interaction between these pathways have begun to be revealed. Here, we review recent advances in our understanding of how autophagy regulates hormone signaling and, conversely, how hormones regulate the activity of autophagy, both in plant growth and development and in environmental stress responses. We highlight in particular recent mechanistic insights into the coordination between autophagy and signaling events controlled by the stress hormone abscisic acid and by the growth hormones brassinosteroid and cytokinin and briefly discuss potential connections between autophagy and other phytohormones.

Keywords: *ATG* genes; autophagy; development; phytohormones; plant pathogens; stress response

Basic mechanisms of autophagy are conserved

To adapt to fast-changing environments, eukaryotes have evolved multiple strategies to maintain cellular homeostasis, optimize nutrient recycling, and for quality control of cellular components under non-stress and stress conditions. Macroautophagy, most commonly simply termed autophagy, meaning "self-eating," is a cellular recycling process with multiple roles during differentiation, development, and stress responses of eukaryotic organisms. The process functions at a basal level under non-stress conditions and is highly induced by environmental stresses. When activated, autophagy delivers cargo into the vacuole (yeast and plants) or lysosome (animals) for degradation and recycling *via* double-membrane vesicles termed autophagosomes. The autophagic machinery was initially identified in yeast [1–3], and the highly conserved *AUTOPHAGY-RELATED* (*ATG*) genes encoding core components for autophagosome formation are also found in other organisms, including plants [4]. Upon autophagy initiation by

Abbreviations
ABA, abscisic acid; AIM, ATG8-INTERACTING MOTIF; AOX, alternative oxidase; ARR, Arabidopsis response regulator; ATG, AUTOPHAGY-RELATED; BR, brassinosteroid; CK, cytokinin; ET, ethylene; JA, jasmonic acid; MVB, multi-vesicular body; PCD, programmed cell death; PI3K, phosphatidylinositol 3-kinase; RAPTOR, regulatory-associated protein of TOR; SA, salicylic acid; SnRK, sucrose non-fermenting-1-related kinase; TOR, target of rapamycin; TSPO, tryptophan-rich sensory protein; VPS, VACUOLAR PROTEIN SORTING.

the Atg1 complex (using the yeast nomenclature), a double-membrane phagophore is formed [5]. Atg9 and Atg2 together mediate lipid transfer to enable phagophore membrane expansion. Next, the Vps34 (VACUOLAR PROTEIN SORTING 34) lipid kinase complex functions in PI3P (phosphatidylinositol 3-phosphate) production [6] and recruitment of PI3P-binding effectors such as Atg18 to enable autophagosome expansion [7]. The Atg5/Atg12/Atg16 E3 ligase-like complex conjugates Atg8 with phosphatidylethanolamine (PE), which tethers Atg8 to the phagophore [8,9]. Finally, Atg8 and other factors act to seal the phagophore [10] to complete the autophagosome (Fig. 1) [4]. Although initially considered to be non-selective and serve as a bulk degradation system, autophagy in many cases has now been shown to have selectivity [11]. Lipidated ATG8 family members associate with various autophagic receptors containing ATG8-INTERACTING MOTIFs (AIM) or LIR-INTERACTING MOTIFs to selectively incorporate specific cargos into autophagosomes [12–15]. In addition to the canonical AIM, ATG8 in some organisms also binds to receptors with a ubiquitin-interacting motif (UIM) for selective autophagic degradation of certain cargos [16,17].

Pathways for regulation of autophagy in plants

The core autophagy machinery is conserved among eukaryotes and is regulated by key energy sensors in response to changes in energy and nutrient status. In plants, the evolutionarily conserved sucrose non-fermenting (SNF)-related kinase 1 (SnRK1) is an essential energy sensor, and the target of rapamycin (TOR) protein kinase complex is required for sensing nutrient concentrations. These kinases coordinate with various other signaling pathways to respond to environmental cues [18,19]. Autophagy in animals and yeast is activated by homologs of SnRK1, AMP-activated protein kinase (AMPK) and Suc non-fermenting 1 (Snf1), respectively, upon low energy status [20]. In Arabidopsis, SnRK1 activates autophagy through direct phosphorylation of ATG1 and through repression of TOR activity [21,22]. In contrast, the TOR complex (TORC) senses nutrient concentrations and negatively regulates autophagy [23–25]. It is composed of three major subunits, the TOR kinase catalytic subunit and two regulatory subunits, Regulatory-Associated Protein of TOR (RAPTOR) [26–29] and Lethal with Sec Thirteen 8 (LST8) [30]. Yeast TORC regulates autophagy through phosphorylation of ATG13 in response to nutrient conditions, and Arabidopsis TORC potentially modulates autophagy in a similar way, as several TOR phosphorylation sites on ATG13 have been identified using large-scale phosphoproteomics [31]. These energy and nutrient sensors act in coordination with various other signaling pathways to regulate autophagy, thereby maintaining the balance between plant growth and stress responses.

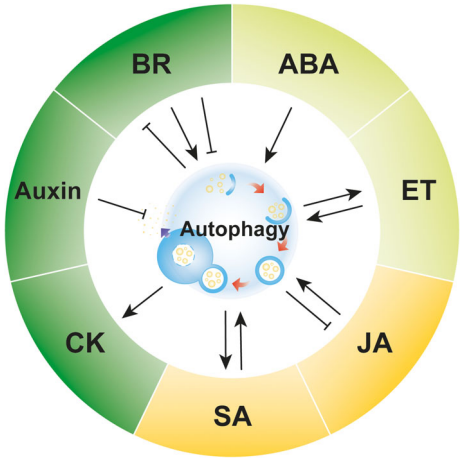

Fig. 1. Regulation of autophagy by diverse phytohormones. Autophagy activity can be regulated by phytohormones; auxin represses autophagy to allow plant growth and development, whereas ABA activates autophagy during abiotic stress. BR can regulate autophagy both positively and negatively, whereas autophagy also can regulate BR signaling. CK, ET, SA, and JA metabolism and signaling are affected by autophagy in certain conditions.

