Plant Communications
Review Article

CellPress
PARTNER JOURNAL

All Roads Lead to Auxin: Post-translational Regulation of Auxin Transport by Multiple Hormonal Pathways

Hana Semeradova[1,2], Juan Carlos Montesinos[1,2] and Eva Benkova[1,*]

[1]Institute of Science and Technology Austria, 3400 Klosterneuburg, Austria

[2]These authors contributed equally to this article.

***Correspondence: Eva Benkova (eva.benkova@ist.ac.at)**

https://doi.org/10.1016/j.xplc.2020.100048

ABSTRACT

Auxin is a key hormonal regulator, that governs plant growth and development in concert with other hormonal pathways. The unique feature of auxin is its polar, cell-to-cell transport that leads to the formation of local auxin maxima and gradients, which coordinate initiation and patterning of plant organs. The molecular machinery mediating polar auxin transport is one of the important points of interaction with other hormones. Multiple hormonal pathways converge at the regulation of auxin transport and form a regulatory network that integrates various developmental and environmental inputs to steer plant development. In this review, we discuss recent advances in understanding the mechanisms that underlie regulation of polar auxin transport by multiple hormonal pathways. Specifically, we focus on the post-translational mechanisms that contribute to fine-tuning of the abundance and polarity of auxin transporters at the plasma membrane and thereby enable rapid modification of the auxin flow to coordinate plant growth and development.

Key words: plant hormones, polar auxin transport (PAT), post-translational regulation, trafficking, PINs, abiotic stress

Semeradova H., Montesinos J.C., and Benkova E. (2020). All Roads Lead to Auxin: Post-translational Regulation of Auxin Transport by Multiple Hormonal Pathways. Plant Comm. **1**, 100048.

INTRODUCTION

Plant hormones, including auxin, cytokinin (CK), gibberellins, jasmonates, strigolactones (SLs), salicylic acid (SA), ethylene, brassinosteroids (BRs), and abscisic acid (ABA), are essential endogenous regulators involved in virtually all aspects of plant growth and development. As signaling molecules, they act at very low concentrations, and through specific signaling pathways contribute to coordination of various processes, including embryogenesis, seed germination, primary and lateral root growth, and adaptive responses to various biotic and abiotic stresses. Regulatory input of a single hormone is a result of orchestrated activities of pathways controlling its metabolism, transport, perception, and signal transduction. Interactions with other hormonal pathways represent an important additional level of control contributing to fine-tuning of the hormone activity (reviewed in Vanstraelen and Benková, 2012). Hormones interconnected through various mechanisms of cross-talk, including transcriptional (Zemlyanskaya et al., 2018; Zubo and Schaller, 2020), post-transcriptional (Liu et al., 2007, 2009), or post-translational (Hill, 2015) regulations of gene activities, fine-tune cellular responses and coordinate growth and developmental processes during plants' entire lifespan.

Among plant hormones, auxin stands out for its dominating function in morpho- and organogenic processes, including embryo patterning, postembryonic initiation, and formation of plant organs as well as regulation of tropic responses (Adamowski and Friml, 2015). A key regulatory feature of auxin action is its graded distribution, established and tightly controlled through the polar auxin transport (PAT) machinery, consisting of auxin influx and efflux transporters such as AUX1/LIKE AUX1 (AUX1/LAX), PIN formed (PINs), and ABC/PGP families (Grebe et al., 2002; Benková et al., 2003; Adamowski and Friml, 2015; Singh et al., 2018; Sauer and Kleine-Vehn, 2019; Swarup and Bhosale, 2019). A number of studies have pointed at PAT as an important point of convergence with other hormonal pathways (Dello Ioio et al., 2008; Shkolnik-Inbar and Bar-Zvi, 2010; Bao et al., 2004; Crawford et al., 2010). Intriguingly, besides transcriptional regulation of genes encoding components of the PAT machinery by various hormones (Vieten et al., 2005; Dello Ioio et al., 2008; Ruzicka et al., 2009; Sun et al., 2009; Lewis

Published by the Plant Communications Shanghai Editorial Office in association with Cell Press, an imprint of Elsevier Inc., on behalf of CSPB and IPPE, CAS.

et al., 2011; Šimášková et al., 2015; Rowe et al., 2016), rapid modulation of activity of auxin transporters at the post-translational level appears as an alternative, highly biologically relevant mode of the hormonal cross-talk. Several plant hormones and signaling molecules, such as CK, gibberellin, jasmonate, SA, BRs, ABA, or nitric oxide (NO), have been shown to execute part of their regulatory functions by targeting pathways mediating delivery of auxin transporters to the plasma membrane (PM), recycling between the PM and endomembrane compartments, or re-directing for lytic degradation to vacuoles. Thereby, hormones can rapidly alter the rate, amount, or direction of auxin transported through tissues and organs and thus coordinate plant growth and development in ever-changing environmental conditions.

In this review, we discuss recent advances in hormonal cross-talk research, with particular focus on the post-translational mechanisms that enable rapid fine-tuning of PAT and play a role in the regulation of plant growth and development.

AUXIN GRADIENTS FORMED BY POLAR AUXIN TRANSPORT

To accomplish its regulatory functions, auxin has to be delivered from sites of its production, such as the shoot apical meristem and leaf primordia, to target tissues (Vernoux et al., 2010). While long-distance transport enables fast relocation of auxin via phloem vasculature (Friml, 2003), short-distance polar cell-to-cell transport facilitated by auxin transporters has a unique regulatory function. It contributes to the formation of local auxin maxima and gradients, which have an instructive function in organ initiation, tissue patterning, or tropic responses (Chandler, 2009; Vanneste and Friml, 2009; Overvoorde et al., 2010). Several gene families have been identified for their ability to transport auxin into cells (influx) and out of cells (efflux), as well as to coordinate intracellular movement of auxin (Abualia et al., 2018). Among them, AUX1/LAX influx, PIN and ABC/PGP efflux carriers are major families of transporters involved in PAT. Their abundance at the PM, polarity, and capacity to transport auxin determine the rate and directionality of the intercellular auxin flow and thereby define the pattern of auxin distribution (reviewed by Adamowski and Friml, 2015).

In *Arabidopsis thaliana*, influx of auxin into cells is facilitated mainly by *AUX1/LAX* transporters belonging to the auxin amino acid permease (AAAP) family of proton-driven transporters (Bennett et al., 1996). The *AUX1/LAX* family encompasses four highly homologous genes (*AUX1*, *LAX1*, *LAX2*, and *LAX3*), which encode transmembrane proteins (Carrier et al., 2008; Yang and Murphy, 2009) involved in numerous developmental processes, including embryogenesis, seed germination, vascular development, root development, leaf morphogenesis, apical hook development, and many others (reviewed in Swarup and Bhosale, 2019; Swarup and Péret, 2012). The amount and polarity of AUX1/LAX proteins at the PM is tightly controlled, and thereby the distribution of auxin essential for proper growth and development of plants is coordinated (Swarup et al., 2004; Kleine-Vehn et al., 2006; Péret et al., 2012; Liu et al., 2017a; Jonsson et al., 2017). For example, in roots, asymmetric localization of AUX1 at the apical PM of protophloem cells facilitates flow of auxin in the acropetal (rootward) direction, while the basal localization of AUX1 in the lateral root cap and epidermal cells drives basipetal (shootward) stream of auxin (Swarup et al., 2001). In root columella cells, increased proportion of AUX1 in the cytosol hints at very dynamic regulation of PM targeting and turnover of AUX1. Overall, the flexible subcellular localization and polarity of AUX1 across root tissues allows rapid control of auxin flow and thereby regulation of root growth in response to gravistimulation or other environmental inputs (Swarup et al., 2001).

Two distinct classes of transporters mediate auxin efflux. The ATP-binding cassette transporter (ABC) family are non-polar transporters uniformly distributed along the PM (reviewed in Fukui and Hayashi, 2018; Geisler et al., 2017). Although ABCB1, ABCB4, and ABCB19 have been characterized as non-polar auxin efflux transporters, recent studies have shown that some homologs, including ABCB14 and ABCB15, might exhibit polar membrane localization and thus contribute to directionality of auxin flow (reviewed by Cho and Cho, 2013; Geisler et al., 2017). Polarly localized transporters, PINs, are components of the PAT machinery with a major impact on the directionality of auxin flow in plant tissues and organs (Okada et al., 1991; Friml et al., 2002; Benková et al., 2003). Eight members of the PIN family are transmembrane proteins localizing either to the PM (PIN1, PIN2, PIN3, PIN4, and PIN7), the ER (PIN5 and PIN8), or exhibit dual ER and the PM localization (PIN6) (Zhou and Luo, 2018). Typically, PINs located in the PM contain a long hydrophilic loop, which separates multiple transmembrane domains, whereas ER-located PINs are characterized by a short hydrophilic loop. The ability of PINs to transport auxin has been demonstrated in single-cell-based plant systems (Petrášek et al., 2006; Barbez et al., 2013), but also in heterologous systems, including mammalian cells or *Xenopus* oocytes (Petrášek et al., 2006; Zourelidou et al., 2014). Developmental and physiological roles of PINs have been widely studied, and their specific functions in the regulation of various developmental processes, including embryogenesis, initiation, positioning, and formation of new organs as well as tropic responses, have been demonstrated (Benková et al., 2003; Billou et al., 2005; Zhang et al., 2019). Importantly, several studies suggest that PINs and ABCBs interact and function both independently and interdependently to control PAT *in planta* (Bandyopadhyay et al., 2007; Blakeslee et al., 2007; Titapiwatanakun et al., 2009).

SUBCELLULAR TRAFFICKING OF AUXIN TRANSPORTERS

Due to the essential impact of PIN transporters on the rate and directionality of auxin flow, the mechanisms that control and determine their localization at the PM and their transport activity have become a major focus in plant cell biology. Various cell biology, genetic, and molecular biology approaches have been implemented to dissect molecular pathways involved in the regulation of PIN subcellular trafficking and polarity establishment with a major focus on PIN1 and PIN2. Several recent studies have demonstrated that polarity and abundance of PINs at the PM are controlled by multiple cell-type and PIN protein-specific

cues, and both the PM abundance and polarity of PINs can flexibly change in response to varying endogenous and environmental signals (Ganguly et al., 2012, 2014; Habets and Offringa, 2014; Zwiewka et al., 2019a).

Constant cycling of PIN1 and PIN2 between the PM and endosomal compartments has been revealed using brefeldin A (BFA), an inhibitor of the subclass of ADP-ribosylation factor guanine nucleotide exchange factors (ARF-GEFs), which act as essential regulators of vesicle trafficking (Geldner et al., 2001, 2003; Adamowski and Friml, 2015; Naramoto, 2017). BFA treatment leads to aggregation of endosomes as well as endosome-resident PIN proteins, forming a subcellular structure called the "BFA body" or "BFA compartment" (Geldner et al., 2001, 2003). The constitutive endocytosis and recycling of PIN proteins depends on a complex subcellular trafficking machinery. Genetic and pharmacological perturbations of endocytosis exhibit dramatic effects on BFA compartmentation of PIN proteins. In particular, this has been reported for the coat protein clathrin, putative clathrin uncoating factors AUXILIN-LIKEs, GNOM, and other BFA-sensitive ARF-GEFs, the ARF-GTPase-activating protein VASCULAR NETWORK DEFECTIVE3, and the small GTPase Rab1b (Geldner et al., 2001, 2003; Kitakura et al., 2011; Feraru et al., 2012; Adamowski et al., 2018; Kania et al., 2018; Mishev et al., 2018; Dejonghe et al., 2019). Notably, clathrin-mediated endocytosis, together with *de novo* protein synthesis, is essential for PIN2 polarity re-establishment post cytokinesis (Glanc et al., 2018). Downstream of endocytosis, the early endosomal trafficking of PINs is controlled by another ARF-GEF, the BFA-visualized endocytic trafficking defective1 (BEN1), and the Sec1/Munc18 family protein BEN2 (Tanaka et al., 2009, 2013). Moreover, membrane lipid compositions are emerging as essential regulators for PIN trafficking and polarity. For instance, PI4P 5-kinases PIP5K1 and PIP5K2, which catalyze the production of phosphatidylinositol 4,5-bisphosphate ($PI(4,5)_2$) at the PM, regulate a general endocytosis process, thereby playing a major role in PIN trafficking and localization (Mei et al., 2012; Ischebeck et al., 2013; Tejos et al., 2014; Marhava et al., 2020). In addition, phosphatidylserine (PS) binds directly to ROP6 (Rho of Plants 6, a small GTPase) and regulates the dynamics of its nanoclustering at the PM, participating in endocytosis of PIN2 (Platre et al., 2019). Recently, aminophospholipid ATPase3 (ALA3), a phospholipid flippase, has been identified as a novel regulatory factor that modulates the distribution of phospholipids at the PM and, together with GNOM and BIG3 ARF-GEFs, controls PIN trafficking and polarity (Zhang et al., 2020a).

Unlike PINs, molecular factors and pathways involved in the regulation of trafficking and polar membrane localization of AUX1/LAX are less characterized. Similarly to PINs, AUX1 also undergoes constant and dynamic recycling from the PM through recycling endosomes; however, it utilizes a distinct, GNOM-independent pathway (Kleine-Vehn et al., 2006; Fan et al., 2015). Recently, using apical hook as a model system, it has been shown that AUX1 trafficking to the PM is mediated by ECHIDNA, ARF1, and BIG proteins (Jonsson et al., 2017). Furthermore, a role of RopGEF1, a guanine nucleotide exchange factor and activator of Rho GTPases of plants (ROPs), and ARF-GTPase-activating proteins in proper trafficking of AUX1 to the PM, has been recognized (Du and Chong, 2011; Liu et al., 2017a).

POST-TRANSLATIONAL MODIFICATIONS OF AUXIN TRANSPORTERS

Post-translational modifications of the auxin transporters have been recognized as an important mechanism underlying control of their polar distribution at the PM and transport activity. Several protein kinase families, including AGCIII kinases, the Ca^{2+}/Calmodulin-Dependent Protein Kinase-Related Kinases (CRKs), and mitogen-activated protein (MAP) kinases (MPKs), have been identified as important regulators of the phosphorylation status of auxin transporters (reviewed by Armengot et al., 2016; Löfke et al., 2013a; Zhou and Luo, 2018). The AGCVIII protein-serine/threonine kinases, including PINOID (PID) and closely related WAVY ROOT GROWTH 1 (WAG1) and WAG2, control phosphorylation of PIN proteins and thereby facilitate their trafficking to the specific polar membrane domains (Friml et al., 2004). In addition to PINs, ABCB1 has also been recognized among targets of PID (Henrichs et al., 2012). Other members of the AGCIII kinase family, D6 PROTEIN KINASE (D6PK) and related proteins D6PK-like (D6PKL), were demonstrated to phosphorylate PIN proteins and thereby regulate their auxin transport activity (Zourelidou et al., 2009). Regulation of PIN2 phosphorylation status by CRK5, a member of the CRK family, has been found to control root gravitropic response (Rigó et al., 2013). Furthermore, several environmentally regulated mitogen-activated protein kinases, including MAP kinase kinase 7 (MKK7)-MPK6 cascade and MPK4, contribute to regulation of PIN phosphorylation and thus might play a role in rapid fine-tuning of auxin transport in response to external stimuli (Dory et al., 2018).

The PID-mediated phosphorylation of PINs is counteracted by phosphatases such as PP6-type phosphatase holoenzyme complex formed by PP2AA proteins (RCN1/PP2AA1, PP2AA2, PP2AA3) and FyPP1/3, SAL (Michniewicz et al., 2007; Dai et al., 2012), as well as type-one protein phosphatase TOPP4 (Guo et al., 2015). In addition to phosphorylation, ubiquitination has been recognized as another developmentally important post-translational modification that determines turnover of PIN2 during root gravity response (Abas et al., 2006).

AUXIN FEEDBACK ON ITS OWN TRANSPORT

Early hypotheses and models of PAT considered feedback of auxin on its own transport as a potential mechanism for the establishment and maintenance of directionality and rate of auxin distribution (Sachs, 1969; 1975, 1981). Together, these ideas merged into a canalization hypothesis that describes a fascinating ability of auxin to focus and polarize its own flux, which consequently results in vasculature formation. Later works provided important experimental support (Sauer et al., 2006; Mazur et al., 2020a, 2020b), and effects of auxin flux and concentrations on localization of its own transporters and vice versa were key assumptions for mathematical models to successfully capture and simulate this process (Grieneisen et al., 2007; van Berkel et al., 2013; Bennett et al., 2014).

In agreement with feedback on its own transport, auxin has been found to transcriptionally (Vieten et al., 2005) and

post-translationally regulate components of PAT, including PINs (Paciorek et al., 2005; reviewed in; Doyle et al., 2015; Prát et al., 2018). A model was proposed in which auxin promotes its own polar transport by inhibiting clathrin-mediated endocytosis of PINs through a pathway mediated by Auxin Binding Protein 1 (ABP1) (Paciorek et al., 2005; Robert et al., 2010). However, the role of ABP1 as a receptor to perceive extracellular auxin levels and the exact cellular effects of 1-naphthaleneacetic acid (NAA), a synthetic auxin analog widely used in these works, were challenged by multiple studies, so the role of auxin feedback on PIN endocytosis is an open question (Gao et al., 2015; Jásik et al., 2016; Paponov et al., 2019). A recent study shows that auxin exhibits a dramatic effect on lipid distribution at the PM, which further stabilizes ROP6 clusters at the nanodomain and inhibits PIN2 endocytosis (Platre et al., 2019). Furthermore, a similar auxin-induced clustering phenomenon was also observed for TRANSMEMBRANE KINASE 1 (TMK1) (Pan et al., 2019), a proposed auxin co-receptor that was reported to form a complex with ABP1 (Xu et al., 2014). Notably, auxin-induced ROP6 clustering was blocked by *tmk1 tmk4* mutations, suggesting involvement of this receptor kinase. However, the underlying mechanism, through which auxin is perceived by TMK1 and how it regulates lipid dynamics, awaits further characterization. Intriguingly, besides inhibition of PIN endocytosis by a higher concentration of auxin, reduced levels of auxin promote lytic degradation of PIN2, thus reinforcing an asymmetry of auxin distribution during the root gravity response (Sieberer et al., 2000; Abas et al., 2006). Furthermore, increased accumulation of auxin at the lower side of root bending in response to gravistimulus might trigger lytic degradation of PIN2 in a $SCF^{TIR1/AFB}$-dependent manner. The high auxin-driven lytic degradation of PIN2 takes place in the later stages of the gravitropic response, and it might prevent the root from further bending (Baster et al., 2013). Importantly, these findings indicate that PIN2 resides on the PM at the auxin concentration optimum, and any deviation from this optimum might lead to PIN2 degradation and hence attenuation of auxin transport. Notably, auxin regulates PIN subcellular (re) localization through the canonical TIR1/AFB signaling pathway in distinct developmental processes, including vascular development (Prát et al., 2018; Verna et al., 2019; Mazur et al., 2020a) and hypocotyl gravitropism (Rakusová et al., 2016; Han et al., 2020). The above-mentioned studies highlight the importance of dynamic changes of auxin fluxes and its self-regulatory abilities in the regulation of various developmental processes and flexible adaptation of plant growth to environmental stimuli.

HORMONAL REGULATION OF SUBCELLULAR TRAFFICKING OF AUXIN TRANSPORTERS AS A MECHANISM TO CONTROL AUXIN GRADIENT FORMATION

A number of recent studies have shown that various environmental and endogenous stimuli, including plant hormones, can interfere with recycling of PINs between the PMs and endomembrane compartments, or trigger their re-targeting for lytic degradation to vacuoles and thus modulate the rate and directionality of auxin flow in plant tissues and organs. In the following paragraphs, we review and discuss current insights into mechanisms that underlie these rapid modes of hormone interactions with PAT.