While these general regulatory mechanisms are present in plants, many key regulators upstream or downstream of TORC and AMPK in animals are not present in plants [32], implying that plants may have evolved unique autophagy regulatory mechanisms that integrate with other plant-specific signaling pathways. Phytohormone biosynthesis and signaling are critical for plant growth, development, and stress responses. Since autophagy plays key roles in numerous biological processes and is activated or repressed by different stimuli, it is not surprising that autophagy integrates with hormone signaling pathways to adapt to rapidly changing environments. For example, autophagy is rapidly induced within 30 min of diverse stimuli, including phytohormone treatment [33]. After this short-term activation of autophagy to promote cell remodeling, hormone signaling either represses or activates autophagy as a long-term response. The precise roles that autophagy plays in response to different phytohormones in various conditions remain largely unknown. In this review, we summarize recent discoveries of how autophagy orchestrates with phytohormone biosynthesis and signaling in response to different environmental cues

(Fig. 1). We discuss how phytohormones participate in regulating autophagy for nutrient reallocation during development processes and for stress tolerance, especially highlighting the regulatory mechanisms controlled by abscisic acid (ABA), brassinosteroid (BR), and cytokinin (CK).

Linking autophagy to phytohormones

Autophagy and ABA

Higher physiological concentrations of the phytohormone ABA act to inhibit plant growth and promote stress responses by integrating various stress signals to control downstream responses to abiotic and biotic environmental cues [34,35]. In response to stresses such as drought, ABA accumulates rapidly and binds to the receptors of the PYR1/PYL/RCAR family (referred to PYLs) to form an ABA-PYL complex, which subsequently inhibits protein phosphatases of the PP2C family. Inhibition of PP2C releases SnRK2, which phosphorylates downstream targets to initiate stress responses [34–37]. In this section, we review recent progress in how ABA signaling interacts with autophagy during stress responses (Fig. 2).

Regulation of autophagy by an ABA-SnRK2-TOR signaling pathway

TORC is a central growth regulator that integrates energy, growth, hormone, and stress signaling in all eukaryotes [38,39] and negatively regulates the induction of autophagy [24]. Mutation of RAPTOR1B in Arabidopsis results in a strong reduction of TOR kinase activity, leading to the induction of autophagy [40] and reduced growth [27,41]. The *raptor1b* mutant also has reduced ABA levels, and ABA feeding can partially complement its growth phenotype, indicating interaction between TOR function and ABA signaling [42]. TORC phosphorylates the PYL ABA receptors, leading to inactivation of SnRK2 kinase in unstressed conditions, while ABA-activated SnRK2 phosphorylates RAPTOR1B, triggering TOR complex dissociation and inhibition under stress conditions, and potentially activating autophagy (Fig. 2(1)). This reciprocal regulation of the TOR kinase and ABA

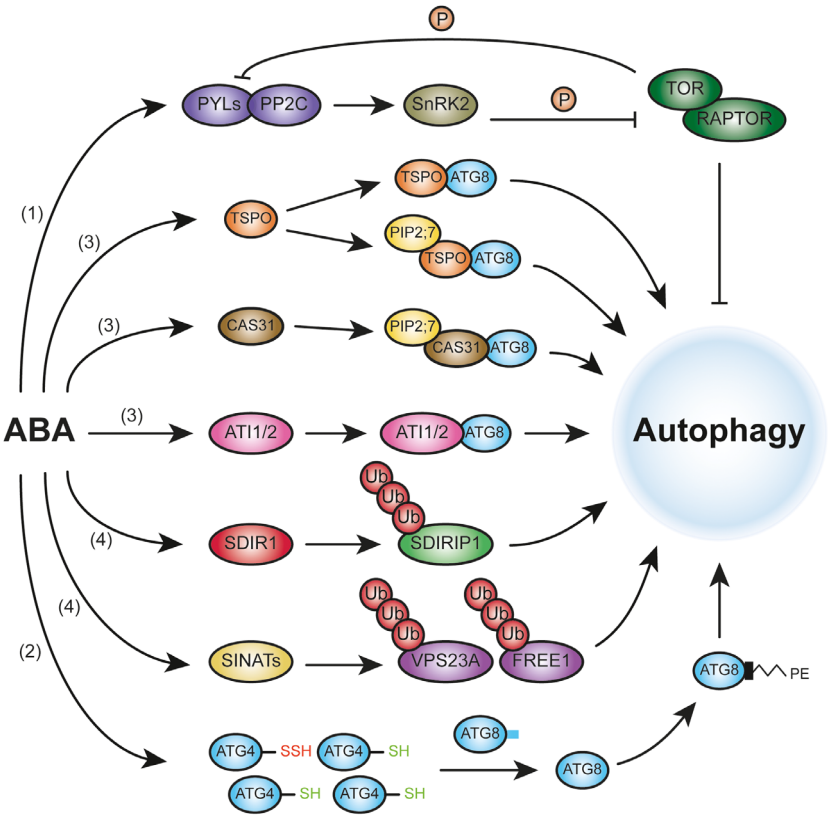

Fig. 2. Interactions between ABA signaling and autophagy. (1) Regulation of autophagy by an ABA-SnRK2-TOR signaling pathway. (2) ABA decreases persulfidation of ATG4, activating ATG4 to promote autophagy. (3) ABA-induced proteins are involved in selective autophagy. (4) E3 ubiquitin ligases in ABA signaling mediate substrate turnover through autophagy.

receptor balances plant growth and stress responses [43].

While SnRK2 kinases are the main drivers of ABA-triggered stress responses, and the repression of TOR by ABA is SnRK2-dependent [43], no interaction of TOR or RAPTOR with SnRK2 was detected either under control conditions or upon ABA treatment. There is, however, a physical interaction between SnRK1 and TOR, and this interaction is enhanced by ABA treatment [44]. SnRK1 and SnRK2 interact, and while this interaction is reduced by ABA and increased in the presence of PP2C, it does not depend on the kinase activity of SnRK2 [44]. SnRK2 promotes SnRK1 signaling, but this does not appear to involve direct SnRK1 activation [44]. SnRK2 kinases are, thus, concluded to perform dual functions in plants. In the absence of ABA, SnRK2 binds to SnRK1 and prevents SnRK1 interaction with TOR, allowing growth in favorable conditions. Under stress conditions, disassembly of the complex releases SnRK2 and SnRK1 to trigger stress responses and inhibit growth *via* inhibition of TOR [44]. These studies revealed possible interactions between autophagy and ABA signaling through phosphorylation of the corresponding key regulators.