Cytokinins Promote Lytic Degradation of PINs in Roots

Cytokinins are N^{6}-substituted adenine derivatives that jointly with auxin control basic cellular processes such as cell division and differentiation (Skoog and Miller, 1957; Dello Ioio et al., 2008; Kieber and Schaller, 2018). Cytokinin signaling is mediated through a multistep phosphorelay pathway with histidine kinase acting as a receptor, represented in *Arabidopsis* by a small family of three histidine kinases (AHK2, AHK3, and CRE1/AHK4). Cytokinins, after binding the receptor, trigger a cascade of auto- and trans-phosphorylation events to activate signaling components, including HISTIDIN-CONTAINING PHOSPHO-TRANSFER (AHP) and downstream acting type-B response regulators (type-B ARR), which trigger transcriptional responses (Keshishian and Rashotte, 2015; Osugi and Sakakibara, 2015; Kieber and Schaller, 2018). Studies focused on cytokinin-regulated plant development have revealed that a number of processes involve cytokinin interaction with PAT (e.g., root and shoot apical meristem activity maintenance, lateral root organogenesis, vasculature differentiation, or phyllotaxis; Dello Ioio et al., 2008; Ruzicka et al., 2009; Zhao et al., 2010; Bishopp et al., 2011; Pernisova et al., 2016; Waldie and Leyser, 2018). Interestingly, besides transcriptional regulation of the PAT machinery components (Dello Ioio et al., 2008; Ruzicka et al., 2009; Šimášková et al., 2015; Pernisova et al., 2016; Street et al., 2016), several recent works have pointed at a post-translational control of PINs (Marhavý et al., 2011; Zhang et al., 2011; Waldie and Leyser, 2018). In roots, cytokinin has been found to interfere with endomembrane trafficking of PIN1 and to promote its re-targeting for lytic degradation to vacuoles, thus reducing PIN1 abundance at the PM (Marhavý et al., 2011, 2014). Consistently, in the type-A *arr* mutant, which lacks multiple negative regulators of the cytokinin response, the post-translational downregulation of several PIN proteins including PIN1 has been demonstrated (Zhang et al., 2011). The cytokinin-mediated targeting of PIN1 to the vacuole is dependent on the intact actin network and regulatory components of the BFA-sensitive trafficking pathway, including BEN1/BIG5/MIN7, an ARF-GEF from the BIG subfamily, and BEN2/VPS45, a member of SEC1/MUNC18 family, both shown to be involved in control of PIN1 endocytosis (Tanaka et al., 2009, 2013). Intriguingly, cytokinin does not trigger bulk flow of proteins to vacuoles but exhibits selectivity for proteins and their polar membrane localization. PIN1 located at the basal PM of cells in the root provasculature is more sensitive to the cytokinin-triggered lytic degradation compared with the PIN7 homolog (also basally located), or AUX1, or PIN2 at the apical PM of epidermal cells (Marhavý et al., 2011, 2014). Furthermore, reduced sensitivity of the phospho-mimetic allele compared with loss-of-phosphorylation allele of PIN1 to cytokinin-triggered lytic degradation suggests that the PIN phosphorylation status might affect the responsiveness of PIN proteins to the hormone (Marhavý et al., 2014). Although the cytokinin effect on PIN1 trafficking is rapid and independent of transcription and *de novo* protein synthesis, it requires components of canonical cytokinin signaling, including cytokinin receptor CRE1/AHK4 and some of type-B ARR (Marhavý et al., 2011). So far, it is unclear whether cytokinin through AHK4 interferes with the

trafficking pathway mediating PIN1 recycling to the PM, and as a consequence, the protein is re-directed to vacuoles or AHK4-mediated signaling targets molecular factors controlling phosphorylation of PIN1 and thereby interferes with its sorting.

A rapid fine-tuning of the PAT machinery through a post-translational regulation of its major components might be important in processes such as maintenance of root apical meristem size or lateral root organogenesis. For example, cytokinin-promoted depletion of PIN1 located at transversal membranes of cells in lateral root primordia might act as a polarizing cue that specify re-direction of auxin flow toward the tip of newly forming primordia and promote their outgrowth (Bielach et al., 2012; Marhavý et al., 2014). Cytokinins have also been found to post-translationally regulate levels of PIN proteins in shoots. However, unlike in roots, cytokinins in shoots promote accumulation of PIN3, PIN4, and PIN7 at the PM, thereby coordinating bud outgrowth and branching (Waldie and Leyser, 2018). Collectively, these studies suggest that cytokinins might regulate trafficking of PINs in a developmental context-dependent manner and thus contribute to regulation of various plant organogenic processes.

Ethylene Acts to Regulate AUX1 Trafficking in the Apical Hook

Ethylene is a gaseous hormone known to regulate various plant growth and developmental processes, in particular fruit ripening, organ abscission, senescence, and adaptive responses to biotic and abiotic stresses (Bleecker and Kende, 2000; Dubois et al., 2018). Ethylene is perceived by a group of partially redundant receptors, ETHYLENE RESPONSE1 (ETR1), ETR2, ETHYLENE RESPONSE SENSOR1 (ERS1), ERS2, and ETHYLENE INSENSITIVE4 (EIN4), which show similarity to bacterial two-component histidine kinases (Hua and Meyerowitz, 1998; Hall et al., 2007). Ethylene-bound receptors inhibit CONSTITUTIVE TRIPLE RESPONSE1 (CTR1) kinase activity toward EIN2. As a result, the C-terminal part of EIN2 is cleaved and translocated to the nucleus (Ju et al., 2012; Qiao et al., 2012; Wen et al., 2012). There, it stabilizes ETHYLENE INSENSITIVE 3 (EIN3) and presumably other transcription factors, which initiate the ethylene response (Chao et al., 1997; Alonso and Ecker, 2001; Guo and Ecker, 2003; Stepanova and Alonso, 2009).

In roots, ethylene has been found to modulate expression of several components of the PAT machinery, including AUX1, and several members of the PIN family (Růžička et al., 2007; Lewis et al., 2011; Méndez-Bravo et al., 2019). Furthermore, several studies highlighted a role of ethylene-mediated regulation of PAT in apical hook development by transcriptional regulation of genes encoding for auxin transporters (Vandenbussche et al., 2010; Žádníkova et al., 2010; Žádníková et al., 2016). Interestingly, fluorescence recovery after photobleaching analysis of AUX1-YFP revealed faster fluorescence recovery in cells at the inner side of the apical hook formed in the presence of ethylene. These results suggest that ethylene-regulated turnover of AUX1 might be part of a mechanism that coordinates apical hook development (Vandenbussche et al., 2010). Recently, Jonsson et al. (2017) has provided important molecular insights into the pathway controlling trafficking of AUX1 during apical hook development. Applying genetic and cell biological approaches, the role of ADP-ribosylation factor1 (ARF1)-GTPase and its activators ARF-guanine-exchange factors (GEFs) of the Brefeldin A-inhibited GEF (BIG) family in the secretion of the AUX1 influx carrier to the PM from the trans-Golgi network (TGN) has been demonstrated. Defects in BIG or ARF1 severely affected the sensitivity of the apical hook to ethylene (Jonsson et al., 2017).

Jasmonates Affect Membrane Localization and Trafficking of PINs

Jasmonates (JAs), including jasmonic acid (JA) and its derivatives, e.g., methylester jasmonate (MeJA), are a group of lipid-derived plant hormones. They play an active role in the plant interaction with the environment, particularly in responses to abiotic and biotic stresses, as well as in regulation of various developmental processes (reviewed in Ahmad et al., 2016; Dar et al., 2015; Wasternack and Song, 2017). JA signaling is mediated through CORONATINE INSENSITIVE 1 (COI1) receptor, an F box protein, component of a SCF^{COI1}E3 ubiquitin ligase complex. In the presence of JA, the receptor promotes ubiquitination and proteosomal degradation of transcriptional repressors, thereby activating transcription of JA-responsive genes (reviewed in Wasternack and Song, 2017). Although cross-talk of JAs with other hormones has been primarily linked with SA in plant responses to pathogen attack (reviewed in Thaler et al., 2012), a number of recent studies demonstrate an active interaction of JAs with the auxin pathway and PAT.

MeJA promotes biosynthesis of auxin through stimulation of the expression of *ANTHRANILATE SYNTHASE* $\alpha 1$ (*ASA1*), encoding a rate-limiting enzyme in the biosynthesis of the auxin precursor tryptophan (Trp) (Sun et al., 2009). In addition to the role in the fine-tuning of endogenous levels of auxin, MeJA has been found to modulate subcellular trafficking and the PM localization of PIN2 in a concentration-dependent manner (Sun et al., 2011). Whereas low levels of MeJA attenuate accumulation of PIN2 in BFA-induced endomembrane compartments, indicating that JAs interfere with PIN2 endocytosis, higher MeJA concentrations reduce the abundance of PIN2 at the PM. Although distinct, both high and low concentration-dependent effects of MeJA on PIN2 require the functional jasmonate receptor COI1 (Yan et al., 2009; Sun et al., 2011).

The inhibitory effect of low MeJA on PIN2 endocytosis is dramatically attenuated in an *asa1* mutant compared with a wild-type control and is fully recovered by exogenous auxin application. This suggests that MeJA at low concentrations stimulates biosynthesis of auxin through transcriptional activation of the *ASA1 gene*, which in turn might inhibit PIN2 endocytosis. This is in line with a study by Paciorek et al. (2005) demonstrating the auxin inhibitory effect on PIN endocytosis. On the contrary, the depletion of PIN2 at the PM triggered by high concentrations of MeJA is enhanced in an *asa1* background. At high MeJA levels, no dramatic alterations of the *PIN2* transcription can be detected, therefore post-translational regulation has been hypothesized to underlie these MeJA effects on PIN2. In addition to PIN2, MeJA promoted weak depletion of PIN1, but not AUX1, which points at a selectivity of MeJA toward certain cargo and/or sorting pathway (Sun et al., 2011).

A reduced gravity response observed in roots treated with high concentrations of MeJA suggests that the hormone, through modulation of PIN2 trafficking, might contribute to fine-tuning of the auxin flow and thereby to steer bending of the root. Although both JA and auxin receptors are involved in JA-regulated PIN2 subcellular trafficking, an underlying molecular mechanism does not require *de novo* protein synthesis. Hence, the nature of this non-conventional receptor-mediated signaling, which acts independently of transcription, remains to be dissected (Sun et al., 2011).

Salicylic Acid Interferes with Endocytosis and Modulates Polar Auxin Transport

SA is a phenolic signaling compound coordinating plant responses to pathogens, as well as many physiological and developmental aspects of plant life (reviewed in Khan et al., 2015; Rivas-San Vicente and Plasencia, 2011). SA signaling acts through a set of NPR (NONEXPRESSER OF PATHOGENESIS RELATED GENES) receptors, which regulate the expression of pathogenesis-related genes and other targets upon SA binding (Cao et al., 1994; Fu et al., 2012; Ding et al., 2018).

The canonical SA signaling cascade steers plant processes via specific transcriptional output, albeit a number of observations have pointed to a role of SA in the regulation of clathrin-mediated endocytosis from the PM (Du et al., 2013; Rong et al., 2016; Wang et al., 2016). For example, exogenous application of SA interfered with the uptake of the endomembrane marker FM4-64 and negatively affected the incidence of clathrin light and heavy chains and ADAPTOR PROTEIN2 (AP-2) at the PM (Du et al., 2013; Wang et al., 2016). Furthermore, the accumulation of early endosomes/TGN markers ARF-1 and VHAa1 in BFA bodies remained unaffected, which supported a conclusion that SA suppresses endocytosis of proteins from the PM rather than interfering with exocytosis or endosomal dynamics. Intriguingly, SA modulation of endomembrane trafficking was found to be independent of the NPR-mediated transduction cascade (Du et al., 2013; Rong et al., 2016), suggesting the existence of a novel SA regulatory pathway. In line with the effects of SA on the endocytic machinery, PIN proteins have been found to react sensitively to alterations in SA concentrations. In particular, the internalization of PIN1 and PIN2 in BFA-endosomal compartments was severely attenuated in roots of the *cpr1* and *cpr5* mutants (CONSTITUTIVE EXPRESSOR OF PATHOGENESIS RELATED GENES; Bowling et al., 1997, 1994) with high endogenous levels of SA. Consistently, exogenous application of SA attenuated accumulation of PIN proteins in BFA bodies, suggesting that part of the regulatory effects of SA on plant growth might involve modulation of PAT.

Recently, important molecular insights into mechanisms underlying SA mediated regulation of PAT has been revealed (Tan et al., 2020). SA through direct biding attenuates activity of the PP2A, the phosphatase involved in de-phosphorylation of PIN (Michniewicz et al., 2007), and thereby enhances phosphorylation of PIN2. Consequently, hyperphosphorylation of PIN2 after prolonged SA treatment results in increased internalization and reduced polar membrane localization of the auxin transporter (Tan et al., 2020). All together, these findings suggest that along with driving the response to pathogens, SA may be able to steer plant growth by targeting PAT.

Strigolactones Promote PIN Depletion from the PM in Shoots

SLs are a class of carotenoid-derived plant hormones with special importance for shoot branching (Brewer et al., 2013; Lumba et al., 2017). SLs are recognized by the D14 receptor, which, after hormone binding, triggers MAX2-dependent degradation of a small family of HSP101-like proteins (in *Arabidopsis* SMXL6, SMXL7, and SMXL8), and activate downstream responses (Stirnberg et al., 2002, 2007; Jiang et al., 2013; Zhou et al., 2013; Soundappan et al., 2015). Regulation of the shoot branching by SLs is tightly linked with auxin and an inhibitory effect of auxin transport from shoot to root on the outgrowth of shoot branches. It has been proposed that auxin moving in the main stem indirectly prevents bud activity by reducing the ability of the axillary buds to establish their own flow of auxin connected with the main auxin stream in the stem (reviewed in Leyser, 2009). The interaction of SLs with PAT has been recognized as one of the important mechanisms underlying SL-regulated shoot branching. GR24, a synthetic SL, has been found to induce a rapid depletion of PIN1 from the PM by stimulation of its endocytosis (Shinohara et al., 2013). This SL-triggered reduction of the PIN1 abundance at the PM is not affected by cycloheximide, an inhibitor of proteosynthesis, but is sensitive to A23, an inhibitor of clathrin-mediated endocytosis, indicating that a post-translational clathrin-dependent mechanism might be involved in the SL-regulated PIN1 trafficking (Shinohara et al., 2013). Loss of the MAX2 function interfered with the effect of SL on the PIN1 endocytosis, pointing to the importance of SL signaling in this process. The PM localization of another membrane protein, aquaporin PIP1, is not affected by SLs, suggesting a protein specificity of the SL action. Based on these observations, it has been proposed that SL regulation of PAT interferes with establishment of canalized auxin flow from buds into the main stem and, as a consequence, branching is reduced (Shinohara et al., 2013). Originally, PIN1-dependent transport of auxin was primarily associated with SL-regulated shoot branching. Currently, a more complex model of the SL-PAT cross-talk has been proposed, which, in addition to PIN1-mediated high-conductance polar auxin transport, recognizes the contribution of the connective less polar auxin transport controlled by PIN3, PIN4, and PIN7 in this developmental process (Bennett et al., 2016). However, whether subcellular trafficking of PIN3, PIN4, and PIN7 is also regulated by SLs, similarly to PIN1, remains to be further studied.

Gibberellic Acid Promotes PM Localization of PINs

Gibberellic acid (GA) is a well-established endogenous regulator of various developmental processes, including seed germination, dormancy, flower development, and elongation growth of plant organs (Ueguchi-Tanaka et al., 2007; Hedden and Sponsel, 2015). The GA signal is perceived by a soluble nuclear protein GID1, which, in the presence of GA, binds the DELLA transcriptional repressors and targets them to the proteasome for degradation. As a result, expression of GA-responsive genes is activated (Achard and Genschik, 2009; Daviere and Achard, 2013). The GA and auxin pathways are intertwined at many levels. Auxin promotes GA biosynthesis and signaling responses (Fu and

Harberd, 2003; Weiss and Ori, 2007), whereas GA modulates accumulation of PINs at the PM, thereby fine-tuning PAT (Willige et al., 2011; Löfke et al., 2013b). The role of GA interaction with PIN-mediated auxin transport has been demonstrated in the regulation of the root response to gravistimulation. GAs, similarly to auxin, accumulate asymmetrically at the lower side of gravistimulated roots (Löfke et al., 2013b). The maximum, local, graviresponse driven formation of GAs in epidermal cells coincides with increased abundance of PIN2 at the PM, whereas reduced levels of GA at the opposite side of the roots correlate with a lower amount of PIN2 at the PM and enhanced vacuolar degradation (Löfke et al., 2013b). A recent study addressing mechanisms underlying the interaction between GA and PIN2-dependent auxin transport revealed that GAs coordinate subcellular trafficking of the PM proteins (including PINs) in a concentration-dependent manner (Salanenka et al., 2018). Whereas at low concentrations, GAs promote vacuolar delivery and lytic degradation of multiple cargos, including PIN proteins, high concentrations of GA enhance their recycling to the PM. Hence, GA might act as a hormonal modulator of the balance between vacuolar trafficking and exocytosis. A role of DELLA signaling pathway repressors in GA-regulated PIN trafficking has been detected, but protein biosynthesis is not required, hinting at a post-translational nature of the mechanism underlying this GA activity. Further cell biology and genetic approaches have pointed at several molecular factors involved in the GA-mediated regulation of PIN2 trafficking. This included a microtubule (MT) cytoskeleton, components of the retromer complex such as Sorting Nexin 1 (SNX1) and a microtubule (MT)-associated protein (the Cytoplasmic Linker-Associated Protein (CLASP), which has been proposed to control tethering of endosomal vesicles to MTs via direct interaction with SNX1 (Ambrose et al., 2013). In light of these findings, an alternative mechanism assuming involvement of the tubulin-folding factors Prefoldins (PFDs) has been proposed. In non-plant organisms, PFDs can control MT folding and dynamics (Le Bot et al., 2003; Lundin et al., 2008), whereas in plants, their interaction with DELLAs has been detected (Locascio et al., 2013). The PDF function in DELLA-mediated regulation of MTs and subcellular trafficking is supported by observation of *pfd* mutants, which were found to be insensitive to GA and to exhibit reduced abundance of PIN2 at the PM (Salanenka et al., 2018).

Hence, in addition to the canonical GA transduction cascade, which coordinates plant growth through transcriptional regulation of target genes, a novel, non-transcriptional regulatory pathway mediating the GA signal has been identified. Through this pathway, GAs can rapidly modulate the final destiny of PIN2, but presumably also other PM proteins, either to be recycled to the PM or to be degraded in the vacuole. So far, this mode of GA interaction with PAT has been mainly implicated in the regulation of the root gravity response, although future research might provide further insights into the role of this cross-talk in other developmental processes.

Brassinosteroids Interfere with PIN Degradation

BRs are a class of steroidal plant hormones that play a role in a broad spectrum of growth and developmental processes, such as cell division and elongation, vascular differentiation, root development, regulation of flowering, and in plant adaptation to biotic and abiotic stresses (Fridman and Savaldi-Goldstein, 2013; Wei and Li, 2016). BR perception is driven by leucine-rich repeat receptor-like kinase BRASSINOSTEROID INSENSITIVE 1 (BRI1) which, together with its co-receptor BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1), initiates a signaling phosphorylation cascade. The BR signal leads to proteasomal degradation of the main inhibitor of the pathway, a kinase BRASSINOSTEROID INSENSITIVE2 (BIN2). Concomitantly, BIN2 interacting partners, transcription factors BRASSINAZOLE RESISTANT1 (BZR1) and BRI1-EMS-SUPPRESSOR1 (BES1)/BZR2, are dephosphorylated and translocated to the nucleus, where they regulate expression of BR-responsive genes (reviewed in Clouse, 2011).

Cross-talk between BR and auxin at the level of hormone metabolism and signaling has been described (Peres et al., 2019). Several studies have reported BR effects on PIN-dependent PAT and indicated that some of the BR-mediated regulations might occur at the post-translational level (Hacham et al., 2012; Keicher et al., 2017). For example, levels of PIN2 proteins were significantly reduced in *bri1* receptor mutant, or after treatment with the inhibitor of BR biosynthesis (BRZ), although the corresponding changes at the transcript level could not be detected consistently (Hacham et al., 2012). Furthermore, studies on 14-3-3 proteins linked with regulation of BR signaling supported a role of the BR pathway in the regulation of PIN trafficking. Five of 12 isoforms of 14-3-3 including 14-3-3ε (epsilon) members were identified as BZR1-interacting partners in a yeast-two hybrid screen (Gampala et al., 2007), and the function of several of the identified isomers as negative regulators of the BR signaling cascade has been demonstrated. In absence of BRs, 14-3-3 proteins interact with the phosphorylated form of BZR1, thus preventing their translocation to the nucleus, which is required for activation of downstream transcriptional responses (Gampala et al., 2007). Intriguingly, interference with the expression of *14-3-3* genes from the ε group resulted in auxin-related phenotypes, such as the absence of lateral roots, a wavy main root, and inability to form an apical hook. On the cellular level, downregulation of the 14-3-3 activity affected expression of PIN1 and PIN2. Reduced expression of 14-3-3 correlated with ectopic expression of PIN1 and PIN2 at the root tip and enhanced accumulation of both PIN1 and PIN2 at the lateral PM of endodermal and cortex cells. This indicated that activity of 14-3-3 of the ε subgroup might be involved in the regulation of PIN trafficking, which was further supported by monitoring of endomembrane trafficking in roots with attenuated activity of 14-3-3. Absence of the 14-3-3 ε group members interfered with two trafficking pathways: from the TGN to vacuoles and to the PM, thus causing a higher accumulation of PIN2 in endosomal vesicles (Keicher et al., 2017). However, although plausible, there is not yet evidence that 14-3-3ε proteins regulate subcellular trafficking through their interaction with the BR signaling pathway, and therefore other BR-independent mechanisms cannot be fully ruled out.