ABA-mediated post-translational modification and regulation of an autophagy protein

Protein persulfidation is a post-translational modification in which a cysteine thiol group is converted to a persulfide (-SSH) by hydrogen sulfide [45]. Recently, a comparative and quantitative proteomic analysis revealed that persulfidation of the cysteine protease ATG4 negatively regulates ATG4 proteolytic activity, in turn regulating autophagy, and this persulfidation is reduced upon ABA treatment. Under normal conditions, a high level of persulfidation of ATG4 at Cys 170 limits ATG8 lipidation and consequently autophagosome formation. ABA treatment reduces the level of persulfidation of ATG4, activating ATG4 protease activity to process ATG8 and promote autophagy [46]. These results provide a novel mechanism for activation of autophagy by ABA through post-translational modification and regulation of a core autophagy protein (Fig. 2(2)).

ABA-induced proteins involved in autophagy

ABA is the hormone that is often accumulated during and associated with major plant responses to stress. The Arabidopsis Tryptophan-rich Sensory Protein (TSPO) is an ER-/Golgi-localized membrane protein that is transiently induced by abiotic stress and ABA. TSPO can be selectively degraded by autophagy, and targeting to this pathway requires heme and AIM-dependent ATG8 binding. TSPO degradation is inhibited in the autophagy-defective *atg5* mutant and is sensitive to inhibitors of phosphatidylinositol 3-kinase (PI3K), a regulator of autophagy. Furthermore, TSPO colocalizes with ATG8 in autophagosomes, directly supporting TSPO degradation through autophagy [47]. These results suggest an important contribution of autophagy to the ABA-mediated stress response. The TSPO-interacting partner PLASMA MEMBRANE INTRISIC PROTEIN 2;7 (PIP2;7) is also degraded through autophagy, and ABA treatment enhances its turnover in the vacuole, suggesting that ABA-dependent induction of TSPO triggers the degradation of PIP2;7 through the autophagic pathway [48]. TSPO interacts with and acts as a negative regulator of PIP2;7, and it has AIM motifs that can bind ATG8 [49]. As these are typical features of receptors for specific cargo during selective autophagy, this raises the possibility that TSPO acts as a selective autophagy receptor under abiotic stress conditions (Fig. 2(3)).

In contrast, the autophagic degradation of PIP2;7 is mediated by the dehydrin COLD ACCLIMATION-SPECIFIC 31 (CAS31) in *Medicago truncatula* [50]. MtCAS31 is a positive regulator of drought responses, and its expression is induced by drought, salt, and ABA treatment. MtCAS31 interacts with MtATG8a through an AIM-like motif and promotes autophagy under drought stress, thus facilitating the autophagic degradation of MtPIP2;7, a negative regulator of drought responses. MtCAS31 was, therefore, proposed to be a cargo receptor for the selective autophagic degradation of MtPIP2;7 during drought [50] (Fig. 2(3)).

Interestingly, two plant-specific ATG8-interacting proteins, ATI1 and its homolog ATI2, which bind ATG8 proteins *via* two putative AIMs, were found to be involved in ABA-mediated seed germination. Increased expression of both ATI genes follows the accumulation of ABA in the dry seed, while decreased expression accompanies ABA decrease during seed imbibition and germination. Consistent with this, knockdown of the ATIs led to decreased seed germination in the presence of ABA, whereas overexpression increased germination. These results suggest potential roles for ATI1 and ATI2 in selective turnover of germination-inhibiting ABA-associated macromolecules during seed germination [51] (Fig. 2(3)).

Role of E3 ubiquitin ligases, substrate ubiquitination, and autophagy in ABA signaling

Multi-vesicular body (MVB)-mediated vacuolar sorting, the ubiquitin-proteasome system (UPS), and

autophagy pathways are predominant routes for protein turnover and quality control [4,52,53]. The MVB-mediated vacuolar sorting pathway depends on the Endosomal Sorting Complex Required for Transport (ESCRT) machinery, which transports ubiquitinated membrane proteins to the vacuole for degradation [53]. Ubiquitination plays important roles in regulating plant hormone signaling pathways [54], and an E3 ubiquitin ligase is the key factor that defines substrate specificity [55]. VACUOLE PROTEIN SORTING23A (VPS23A) and FYVE DOMAIN PROTEIN REQUIRED FOR ENDOSOMAL SORTING (FREE1) are key components of ESCRT-I in Arabidopsis [56,57]. Both are reported to play a role in the ABA signaling pathway. Upon recognition by FREE1 and VPS23A, the ubiquitinated ABA receptors PYR-ABACTIN RESISTANCE1 (PYR1)/PYR1-LIKE4 (PYL4) are targeted for vacuolar degradation, and mutants in *FREE1* or *VPS23A* are, therefore, hypersensitive to ABA [58,59]. Furthermore, upon ABA exposure, SnRK2 phosphorylates FREE1, leading to its translocation to the nucleus and interaction with the transcription factors ABA-RESPONSE ELEMENT BINDING FACTOR4 (ABF4) and ABA-INSENSITIVE5 (ABI5), attenuating their transcriptional activity [60]. FREE1 and VPS23A are reported to be targets of a RING-type E3 SEVEN IN ABSENTIA OF ARABIDOPSIS THALIANA (SINAT). SINAT1 to SINAT4 promote ABA signaling by controlling the ubiquitination and degradation of FREE1 and VPS23A. SINATs co-localize with autophagosome and MVB markers and physically interact with FREE1 and VPS23A to promote their ubiquitination and degradation. Furthermore, during recovery post-ABA exposure, SINATs form homo- and hetero-oligomers in vivo, which are selectively degraded by the autophagy pathway (Fig. 2(4)). These results reveal a mechanism in which multiple degradation pathways coordinately mediate the turnover of SINAT-FREE1/VPS23A complex proteins to regulate ABA signaling and stress responses [61].

A RING-type E3, SALT- AND DROUGHT-INDUCED RING FINGER1 (SDIR1), is involved in ABA-related salt and drought stress responses and is a positive regulator of ABA signaling [62]. A yeast two-hybrid screen identified a substrate of SDIR1, SDIR1-INTERACTING PROTEIN1 (SDIRIP1), which is involved in plant responses to salt stress and ABA signaling. Moreover, SDIRIP1 is degraded through both the 26S proteasome pathway and autophagy, although the mechanism of SDIRIP1 degradation through autophagy is unknown [63]. How ABA regulates the turnover of SDIR1 or its substrates in specific stress conditions, which in turn regulates ABA signaling, remains to be determined (Fig. 2(4)).

As discussed above, the turnover of important proteins induced by ABA or other stresses through autophagy is a critical mechanism for stress response. The ubiquitination of target proteins involved in ABA signaling pathways by specific E3 ligases and their degradation mediated by specific cargo adaptors under specific conditions will be an interesting area to explore in future.

Autophagy and BR

Brassinosteroids are steroid phytohormones that play critical roles in plant growth, development, and responses to stress [64,65]. BRs are perceived by the leucine-rich repeat receptor-like kinase BRASSINOSTEROID INSENSITIVE1 (BRI1), which interacts with co-receptor BRI1-ASSOCIATED RECEPTOR KINASE (BAK1) [66–68]. After BRI1 and BAK1 are activated by BR, a cascade of signaling events lead to the inhibition of GLYCOGEN SYNTHASE KINASE 3 (GSK3)-like kinase BIN2, a pivotal negative regulator of the BR pathway. The inhibition of BIN2 leads to the accumulation of unphosphorylated BRI1-EMS-SUPPRESSOR1 (BES1) and BRASSINAZOLE-RESISTANT1 (BZR1) family transcription factors (TFs), which control the expression of thousands of BR-regulated genes [69–74]. In this section, we review how BR signaling interacts with the autophagy pathway (Fig. 3).

Regulation of autophagy by BR signaling

In tomato, the transcripts of autophagy-related genes (*ATGs*) and the formation of autophagosomes are induced by enhanced levels of BR, indicating activation of autophagy by BR [75]. BZR1 was shown to be involved in BR-induced autophagy by binding to the promoters of *ATG2* and *ATG6* genes, and knockdown of *ATG2* or *ATG6* compromises the formation of BR-induced autophagosomes. In addition, nitrogen starvation-induced expression of *ATGs* and autophagosome formation are compromised in BZR-silenced plants but are increased in BZR1-overexpressing plants [75]. These results indicate that BZR1-dependent BR signaling positively regulates autophagy induction under nitrogen starvation. Another recent report in tomato showed that BRs and BZR1 play an important role in response to cold by inducing autophagy and accumulation of the selective autophagy receptor NBR1. Cold and BR lead to increased BZR1 stability, which activates the transcription of several *ATG* and

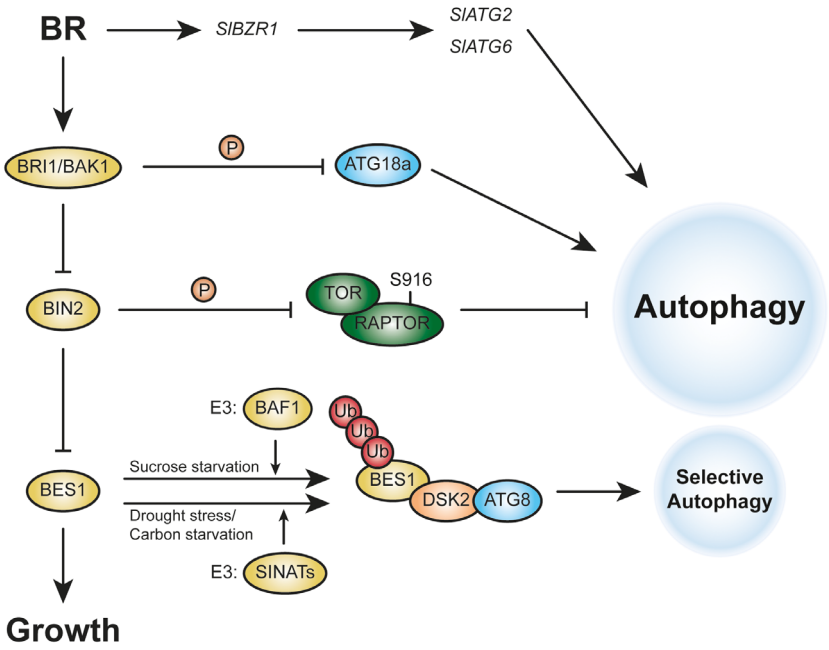

Fig. 3. Interactions between BR signaling and autophagy. In tomato, BR can activate autophagy through BZR/BES family transcription factor *SlBZR1*, which in turn promotes *SlATG2* and *SlATG6* gene expression. In Arabidopsis, BR co-receptor BAK1 phosphorylates ATG18a to inhibit autophagy in response to *Botrytis cinerea*. Next, BIN2 phosphorylates RAPTOR1B at Ser916 to promote autophagy. Depending on the conditions, BES1 is ubiquitinated by the E3s BAF1 or SINATs and selectively degraded by autophagy through the ubiquitin receptor DSK2.

NBR1 genes by directly binding to their promoters to induce autophagy. Consistent with this effect, silencing of these *ATG* or *NBR1* genes compromises both BR-induced autophagy and tolerance to cold stress. These findings provide insight into important roles of BRs in preventing the accumulation of cold-induced protein aggregates by activating NBR1-mediated selective autophagy [76].

There are also indications that autophagy can be negatively regulated by BRs in some conditions. Application of a high concentration of BR to peach leaves decreased *PpATG* gene expression levels and reduced the number of autophagosomes observed under drought stress [77]. BAK1, the BR co-receptor with BRI1 [67], also functions as an important regulator of plant disease resistance [78–80]. BAK1 physically interacts with and phosphorylates ATG18a, a key protein in autophagosome formation. Phosphorylation of ATG18a decreases autophagy induction and compromises plant resistance to *Botrytis cinerea* [81,82]. However, whether or not BAK1-mediated ATG18a phosphorylation affects BR-regulated autophagy remains unknown. It appears that the role of BR as a positive or negative regulator of autophagy is dependent on the BR concentration and treatment duration in specific conditions.