In the recent study aiming at identification of signals and mechanisms controlling subcellular trafficking and abundance of PIN2, BR was recognized as a strong hormonal antagonist of the endocytic sorting of PIN2 destined for degradation (Retzer et al., 2019). BR through the canonical brassinosteroid signaling pathway, but independently of *de novo* protein synthesis, interfered with endocytosis and targeting of ubiquitinated PIN2

to vacuoles. Retzer et al. (2019) proposed that the BR effect on PIN2 sorting might play a role during the root response to gravity. Experimental data reveal correlation between asymmetric BR signaling, with a maximum at the lower side of gravistimulated roots, accumulation of PIN2 at the PM, and a BR effect on root gravity response. Together with mathematical modeling, these findings point to a role of BR as a hormonal factor that, in concert with auxin, determines the rate of gravity-induced root curvature.

Another study focused on the role of BR in the regulation of the root gravity response supported a post-translational mechanism of BR cross-talk with the PAT machinery. Li et al. (2005) found a correlation between expansion of the PIN2 domain into the proximal root elongation zone and accumulation of ROP2, a member of the RAC/ROP GTPase family involved in cortical F-actin formation (Fu et al., 2002). Overexpression of ROP2 as well as its dominant/negative forms affected both PIN2 expression and root gravity response. Based on these observations, a model for BR-regulated PAT has been proposed, in which ROP2 stimulated by BR modulates the localization of PIN2 through the assembly/reassembly of F-actins, and thereby mediates the BR effect of root gravity response (Li et al., 2005).

Abscisic Acid Attenuates PIN Endocytosis

ABA is a plant hormone primarily involved in the regulation of plant adaptive responses to various types of abiotic stresses. It acts as an endogenous regulator of stomatal guard cell closure during drought stress, increases heat tolerance through facilitated accumulation of osmo-protectant solutes and mediates adaptation of root system to salt or drought stresses. In addition to these stress tolerance roles, it controls early phases of seed maturation and germination (reviewed in Cutler et al., 2010; Finkelstein, 2013; Moriwaki et al., 2013). ABA is perceived by intracellular PYR/PYL/RCAR ABA receptors (PYLs). The hormone binding promotes receptor interaction with type 2C protein phosphatases (PP2Cs), and thus prevents dephosphorylation of class III SNF-1-related protein kinase 2 (SnRK2s). The released SnRK2s through phosphorylation of downstream signaling components, including basic leucine zipper (bZIP) transcription factors (AREBs/ABFs) and S-type anion channels (e.g. slow anion channel 1, SLAC1) induce ABA responses (Fujii et al., 2009; Geiger et al., 2009; Umezawa et al., 2009; Melcher et al., 2010; Brandt et al., 2012; Finkelstein, 2013).

Besides well-established cross-talk of ABA with GA in regulation of seed development, root growth and adaptation to abiotic stresses (Liu and Hou, 2018), interaction of ABA with auxin pathway through regulation of PAT has been revealed (Xu et al., 2013). Exogenous ABA treatment and salt stress or osmotic stress, which are typically associated with an increase of endogenous ABA levels, upregulate levels of PIN2 but reduce AUX1, PIN1, and PIN4 (Rowe et al., 2016).

Several studies focused on the mechanism mediating the ABA effects on the primary root growth and branching showed that ABA interacts with pathways controlling subcellular trafficking of PIN proteins and their abundance at the PM (Yang et al., 2014; Zhu et al., 2019). ABA has been found to decrease accumulation of PIN2 in BFA bodies and to attenuate re-targeting of PIN2 for lytic degradation to vacuoles in epidermal cells at the upper side of roots after the gravistimulation. The ABA mediated regulation of PROTEIN PHOSPHATASE 2A (PP2A) activity and thereby phosphorylation status of PIN2 was found to underlie the effects of ABA on PIN2 trafficking (Michniewicz et al., 2007; Li et al., 2020).

Potential regulatory component of ABA sensitive PIN trafficking has been identified by profiling of ABA responsive transcriptome. *HEATSHOCK PROTEIN 22* (*sHSP22*) emerged as a gene whose expression is regulated by both ABA and auxin (Li et al., 2018). Interestingly, the induction of *sHSP22* expression by auxin is dependent on ABI1, a key component of the ABA signal transduction pathway, hinting at cross-talk between auxin and ABA signaling. Importantly, overexpression of sHSP22 decreases the levels of PIN1 and other homologous proteins (including PIN3, PIN4, and PIN7) in a transcription-independent manner. Reduction of PIN1 at the PM in *sHSP22ox* line correlates with its rapid accumulation in BFA bodies, suggesting that sHSP22 might affect subcellular trafficking of PIN1.

In maize (*Zea mays*), increased levels of ABA or salt stress also led to alterations in the accumulation and polar localization of ZmPIN1 in lateral root primordia (Lu et al., 2019). The observed changes in ZmPIN1 localization correlated with defects in auxin distribution and severe defects in lateral root primordia growth. However, whether it is regulation on transcription level or an interference of ABA with trafficking of the maize PIN1 remains to be elucidated.

In addition, several recent studies with a focus on ABA signaling have provided important hints on potential mechanisms mediating the effect of ABA on PIN subcellular trafficking. For example, ABA has been found to enhance degradation of Rop GEF1 and 2, which act as upstream regulators of Rop GTPases, including ROP2 and ROP6 (Zhao et al., 2015; Li et al., 2016). Intriguingly, ROP2 as well as ROP6 are implicated in the establishment of PIN1 and PIN2 polarity through control of cytoskeleton dynamics (Chen et al., 2012; Nagawa et al., 2012). Furthermore, a recently reported effect of ABA on exocysts offers a viable scenario of the mechanism behind ABA-controlled trafficking of PIN (Drdová et al., 2013; Seo et al., 2016). Although plausible, whether and how the outlined pathways mediate the effect of ABA on PIN subcellular trafficking awaits further experimental work.

Nitric Oxide Affects PIN Internalization

NO is a small gaseous molecule acting as a key signaling molecule with a wide range of biological functions across kingdoms (Wendehenne et al., 2004). In plants, NO participates in regulation of stomata closure, cell death, and root gravitropism, as well as adaptive responses to various biotic and abiotic stresses (Durner et al., 1998; Neill et al., 2002, 2003; Romero-Puertas et al., 2004; Hu et al., 2005; Ye et al., 2012; Begara-Morales et al., 2019; Sánchez-Vicente et al., 2019). At the molecular level, NO regulates biological processes through S-nitrosylation, a post-translational modification of proteins analogous to phosphorylation (Hess et al., 2005). S-Nitrosylation has an impact on the conformation, activity, or

localization of the target proteins. The level of protein S-nitrosylation is dynamic and governed by NO cellular levels and de-nitrosylation catalyzed by S-nitrosoglutathione reductase (GSNOR) (Liu et al., 2001; Feechan et al., 2005) and thioredoxin (Benhar et al., 2009; Tada et al., 2009; Sengupta and Holmgren, 2012). GSNOR is the key enzyme controlling S-nitrosoglutathione (GSNO) levels, and loss of its function leads to increased cellular levels of S-nitrosylated proteins (Liu et al., 2001, 2004; Feechan et al., 2005).

A number of studies in plants have demonstrated that NO-regulated processes might involve interaction with auxin signaling and PAT. An increase of NO, either by exogenous NO donor treatment or in an NO-overproducing mutant (*nox1*) (He et al., 2004), results in decreased PIN1-GFP signal (Fernández-Marcos et al., 2011). Likewise, in mutants lacking GSNOR1, the levels of endogenous PIN1, PIN2 and their homologs PIN3, PIN4, and PIN7 were significantly reduced compared with wild type. While no corresponding changes in transcription of *PIN* genes could be detected, it has been proposed that NO might affect PINs at the post-translational level (Shi et al., 2015). This notion has been further supported by monitoring of PIN subcellular trafficking in plants with altered levels of NO. Ni et al. (2017) used the vesicle trafficking inhibitor BFA to demonstrate the effects of NO on internalization of PIN2.

NO-mediated regulation of PIN2 trafficking appears to play an important regulatory role in root response to gravity. Monitoring of NO in gravistimulated roots revealed asymmetric distribution and accumulation of this signaling molecule in epidermal cells at the lower side of roots. Importantly, overall reduction of NO levels in roots using the NO scavenger cPTIO attenuated asymmetric distribution of both NO and PIN2. Consequently, roots with reduced levels of NO exhibited defects in responses to gravistimulation (París et al., 2018).

Collectively, these studies demonstrate that regulation of PAT through modulation of PIN trafficking might be an important part of the mechanisms underlying the action of NO in plants. However, detailed molecular mechanisms need to be further investigated.

Modulation of Polar Auxin Transport in Response to Environmental Stresses

Over the last decades, it has become evident that hormones have an important regulatory role in plant adaptation and defense mechanisms and act as internal mediators of the interaction between plants and their surrounding environment. Auxin and PAT play a major role in plant adaptive responses to environmental stresses as key factors in the regulation of growth and development.

Genome-wide analyses of transcriptomes performed in rice (*Oryza sativa*) and maize (*Zea mays*) after various abiotic stresses, such as drought, salt, and cold, revealed alterations in expression of major components of PAT, including PIN, PILS, LAX, and ABCB auxin transporters (Yue et al., 2015; Chai and Subudhi, 2016).

In addition to transcriptional regulation of individual auxin transporters in plants exposed to abiotic stresses, several recent studies pointed at impacts of abiotic stress on the subcellular trafficking and accumulation of auxin transporters at the PM. Rapid modulation of PAT has a significant impact on the direction and amount of auxin distributed in plant tissues and consequently on flexible adaptation of plant growth and development to stress. A typical example of such an adaptive response is a rapid bending of roots away from high-salt-containing environments, which is known as halotropism (Rosquete and Kleine-Vehn, 2013). The halotropic bending of roots is a result of tuning PAT that leads to asymmetric redistribution of auxin at the root tip (Galvan-Ampudia et al., 2013; van den Berg et al., 2016; Korver et al., 2020). It has been shown that on the side of root that faces a high-salinity environment, clathrin-mediated endocytosis of PIN2 is increased. Consequently, as result of the reduced amount of PIN2 at the PM in epidermal cells at the salt exposed side of the root, auxin at the root tip is asymmetrically redistributed, which steers the root away from the salty surroundings (Galvan-Ampudia et al., 2013). Phospholipases (PLDs) and phosphatidic acid (PA), a signaling molecule formed by the action of PLD, have been identified as important molecular players in the regulation of auxin transport mediated through AUX1 and PIN2 in response to salt stress (Li and Xue, 2007; Testerink and Munnik, 2011; Galvan-Ampudia et al., 2013; Korver et al., 2020). Salt-induced stimulation of PLD activity increases the clathrin-mediated endocytosis of PIN2 at the side of the root facing the higher salt concentration, suggesting that PA controls the polar distribution of PIN and auxin polarity during halotropism in plants (Galvan-Ampudia et al., 2013). Several lines of genetic and biochemical evidence suggested that PLD-derived PA might be involved in PAT through regulation of PIN phosphorylation. Interaction of PA with PINOID and D6PK, kinases from the AGCVIII family that control PIN phosphorylation status (Barbosa et al., 2018), provides a possible link between lipid responses and PAT (Zegzouti et al., 2006; Barbosa et al., 2016; Simon et al., 2016; Wang et al., 2019). Interestingly, RCN1, one of the PP2A regulatory subunits that is required for dephosphorylation and proper targeting of PIN2 (Michniewicz et al., 2007), was also identified in a screen for PA-binding proteins (Testerink et al., 2004), hinting at other possible mechanisms underlying adjustment of PAT to stresses.

An excessive accumulation of metals in soil also poses a challenge for plant growth and development. High amounts of metals such as cadmium, coper, or iron were found to affect transcription of the PAT components (Hu et al., 2013; Yuan et al., 2013; Li et al., 2015). It is noteworthy that in roots exposed to high levels of nickel, a rapid decrease in the PIN2-GFP signal was not accompanied by a concordant drop in gene transcription. Under high-nickel stress, PIN2 exhibited less pronounced polar localization at the PM and increased accumulation inside epidermal cells. Changes in PIN2 subcellular localization correlated with root growth defects and attenuated a response to gravity stimulus (Lešková et al., 2020).

PAT is also affected in roots exposed to cold stress. Detailed analyses revealed that cold stress dramatically decreases the amount of PIN2 recycling from the PM into BFA bodies and attenuates PIN3 re-localization to the lower side of columella cells upon gravitropic stimulus. The observed changes in subcellular

	Auxin Transporter	Canonical Receptor	Other Molecular Factors Involved	Dependence of a Hormonal Effect on Transcription (Chemical Used)	Dependence of a Hormonal Effect on Translation (Chemical Used)	References
Auxin	PIN1, PIN2, PIN4	TIR1 independent (PIN endocytosis), TIR1 dependent (PIN lytic degradation)	BIG, clathrin, ROP6, TMK1	No (cordycepin)	No (CHX)	Paciorek et al., 2005; Abas et al., 2006; Robert et al., 2010; Baster et al., 2013; Xu et al., 2014
Cytokinin	PIN1, PIN3, PIN4, PIN7	CRE1/AHK4 dependent	BEN1, BEN2	No (cordycepin)	No (CHX)	Marhavý et al., 2011, 2014; Zhang et al., 2011; Waldie and Leyser, 2018
Ethylene	AUX1	NA	BIG3, ARF1	NA	Yes (CHX)	Jonsson et al., 2017
Jasmonates	PIN1, PIN2	COI1 dependent	ASA1, AXR1, TIR1, AFB1,2,3	NA	No (CHX)	Sun et al., 2011
Salicylic acid	PIN1, PIN2	NPR1,2,3 independent	CHC2, AP-2, PP2A	No (cordycepin)	No (CHX)	Du et al., 2013; Tan et al., 2020
Strigolactones	PIN1	MAX2 dependent	clathrin	NA	No (CHX)	Shinohara et al., 2013
Gibberellic acid	PIN1, PIN2, PIN3, PIN4, PIN7	DELLA dependent	SNX1, CLASP, PFDs, KTN	NA	No (CHX)	Willige et al., 2011; Löfke et al., 2013a, 2013b; Salanenka et al., 2018
Brassinosteroids	PIN1, PIN2, PIN4	BRI1 dependent	14-3-3, ROP2, GSK3/ Shaggy-type kinases	NA	No (CHX)	Li et al., 2005; Keicher et al., 2017; Retzer et al., 2019
Abscisic acid	PIN1, PIN2, PIN3, PIN4, PIN7	PYLs dependent	PP2A, ABI1	NA	NA	Yang et al., 2014; Li et al., 2018, 2020; Zhu et al., 2019
Nitric oxide	PIN2	NA	GSNOR1	NA	No (CHX)	Ni et al., 2017; París et al., 2018

Table 1. Post-translational Regulation of Auxin Transporters by Plant Hormones.
Summary of hormonal effects on auxin transporters. Canonical receptors and molecular factors involved are indicated. For detailed information, please see the main text. CHX, cycloheximide; NA, not available; PM, plasma membrane.

trafficking of PIN2 and PIN3 correlate with attenuated root response to gravistimulation in cold-treated plants (Shibasaki et al., 2009).

The studies discussed above convincingly demonstrate that plant adaptation to various stresses might rely also on rapid adjustment of PAT. However, underlying molecular pathways, including perception and transduction of the signals to adequate responses, await further investigation. Factors such as Ca^{2+} and reactive oxygen species as well as hormonal pathways, including ABA, ethylene, and JA, need to be integrated to obtain a full picture of the dynamic regulation of PAT in plants challenged by stresses (Vanneste and Friml, 2013; Julkowska and Testerink, 2015; Tognetti et al., 2017; Zwiewka et al., 2019b; Li et al., 2019; Zhang et al., 2020b).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

PAT is one of the core mechanisms determining auxin distribution and the formation of auxin gradients, which have instructive functions in plant morpho- and organogenesis. In the course of a plant's lifespan, whether as part of the developmental program or in response to environmental factors, a rate, a capacity, and a directionality of auxin flux can be rapidly modulated, thereby allowing for flexible developmental adaptations. Hormones act as essential endogenous translators of these developmental and exogenous signals, and their interaction with PAT might have evolved as an effective feedback mechanism to fine-tune growth and developmental processes. Although transcriptional regulation of the PAT components is an efficient way to adjust the rate and amount of auxin transported in tissues and organs, the non-transcriptional mechanisms that target trafficking, turnover, or polarity of auxin transporters provide another regulatory level that additionally enables rapid modulation of the auxin flow directionality. Nearly all classes of hormones have been demonstrated to impinge on PAT; however, investigation of the underlying molecular pathways is still only beginning. In light of recent findings, there are some aspects of hormone–PAT interactions that deserve to be highlighted, and potentially taken into consideration in future studies (Table 1). Hormonal effects on PAT exhibit striking differences in terms of protein specificity. Some, such as GA and SA, interfere with subcellular transport of a

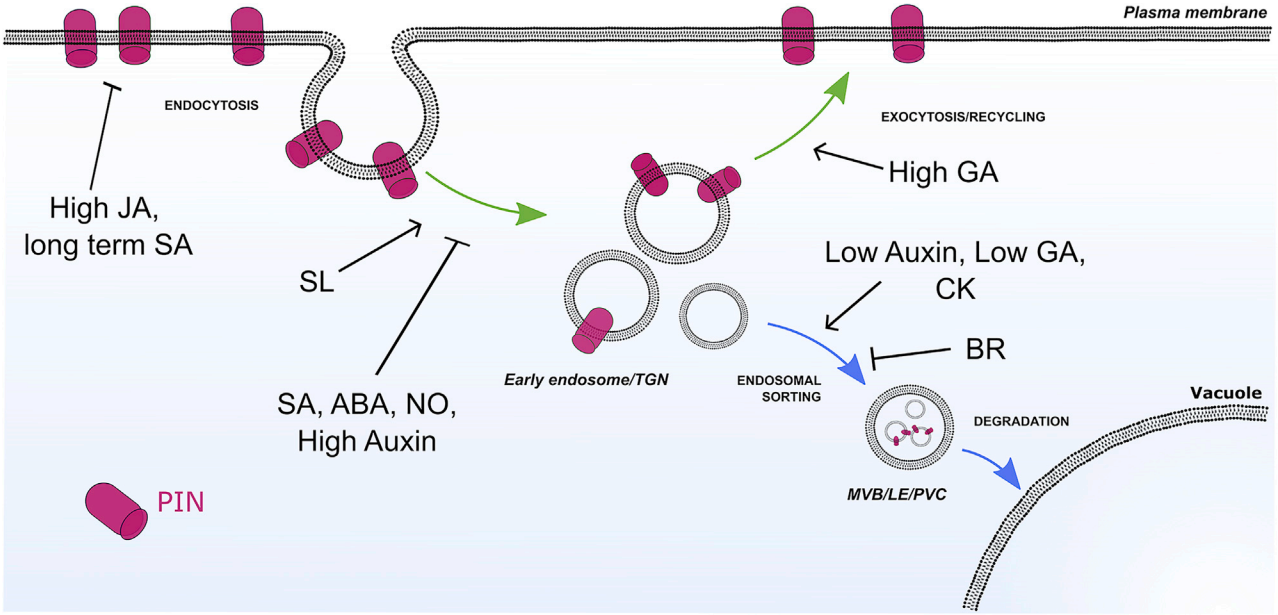

Figure 1. Hormonal Regulation of PIN Trafficking.
Polar auxin transporters (e.g., PINs) undergo constant recycling between the plasma membrane and endosomal compartments (green arrows). In response to developmental or environmental signals, the levels of PINs can be downregulated by their re-direction for lytic degradation to vacuoles (blue arrows). Plant hormones interfere with distinct steps of the PIN trafficking pathway, thereby contributing to fine-tuning of auxin transport and regulation of plant growth and development. ABA, abscisic acid; BR, brassinosteroids; CK, cytokinins; GA, gibberellic acid; JA, jasmonic acid; NO, nitric oxide; SA, salicylic acid; SL, strigolactones; LE, late endosome; MVB, multivesicular body; PVC, prevacuolar compartment; TGN, trans-Golgi network.

larger spectrum of PM proteins, hinting at their interaction with more generic regulators of protein sorting machinery. Others, including CK, JA, or SL, exhibit a higher level of selectivity, presumably as a result of their impact on specialized pathways or steps in sorting of specific proteins.