BIN2 is an important negative regulator of the BR pathway, negatively regulating plant growth [70], whereas TOR positively regulates plant growth and development but negatively regulates autophagy [24]. Both BIN2 and TOR control plant growth and stress responses *via* phosphorylation of multiple substrates, exerting molecular changes to many different pathways [31,69]. The molecular connections between BR and TOR signaling provide hints as to how BR signaling regulates autophagy through regulation of TOR. Recently, a multi-omic analysis detailing transcriptome, proteome, and phosphoproteome changes in *bin2* and *raptor1b* mutants was reported [83]. Integrated analysis revealed a significant overlap of gene products (i.e., transcript, protein, or phosphosites) that are regulated by both BIN2 and RAPTOR1B, suggesting that there is a shared regulatory core between BR and TOR signaling pathways. Network analysis identified proteins that are required for both normal BR response and autophagy, which possibly participate in the balancing of plant growth and stress responses orchestrated by BIN2 and TOR [83]. From this proteome-wide dataset of BIN2, the phosphosite Serine 916 (Ser916) in RAPTOR1B was identified as potentially phosphorylated by BIN2. In the presence of BR, when BIN2 is inhibited, RAPTOR1B Ser916

phosphorylation is decreased, which promotes phosphorylation of ATG13a by TOR and thus represses autophagy. This suggests a model in which when BR is absent, active BIN2 can suppress the TOR complex through phosphorylation of RAPTOR1B to induce autophagy [84]. These studies provide valuable resources and mechanistic insights into the interaction between BR signaling and TOR-dependent autophagy.

Selective autophagy of BES1 in the control of BR signaling

BES1 and BZR1 are hubs in the BR signaling pathway, and their protein stability is crucial for their function. BES1 and BZR1 can be regulated by multiple E3 ubiquitin ligases that control their degradation through the 26S proteasome pathway or selective autophagy [65,85–89]. Sugar signaling through TOR stabilizes BZR1 to promote plant growth, while sugar starvation-triggered TOR inactivation leads to BZR1 degradation, likely through autophagy, to inhibit plant growth, implying that autophagy contributes to the homeostasis of BR signaling [90]. The identification of a selective autophagy cargo receptor, DOMINANT SUPPRESSOR OF KAR 2 (DSK2), provided clear evidence of BES1 degradation through selective autophagy and revealed the underlying mechanism [86]. DSK2 contains a ubiquitin-associated domain and ATG8-interacting motif (AIM) and, therefore, can both recognize poly-ubiquitin chains and bind to ATG8 [86,91]. DSK2 interacts with BES1 and ATG8 to target BES1 for autophagy-mediated degradation during drought or fixed-carbon starvation stresses. Moreover, BIN2 phosphorylates DSK2 proximal to its AIMs to promote DSK2-ATG8 interaction and thus enhance BES1 degradation *via* autophagy. A RING E3 ubiquitin ligase, SINAT2, interacts with BES1 and DSK2, suggesting that SINAT E3 ubiquitin ligases may be involved in the ubiquitination and degradation of BES1 [86].

Recently, we also identified another E3 ubiquitin ligase, BES1-ASSOCIATED F-BOX1 (BAF1), involved in the degradation of BES1 through selective autophagy during sucrose starvation [87]. BAF1 interacts with BES1 and mediates its ubiquitination and degradation. BAF1 inhibits BR-mediated growth in a BES1-dependent manner, and BAF1-triggered selective autophagy of BES1 upon sucrose starvation depends on the autophagy machinery and DSK2. Double mutant analysis also indicates that BAF1 functions redundantly in the light or dark with SINATs and MAX2 E3 ligases, which are involved in BES1 degradation [86,88,89,92]. These studies suggest that selective autophagy of BES1, mediated by the autophagy receptor DSK2 and by the BAF1 and SINAT E3 ligases, controls BR signaling under specific stress conditions. Important hormonal signaling components such as BES1 can, therefore, be targeted by the autophagy pathway to adjust plant growth in response to stress conditions.

Autophagy and auxin

Auxin is a major phytohormone that influences a wide range of physiological and developmental processes in plants. The regulation of auxin biosynthesis and signaling also provides developmental plasticity of the plant root in response to various stresses [93]. Auxin levels are determined by its biosynthesis, conjugation, and transport, which are affected by abiotic stresses [93]. Effects of auxin on autophagy regulation during plant development vary in the shoot and root apices and are modulated through activating TOR signaling or transcriptional regulation of auxin-responsive elements within *ATG* promoters. In this section, we review how auxin integrates with other regulators to control autophagy and how autophagy regulates auxin pathways during root development.

Interaction between auxin signaling and autophagy

Over the past few years, links between auxin and autophagy regulation have emerged. Auxin activates TOR through the small GTPase ROP2 [94], reciprocally regulating growth responses and autophagy. Auxin-activated TOR signaling represses autophagy induced by nutrient starvation and salt and osmotic stress [40]. As most of the evidence for auxin-autophagy cross talk relates to Arabidopsis, it is unclear whether this interaction is conserved in other plant species. A recent finding in maize shows that the expression levels of *ZmATG18b* (autophagy gene) and *ZmGH3.8* (auxin metabolism gene) in different maize lines affect leaf senescence and yield [95]. Lower *ZmATG18b* expression and higher *ZmGH3.8* expression lead to a delay in leaf senescence and increase in ear weight, suggesting a potential interaction between autophagy and auxin during maize leaf senescence at the transcriptional level.

Autophagy-mediated auxin metabolism, signaling, and transport in regulating root development

Emerging evidence indicates that autophagy plays important roles in root development, especially under different nutrient stresses, by regulating auxin metabolism and accumulation. During phosphate starvation, S-domain Arabidopsis Receptor Kinase 2 (ARK2) and plant U-box/armadillo repeat protein 9 (PUB9) E3 ligase modulate lateral root (LR) development [96].

The authors hypothesized that, under these conditions, the degradation of repressors of the accumulation of auxin by autophagy is inhibited. This in turn leads to increased lateral root growth [96,97]. This reveals a potential role of the ARK2/AtPUB9 module in regulation of lateral root development upon phosphate starvation, possibly through selective autophagy. Auxin accumulation also occurs in roots of *atg* mutants upon high glucose stress. The increased auxin gradients and auxin responses enhance the root meristem activity, resulting in increased tolerance to high glucose concentrations [98].

In addition to affecting auxin metabolism, autophagy can also influence the transport of auxin. In plants, unlike in animals, PI3P is synthesized entirely by the class-III PI3K complex [99]. VACUOLAR PROTEIN SORTING (VPS) 38 is a subunit of the PI3K complex II isoform, which directs trafficking events required for vacuolar protein sorting [100,101]. *vps38* mutants have phenotypes related to impaired autophagy, such as hypersensitivity to nitrogen and fixed-carbon starvation, and vesicle trafficking phenotypes, including reduced plasma membrane to endosome cycling of the PIN-FORMED (PIN) auxin efflux carriers, leading to defects in the auxin flow necessary for robust root development [102]. These findings provide links between auxin and autophagy, although the precise mechanisms of coordination between these pathways are yet to be clarified.

Autophagy and cytokinin

Cytokinins are N^6-substituted adenine derivatives that affect many aspects of plant growth and development [103]. In Arabidopsis, the CK signaling cascade is similar to bacterial two-component signaling systems (TCS) and initiates with binding of CK to histidine kinase receptors. After a series of phosphotransfers, the type-A and type-B Arabidopsis response regulators (ARR) are phosphorylated. Type-A ARRs act as negative regulators in CK signaling, forming feedback loops to regulate the CK pathways [103]. CK-autophagy cross talk plays important roles in leaf senescence, nutrient remobilization, root and vascular development, and response to stresses. Here, we review current findings that link CK to autophagy regulation during development and how selective autophagy modulates CK signaling *via* degradation of type-A ARRs.

Autophagy and CK-regulated plant development

Autophagy can affect CK perception and biosynthesis in different plant organs. For example, overexpression of *GFP-ATG8f* results in altered sensitivity to exogenous CK of root architecture and reduces shoot anthocyanin accumulation [104]. Moreover, CK treatment triggers the production of unknown GFP-ATG8-containing structures in the vicinity of the root vascular system [104], possibly caused by sequestration of proteins involved in CK transport or signaling, leading to the slowdown of root-stimulated anthocyanin production in the shoots. These observations imply that autophagy participates in CK-regulated root-shoot communication in Arabidopsis. In rice, *Osatg7* mutants have decreased levels of the endogenous CK trans-zeatin in anthers and are male-sterile [105]. Although the physiological functions of CK and autophagy during anther development remain largely unknown, autophagy may be involved in regulating CK content. Transcriptomic analyses also reveal an overlap between differentially expressed genes in CK signaling mutants and in *atg5* mutants [106], further indicating an integration between CK signaling and autophagy.

Exocyst subunit-mediated selective autophagy and CK sensitivity

Despite the links between CK and autophagy, the regulatory mechanisms underlying CK-autophagy interactions in plant development were unclear. In the past few years, selective autophagy receptors have been discovered that link autophagy with various signaling pathways not previously directly connected to autophagy regulation. One example is the exocyst subunit-mediated selective autophagic degradation of CK signaling regulators. The octameric exocyst complex is an exocytic tethering complex between vesicles and plasma membrane prior to SNARE-mediated membrane fusion [107,108]. EXO70B1, one of the 23 paralogs of EXO70 in Arabidopsis, contains an AIM domain and colocalizes with ATG8 proteins in autophagosomes [109]. Loss-of-function of EXO70B1 leads to fewer vacuolar autophagic vesicles, suggesting a link between the exocyst complex (especially the EXO70 family) and autophagy [109]. Type-A ARR proteins are negative regulators of CK signaling and usually have a short half-life, which is either regulated by the ubiquitin-proteasome system or other alternative ubiquitin-independent pathways [110–113]. A recent study revealed that EXO70D family members act as selective autophagy receptors and interact with type-A ARR for autophagic degradation in Arabidopsis [114]. This finding unravels an alternative ubiquitin-independent pathway regulating type-A ARR turnover in an autophagy-dependent manner. These examples, together with BES1 regulation by autophagy, suggest a

common theme in autophagy and hormone signaling pathways in which hormone signaling components can be targeted to selective autophagy to modulate specific hormonal responses.

Autophagy and ethylene

The phytohormone ethylene (ET) is produced in response to multiple stresses and plays important roles in the regulation of organ growth and yield under abiotic stress [115]. This small molecule exerts various functions in regulation of leaf development, senescence, fruit ripening, and germination and in response to multiple environmental stresses, such as submergence, which triggers ET synthesis [115]. This section describes links between ET and autophagy in stress responses and organ senescence.

Relationship between autophagy and ethylene in stress responses

A few ET signaling-associated genes (e.g., ETHYLENE RESPONSE2 and CONSTITUTIVE TRIPLE RESPONSE1) are significantly upregulated in *atg5* and *atg9* mutants, which suggests that ET is overproduced in the *atg* mutants at the rosette stage [106]. Recently, direct regulation of autophagy by ET has been shown. ET can upregulate *GmATG8i* in soybean plants, and starvation stress stimulates ethylene production and ET-induced gene expression, including the expression of *GmATG8i* and *GmATG4* genes [116]. Mitochondrial alternative oxidase (AOX) functions to balance mitochondrial redox status by limiting the formation of mitochondrial ROS [117]. ET increases AOX capacity and enhances drought responses in tomato, and both AOX and autophagy are indispensable for ethylene-mediated drought tolerance. In *AOX1a-RNAi* plants, ET-induced drought tolerance and autophagy are decreased, whereas drought tolerance and autophagy are increased in *AOX1a* overexpressing plants. ACC (1-amino-cyclopropane-1-carboxylic acid, an ET precursor)-pretreated tomato plants exhibit higher autophagy activity and increased expression of transcripts of *SlATG8d* and *SlATG18h* genes under drought, potentially mediated by direct binding of ethylene response factor 5 (ERF5) to their promoters [118].

Ethylene is also essential for regulating the plant hypoxia response [119]. Hypoxia induces the transcription of *ATG* genes and the formation of autophagosomes, and *atg* mutants have reduced expression of ethylene-responsive genes, which correlates with hypersensitivity of *atg* mutants to hypoxia. This hypersensitive phenotype requires functional SA signaling, suggesting that, at least in part, suppression of ET signaling is responsible for this *atg* mutant phenotype [120]. The phenotype can also be suppressed by the ET overproducer mutation *eto1*, and similarly, the negative effect on banana disease resistance of inhibition of autophagy by 3-methyladenine (3-MA) can be rescued by exogenous ethylene [121]. These effects of autophagy are, therefore, likely to be due to suppression of ET responses.