Individual hormones seem to target distinct steps of subcellular trafficking, often depending on their concentrations. For example, auxin at high concentration and SA attenuate PIN endocytosis, thereby promoting their accumulation at the PM. Conversely, SLs deplete PIN1 from the PM by promoting its endocytosis. In addition, auxin, a low concentrations of GA, as well as CK, re-direct some PIN family members for degradation to vacuoles, while in contrast, BR blocks vacuolar sorting of PIN2 (Figure 1).

So far, it is unclear whether alteration of subcellular trafficking is a consequence of a direct, hormone-triggered post-translational modification of auxin transporters (e.g., phosphorylation, sumoylation, ubiquitination), or indirect interference with transport and sorting machineries, thereby affecting cellular movements of PIN proteins. Another intriguing question is the role of canonical hormonal signaling pathways, typically acting through transcriptional regulatory outputs. Although in nearly all hormone–PAT interactions, receptors and/or downstream components of transduction cascades are involved, this contrasts with the transcription-/proteosynthesis-independent nature of hormone–PAT cross-talk discussed earlier. Could this mean that in parallel to well-established hormone signaling pathways, there are other, so far unknown signal transduction cascades to be discovered?

With an increasing number of confirmed molecular interactions and circuits that determine and fine-tune PAT, modeling and mathematical simulations might offer important tools to provide novel insights into the dynamics of PAT (Prusinkiewicz et al., 2009; Voß et al., 2014; Allen and Ptashnyk, 2020). Several models have been developed to gain a better understanding of the hormonal regulation of PAT in the context of various developmental processes, such as root growth (Di Mambro et al., 2017), apical hook development (Žádníková et al., 2016), and vasculature differentiation (De Rybel et al., 2014; Mellor et al., 2019). Typically, the models are focused on specific hormonal pathways, such as cytokinin, ethylene, or gibberellin, converging at the regulation of PAT and auxin signaling (Moore et al., 2015; Muraro et al., 2016; Liu et al., 2017b). Nevertheless, a complex, all-embracing model of the hormonal effects on PAT remains a challenge for future research.

ACKNOWLEDGMENTS

H.S. is the recipient of a DOC Fellowship of the Austrian Academy of Sciences at the Institute of Science and Technology, Austria. J.C.M. is the recipient of an EMBO Long-Term Fellowship (ALTF number 710-2016). We would like to thank Jiri Friml and Carina Baskett for critical reading of the manuscript and Shutang Tan and Maciek Adamowski for helpful discussions. No conflict of interest declared.

Received: February 25, 2020
Revised: March 26, 2020
Accepted: April 18, 2020
Published: April 22, 2020

REFERENCES

Abas, L., Benjamins, R., Malenica, N., Paciorek, T., Wiřniewska, J., Moulinier–Anzola, J.C., Sieberer, T., Friml, J., and Luschnig, C. (2006). Intracellular trafficking and proteolysis of the *Arabidopsis*

auxin-efflux facilitator PIN2 are involved in root gravitropism. Nat. Cell Biol. **8**:249–256.

Abualia, R., Benkova, E., and Lacombe, B. (2018). Transporters and mechanisms of hormone transport in *Arabidopsis*. Adv. Bot. Res. **87**:115–138.

Achard, P., and Genschik, P. (2009). Releasing the brakes of plant growth: how GAs shutdown della proteins. J. Exp. Bot. **60**:1085–1092.

Adamowski, M., and Friml, J. (2015). PIN-dependent auxin transport: action, regulation, and evolution. Plant Cell Online **27**:20–32.

Adamowski, M., Narasimhan, M., Kania, U., Glanc, M., De Jaeger, G., and Friml, J. (2018). A functional study of AUXILIN-LIKE1 and 2, two putative clathrin uncoating factors in *Arabidopsis*. Plant Cell **30**:700–716.

Ahmad, P., Rasool, S., Gul, A., Sheikh, S.A., Akram, N.A., Ashraf, M., Kazi, A.M., and Gucel, S. (2016). Jasmonates: multifunctional roles in stress tolerance. Front. Plant Sci. **7**:813.

Allen, H.R., and Ptashnyk, M. (2020). Mathematical modelling of auxin transport in plant tissues: flux meets signalling and growth. Bull. Math. Biol. **82**:1–35.

Alonso, J.M., and Ecker, J.R. (2001). The ethylene pathway: a paradigm for plant hormone signaling and interaction. Sci. STKE **2001**:1–11.

Ambrose, C., Ruan, Y., Gardiner, J., Tamblyn, L.M., Catching, A., Kirik, V., Marc, J., Overall, R., and Wasteneys, G.O. (2013). CLASP interacts with sorting Nexin 1 to link microtubules and auxin transport via PIN2 recycling in *Arabidopsis thaliana*. Dev. Cell **24**:649–659.

Armengot, L., Marquès-Bueno, M.M., and Jaillais, Y. (2016). Regulation of polar auxin transport by protein and lipid kinases. J. Exp. Bot. https://doi.org/10.1093/jxb/erw216.

Bandyopadhyay, A., Blakeslee, J.J., Lee, O.R., Mravec, J., Sauer, M., Titapiwatanakun, B., Makam, S.N., Bouchard, R., Geisler, M., Martinoia, E., et al. (2007). Interactions of PIN and PGP auxin transport mechanisms. Biochem. Soc. Trans. **35**:137–141.

Barbez, E., Laňková, M., Pařezová, M., Maizel, A., Zažímalová, E., Petrášek, J., Friml, J., and Kleine-Vehn, J. (2013). Single-cell-based system to monitor carrier driven cellular auxin homeostasis. BMC Plant Biol. **13**:20.

Barbosa, I.C.R., Shikata, H., Zourelidou, M., Heilmann, M., Heilmann, I., and Schwechheimer, C. (2016). Phospholipid composition and a polybasic motif determine D6 PROTEIN KINASE polar association with the plasma membrane and tropic responses. Development **143**:4687–4700.

Barbosa, I.C.R., Hammes, U.Z., and Schwechheimer, C. (2018). Activation and polarity control of PIN-formed auxin transporters by phosphorylation. Trends Plant Sci. **23**:523–538.

Bao, F., Shen, J., Brady, S.R., Muday, G.K., Asami, T., and Yang, Z. (2004). Brassinosteroids Interact with Auxin to Promote Lateral Root Development in Arabidopsis. Plant Physiol. **134**:1624–1631.

Baster, P., Robert, S., Kleine-Vehn, J., Vanneste, S., Kania, U., Grunewald, W., De Rybel, B., Beeckman, T., and Friml, J. (2013). SCFTIR1/AFB-auxin signalling regulates PIN vacuolar trafficking and auxin fluxes during root gravitropism. EMBO J. **32**:260–274.

Begara-Morales, J.C., Chaki, M., Valderrama, R., Mata-Pérez, C., Padilla, M.N., Barroso, J.B., and Brouquisse, R. (2019). The function of S-nitrosothiols during abiotic stress in plants. J. Exp. Bot. **70**:4429–4439.

Benhar, M., Forrester, M.T., and Stamler, J.S. (2009). Protein denitrosylation: enzymatic mechanisms and cellular functions. Nat. Rev. Mol. Cell Biol. **10**:721–732.

Benková, E., Michniewicz, M., Sauer, M., Teichmann, T., Seifertová, D., Jürgens, G., and Friml, J. (2003). Local, efflux-dependent auxin gradients as a common module for plant organ formation. Cell **115**:591–602.

Bennett, M.J., Marchant, A., Green, H.G., May, S.T., Sally, P., Millner, P.A., Walker, A.R., Schulz, B., Feldmann, K.A., Bennett, M.J., et al. (1996). *Arabidopsis* AUX1 Gene : A Permease-like Regulator of Root Gravitropism (American Association for the Advancement of Science Stable), pp. 948–950. http://www.jstor.org/stable/2891528.

Bennett, T., Hines, G., and Leyser, O. (2014). Canalization: what the flux? Trends Genet. **30**:41–48.

Bennett, T., Hines, G., van Rongen, M., Waldie, T., Sawchuk, M.G., Scarpella, E., Ljung, K., and Leyser, O. (2016). Connective auxin transport in the shoot facilitates communication between shoot apices. PLoS Biol. **14**:1–33.

Bielach, a., Podlesakova, K., Marhavy, P., Duclercq, J., Cuesta, C., Muller, B., Grunewald, W., Tarkowski, P., and Benkova, E. (2012). Spatiotemporal regulation of lateral root organogenesis in *Arabidopsis* by cytokinin. Plant Cell **24**:3967–3981.

Billou, I., Xu, J., Wildwater, M., Willemsen, V., Paponov, I., Frimi, J., Heldstra, R., Aida, M., Palme, K., and Scheres, B. (2005). The PIN auxin efflux facilitator network controls growth and patterning in *Arabidopsis* roots. Nature **433**:39–44.

Bishopp, A., Lehesranta, S., Vate, A., Help, H., El-showk, S., and Scheres, B. (2011). Report phloem-transported cytokinin regulates polar auxin transport and maintains vascular pattern in the root meristem. Curr. Biol. https://doi.org/10.1016/j.cub.2011.04.049.

Blakeslee, J.J., Bandyopadhyay, A., Ok, R.L., Mravec, J., Titapiwatanakun, B., Sauer, M., Makam, S.N., Cheng, Y., Bouchard, R., Adamec, J., et al. (2007). Interactions among PIN-FORMED and P-glycoprotein auxin transporters in *Arabidopsis*. Plant Cell **19**:131–147.