Relationship between autophagy and ethylene in development

Pollination can dramatically accelerate flower petal senescence in many plant species and is accompanied by a burst of ET production [122]. Studies have shown that pollination increases both the expression of *PtATG8s* and autophagosome formation, together with an increase in ET production, in petunia petals [123]. ET treatment rapidly upregulates transcripts of *PhATG8s,* while the ethylene inhibitor 1-methylcyclopropene blocks this induction [123,124]. ET is also responsible for rapid ripening and senescence of fruits and vegetables [125] and induces *ATG8* gene expression in postharvest maturation and senescence of button mushrooms [126]. These results indicate that ET is a key regulator of autophagy during certain senescence processes.

Conversely, autophagy also modulates ET biosynthesis. Overexpression of PI3K enhances the biosynthesis of ethylene and accelerates flower senescence in tobacco (*Nicotiana tabacum* L.) [127], while silencing of *PtATG6* and *PtPI3K* suppresses the expression of an ET biosynthesis gene (*PtACS*) in petunia [128]. These studies together show that ET and autophagy have a strong interaction during organ senescence, although the molecular details remain to be determined.

Autophagy, salicylic acid, and jasmonic acid

The phytohormones salicylic acid (SA) and jasmonic acid (JA) are required for plant defense against pathogens, and SA also plays important roles during senescence and plant immunity-related programmed cell death (PCD). Autophagy negatively regulates PCD *via* the SA signaling pathway during aging and biotic stresses. Large-scale transcriptomic and metabolomic analyses using *atg* mutants also reveal that autophagy impacts SA and JA metabolism and signaling [106]. In plant defense against biotic stress, SA and JA pathways can have different activities depending on the lifestyle of the pathogens [129]. Defense against biotrophs is mediated by the SA pathway, while defense

against necrotrophs is primarily mediated by JA [130]. SA has been proposed to antagonize JA pathways, although synergism between SA and JA pathways also exists in some cases [131,132].

Effect of SA on autophagy and senescence

Typically, autophagy-defective plants show early leaf senescence, excessive immunity-related PCD, and hyperaccumulation of SA [133]. In addition to SA, JA and ET are both involved in senescence modulation [134,135]. Although the JA-responsive marker *PDF1.2* is induced, and levels of JA and JA-Ile (active jasmonate) increase significantly during senescence in *atg2* and *atg5* mutants, JA and ET signaling is not required for autophagy induction during senescence [133]. The early senescence phenotypes observed in *atg* mutants depend on SA signaling and are regulated by NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1 (NPR1) [133]. These results suggest a model in which autophagy is induced due to increased SA production during senescence, generating a negative feedback loop that reduces the SA level to limit the senescence process [133]. The complexity of the interaction between senescence and autophagy is demonstrated by the observation that autophagy upregulation by a low concentration of SA can delay JA-induced leaf senescence [136].

Interaction between SA and autophagy in pathogen defense

The SA-dependent feedback loop regulation of autophagy is also observed during the innate immune response. Autophagy has opposite effects on infection by biotrophic and necrotrophic plant pathogens, which is independent of pathogen-associated molecular pattern (PAMP)-triggered immune responses [129]. For example, ATG2, which functions in early steps of autophagosome biogenesis, negatively regulates resistance to the biotrophic pathogen powdery mildew, and the cell death induced by this pathogen is not sufficient to stop pathogen invasion [137]. In *atg2* and other *atg* mutants, plants exhibit mildew-induced cell death and enhanced disease resistance, which is dependent on the SA pathway rather than the JA/ET pathway. This mildew-induced cell death in *atg* mutants is not fully suppressed by blocking SA signaling, suggesting that both SA-dependent and SA-independent pathways are involved and that the cell death may be uncoupled from the resistance [137]. This example shows that SA-dependent autophagy acts as a negative regulator in defense against biotrophic pathogens such as powdery mildew. In another example, infection with *Cauliflower mosaic virus* (CaMV) or expression of CaMV silencing suppressor P6 enhances susceptibility to *Pseudomonas syringae* pv. *tomato* (Pst) in Arabidopsis plants [138]. This repression of antibacterial defense correlates with a reduction in SA accumulation, thereby dampening SA-dependent autophagy [138]. Although defense against necrotrophs is usually controlled by JA signaling, high susceptibility of an *atg2* mutant to the necrotrophic bacterium *Dickeya dadantii* was recently described, primarily due to high levels of SA signaling rather than JA [139].

In most cases, autophagy increases SA accumulation to promote defense against pathogens. In pear, calcium enhances resistance to *Botryosphaeria dothidea* in leaves by increasing both autophagy and SA accumulation [140]. In apple, overexpression of *MdATG18a* enhances resistance to *Diplocarpon mali* and positively regulates H_2O_2-scavenging and SA accumulation in leaves [141]. As an exception, cucumber mosaic virus (CMV) infection in Arabidopsis dampens the SA-induced autophagy and, therefore, evades the SA resistance responses. Autophagy is induced during CMV infection and facilitates the turnover of the major CMV virulence factor and RNA silencing suppressor 2b [142]. This induction of autophagy is mediated by SA and negatively regulated by the CMV virulence factor 2b [142]. The degradation of 2b leads to increased resistance to CMV *via* RNA silencing-dependent reduction of viral RNA accumulation [142]. These studies suggest that SA plausibly has multiple roles in pathogen and autophagy interactions and that pathogens can subvert these effects to promote pathogenicity. Further studies of the molecular mechanisms are needed to explain the role that autophagy plays in SA responses and to understand the complicated co-adaptation between hosts and pathogens.

Interaction between JA and autophagy in defense against biotic stress

Both JA signaling and autophagy play critical roles in defense during pathogen infection; however, there is still little evidence showing direct interaction between the autophagy and JA pathways. Overexpression of Arabidopsis *WRKY33* transcription factor increases resistance to necrotrophic fungal pathogens, and autophagy is induced by *Botrytis* (a necrotrophic fungal pathogen) infection [82]. Both *wrky33* and *atg* mutants are more susceptible to necrotrophic fungal pathogens. Considering the fact that an important autophagy protein, ATG18a, interacts with WRKY33, autophagy is likely to promote resistance to these

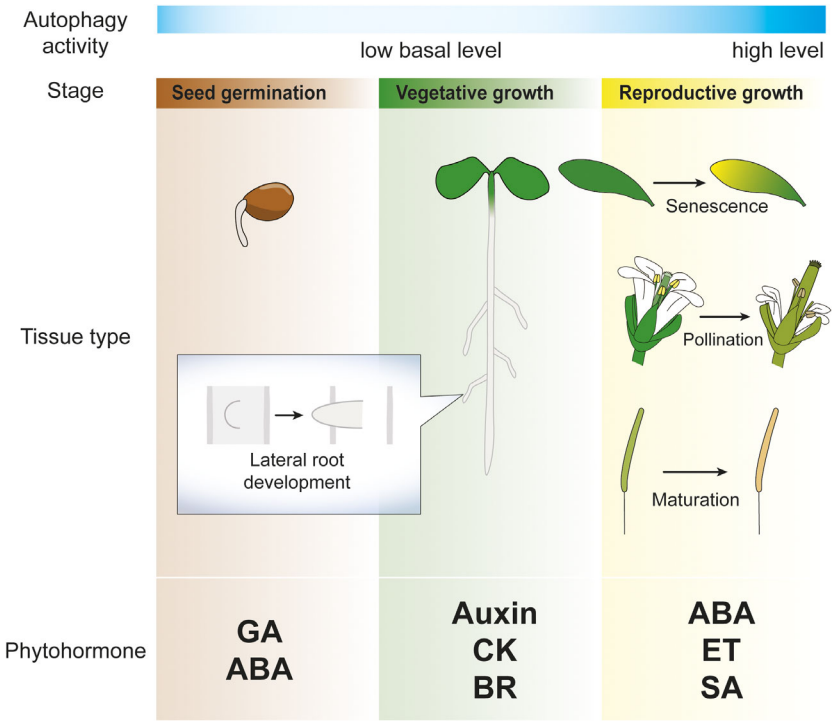

Fig. 4. Tissue-specific autophagy with potential interacting hormone signaling pathways. During different developmental stages in Arabidopsis, autophagy activity varies and may coordinate with phytohormone signaling pathways in a tissue-specific manner. GA-ABA antagonism is critical during seed germination, and autophagy may be activated by GA-ABA signaling for the degradation of germination repressors or storage proteins in the seeds. Auxin, CK, and BR are required for photoautotrophic growth and root development, and autophagy may play different roles in shoots versus roots. At later stages of reproductive growth, autophagy may be regulated by ABA, ET, and SA to control organ senescence. Although no direct evidence in Arabidopsis yet exists, petal senescence after pollination and fruit ripening processes also involve ET-mediated autophagy. [Flower image adapted from Figshare (F. Bouché, 2018_Flower_Arabidopsis, https://figshare.com/articles/Flower_Arabidopsis_2018/7159928); CC BY 4.0.]

pathogens *via* WRKY33-mediated signaling [82]. After *Botrytis* infection, the expression of *PDF1.2* (a JA-responsive marker) is induced in WT plants but is reduced in *atg* mutants. On the contrary, in uninfected *atg* mutants a basal expression of *PDF1.2* is detected, while no expression is found in WT under the same conditions [82]. These observations suggest that autophagy plays opposite roles in the regulation of expression of *PDF1.2*, increasing its expression in pathogen-infected plants but suppressing its basal expression in uninfected plants [82]. Autophagy, therefore, cooperates with WRKY33- and JA- mediated signaling in the regulation of plant defense responses against necrotrophs [82]. Recently, evidence linking autophagy to antiviral JA pathways has also been reported. The highly conserved chloroplast protein cpSRP54 is downregulated in *Nicotiana benthamiana* infected by turnip mosaic virus (TuMV) [143]. TuMV P1 directly interacts with cpSRP54 and mediates its degradation through the 26S proteasome and autophagy pathways [143]. As cpSRP54 is a trafficking component which delivers allene oxide cyclases, key JA biosynthesis enzymes, onto the thylakoid membrane, its degradation reduces JA biosynthesis and enhances viral infection. Despite the close relationship between JA metabolism and signaling and autophagy, the detailed mechanisms are poorly understood, and how JA signaling and autophagy are integrated for pathogen defense remains to be discovered.

Conclusions and perspectives

To cope with environmental changes, plants use complex networks coordinating multiple signaling pathways to optimize growth and survival during stress. Over the past few years, evidence linking autophagy and phytohormone signaling pathways has emerged. Here, we discussed the relationship between autophagy and phytohormones in response to different conditions. Although recent advances have revealed multiple links between autophagy and the hormones ABA, BR, and CK, many questions remain about the

mechanisms of regulation of autophagy by other hormones, and the developmental and stress-related processes in which autophagy modulates hormone actions. Current evidence shows mostly an indirect interplay between hormones and autophagy, in which autophagy can affect hormone levels during stress or in certain tissues. Identification and characterization of specific and direct targets for autophagy in each signaling pathway are needed for a full understanding of the cross talk between autophagy and hormone signaling.

While most studies have looked at the effects of autophagy either in individual cells or in the entire plant, it is likely that autophagy activity in different organs of a plant is coordinated. The activity of autophagy activators or repressors may vary between sink and source tissues, leading to the differential modulation of autophagy dependent on the organ. Plants may regulate autophagy in a tissue-specific manner in response to changes in nutrient status and/or to different stimuli. A developmental role for autophagy in the transition between developmental stages too may be controlled by hormone signaling pathways (Fig. 4).

In the search for major targets that are modulated by phytohormones and autophagy, multi-omics-based approaches using autophagy and hormone signaling mutants provide robust ways to study the global impacts of the interactions between these pathways. In addition, selective autophagy receptors may directly link autophagy to regulation of hormone signaling; functional characterization of novel receptors by analyzing potential AIM or UIM motifs in proteins involved in hormone signaling holds promise to reveal the role of autophagy in hormone-mediated regulatory mechanisms. These approaches may allow further elucidation of such mechanisms and also identify potential connections between autophagy and other phytohormones, such as gibberellin and strigolactone, for which there is currently little evidence for an interaction with autophagy. Understanding how autophagy is modulated by phytohormones, and how phytohormone signaling is regulated by autophagy, will expand our appreciation of how plants control the trade-off between growth and stress responses. This may in turn aid in choosing appropriate breeding targets or developing new strategies for improving crop breeding to ameliorate the losses caused by environmental stress and global climate change.

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