Bleecker, A.B., and Kende, H. (2000). Ethylene: a gaseous signal molecule in plants. Annu. Rev. Cell Dev. Biol. **16**:1–18.

Bowling, S.A., Clarke, J.D., Liu, Y., Klessig, D.F., and Dong, X. (1997). The cpr5 mutant of *Arabidopsis* expresses both NPR1-dependent and NPR1-independent resistance. Plant Cell **9**:1573–1584.

Bowling, S.A., Guo, A., Cao, H., Gordon, A.S., Klessig, D.F., and Dong, X. (1994). A mutation in *Arabidopsis* that leads to constitutive expression of systemic acquired resistance. Plant Cell **6**:1845–1857.

Brandt, B., Brodsky, D.E., Xue, S., Negi, J., Iba, K., Kangasjärvi, J., Ghassemian, M., Stephan, A.B., Hu, H., and Schroeder, J.I. (2012). Reconstitution of abscisic acid activation of SLAC1 anion channel by CPK6 and OST1 kinases and branched ABI1 PP2C phosphatase action. Proc. Natl. Acad. Sci. U S A **109**:10593–10598.

Brewer, P.B., Koltai, H., and Beveridge, C.A. (2013). Diverse roles of strigolactones in plant development. Mol. Plant **6**:18–28.

Cao, H., Bowling, S.a., Gordon, a.S., and Dong, X. (1994). Characterization of an *Arabidopsis* mutant that is nonresponsive to inducers of systemic acquired resistance. Plant Cell **6**:1583.

Carrier, D.J., Bakar, N.T.A., Swarup, R., Callaghan, R., Napier, R.M., Bennett, M.J., and Kerr, I.D. (2008). The binding of auxin to the *Arabidopsis* auxin influx transporter AUX1. Plant Physiol. **148**:529–535.

Chai, C., and Subudhi, P.K. (2016). Comprehensive analysis and expression profiling of the OsLAX and OsABCB auxin transporter gene families in rice (*Oryza sativa*) under phytohormone stimuli and abiotic stresses. Front. Plant Sci. **7**:1–13.

Chandler, J.W. (2009). Local auxin production: a small contribution to a big field. BioEssays **31**:60–70.

Chao, Q., Rothenberg, M., Solano, R., Roman, G., Terzaghi, W., and Ecker, J.R. (1997). Activation of the ethylene gas response pathway in *Arabidopsis* by the nuclear protein ETHYLENE-INSENSITIVE3 and related proteins. Cell **89**:1133–1144.

Chen, X., Naramoto, S., Robert, S., Tejos, R., Löfke, C., Lin, D., Yang, Z., and Friml, J. (2012). ABP1 and ROP6 GTPase signaling regulate clathrin-mediated endocytosis in *Arabidopsis* roots. Curr. Biol. **22**:1326–1332.

Cho, M., and Cho, H.T. (2013). The function of ABCB transporters in auxin transport. Plant Signal. Behav. **8**:6–9.

Clouse, S.D. (2011). Brassinosteroid signal transduction: from receptor kinase activation to transcriptional networks regulating plant development. Plant Cell **23**:1219–1230.

Crawford, S., Shinohara, N., Sieberer, T., et al. (2010). Strigolactones enhance competition between shoot branches by dampening auxin transport. Development **137**:2905–2913.

Cutler, S.R., Rodriguez, P.L., Finkelstein, R.R., and Abrams, S.R. (2010). Abscisic acid: emergence of a core signaling network. Annu. Rev. Plant Biol. **61**:651–679.

Dai, M., Zhang, C., Kania, U., Chen, F., Xue, Q., McCray, T., Li, G., Qin, G., Wakeley, M., Terzaghi, W., et al. (2012). A PP6-type phosphatase holoenzyme directly regulates PIN phosphorylation and auxin efflux in *Arabidopsis*. Plant Cell **24**:2497–2514.

Dar, T.A., Uddin, M., Khan, M.M.a., Hakeem, K.R., and Jaleel, H. (2015). Jasmonates counter plant stress: a review. Environ. Exp. Bot. **115**:49–57.

Daviere, J.-M., and Achard, P. (2013). Gibberellin signaling in plants. Development **140**:1147–1151.

De Rybel, B., Adibi, M., Breda, A.S., Wendrich, J.R., Smit, M.E., Novák, O., Yamaguchi, N., Yoshida, S., Van Isterdael, G., Palovaara, J., et al. (2014). Integration of growth and patterning during vascular tissue formation in *Arabidopsis*. Science **345**. https://doi.org/10.1126/science.1255215.

Dejonghe, W., Sharma, I., Denoo, B., De Munck, S., Lu, Q., Mishev, K., Bulut, H., Mylle, E., De Rycke, R., Vasileva, M., et al. (2019). Disruption of endocytosis through chemical inhibition of clathrin heavy chain function. Nat. Chem. Biol. **15**:641–649.

Dello Ioio, R., Nakamura, K., Moubayidin, L., Perilli, S., Taniguchi, M., Morita, M.T., Aoyama, T., Costantino, P., and Sabatini, S. (2008). A genetic framework for the control of cell division and differentiation in the root meristem. Science **322**:1380–1384.

Di Mambro, R., De Ruvo, M., Pacifici, E., Salvi, E., Sozzani, R., Benfey, P.N., Busch, W., Novak, O., Ljung, K., Di Paola, L., et al. (2017). Auxin minimum triggers the developmental switch from cell division to cell differentiation in the *Arabidopsis* root. Proc. Natl. Acad. Sci. U S A **114**:E7641–E7649.

Ding, Y., Sun, T., Ao, K., Peng, Y., Zhang, Y., Li, X., and Zhang, Y. (2018). Opposite roles of salicylic acid receptors NPR1 and NPR3/NPR4 in transcriptional regulation of plant immunity. Cell **173**:1454–1467.e10.

Dory, M., Hatzimasoura, E., Kállai, B.M., Nagy, S.K., Jäger, K., Darula, Z., Nádai, T.V., Mészáros, T., López-Juez, E., Barnabás, B., et al. (2018). Coevolving MAPK and PID phosphosites indicate an ancient environmental control of PIN auxin transporters in land plants. FEBS Lett. **592**:89–102.

Doyle, S.M., Vain, T., and Robert, S. (2015). Small molecules unravel complex interplay between auxin biology and endomembrane trafficking. J. Exp. Bot. **66**:4971–4982.

Drdová, E.J., Synek, L., Pečenková, T., Hála, M., Kulich, I., Fowler, J.E., Murphy, A.S., and Žárský, V. (2013). The exocyst complex contributes to PIN auxin efflux carrier recycling and polar auxin transport in *Arabidopsis*. Plant J. **73**:709–719.

Du, C., and Chong, K. (2011). ARF-GTPase activating protein mediates auxin influx carrier AUX1 early endosome trafficking to regulate auxin dependent plant development. Plant Signal. Behav. **6**:1644–1646.

Du, Y., Tejos, R., Beck, M., Himschoot, E., Li, H., Robatzek, S., Vanneste, S., and Friml, J. (2013). Salicylic acid interferes with clathrin-mediated endocytic protein trafficking. Proc. Natl. Acad. Sci. U S A **110**:7946–7951.

Dubois, M., Van den Broeck, L., and Inzé, D. (2018). The pivotal role of ethylene in plant growth. Trends Plant Sci. **23**:311–323.

Durner, J., Wendehenne, D., and Klessig, D.F. (1998). Defense gene induction in tobacco by nitric oxide, cyclic GMP, and cyclic ADP-ribose. Proc. Natl. Acad. Sci. U S A **95**:10328–10333.

Fan, L., Li, R., Pan, J., Ding, Z., and Lin, J. (2015). Endocytosis and its regulation in plants. Trends Plant Sci. **20**:388–397.

Feechan, A., Kwon, E., Yun, B.W., Wang, Y., Pallas, J.A., and Loake, G.J. (2005). A central role for S-nitrosothiols in plant disease resistance. Proc. Natl. Acad. Sci. U S A **102**:8054–8059.

Feraru, E., Feraru, M.I., Asaoka, R., Paciorek, T., De Rycke, R., Tanaka, H., Nakano, a., and Friml, J. (2012). BEX5/RabA1b regulates trans-Golgi network-to-plasma membrane protein trafficking in *Arabidopsis*. Plant Cell **24**:3074–3086.

Fernández-Marcos, M., Sanz, L., Lewis, D.R., Muday, G.K., and Lorenzo, O. (2011). Nitric oxide causes root apical meristem defects and growth inhibition while reducing PIN-FORMED 1 (PIN1)-dependent acropetal auxin transport. Proc. Natl. Acad. Sci. U S A **108**:18506–18511.

Finkelstein, R. (2013). Abscisic acid synthesis and response. Arabidopsis Book **11**:e0166.

Fridman, Y., and Savaldi-Goldstein, S. (2013). Brassinosteroids in growth control: how, when and where. Plant Sci. **209**:24–31.

Friml, J. (2003). Auxin transport - shaping the plant. Curr. Opin. Plant Biol. https://doi.org/10.1016/S1369526602000031.

Friml, J., Benková, E., Blilou, I., Wisniewska, J., Hamann, T., Ljung, K., Woody, S., Sandberg, G., Scheres, B., Jürgens, G., et al. (2002). AtPIN4 mediates sink-driven auxin gradients and root patterning in *Arabidopsis*. Cell **108**:661–673.

Friml, J., Yang, X., Michniewicz, M., Weijers, D., Quint, A., Tietz, O., Benjamins, R., Ouwerkerk, P.B.F., Ljung, K., Sandberg, G., et al. (2004). A PINOID-dependent binary switch in apical-basal PIN polar targeting directs auxin efflux. Science **306**:862–865.

Fu, X., and Harberd, N.P. (2003). Auxin promotes *Arabidopsis* root growth by modulating gibberellin response. Nature **421**:740–743.

Fu, Y., Li, H., and Yang, Z. (2002). The ROP2 GTPase controls the formation of cortical fine F-actin and the early phase of directional cell expansion during *Arabidopsis* organogenesis. Plant Cell **14**:777–794.

Fu, Z.Q., Yan, S., Saleh, A., Wang, W., Ruble, J., Oka, N., Mohan, R., Spoel, S.H., Tada, Y., Zheng, N., et al. (2012). NPR3 and NPR4 are receptors for the immune signal salicylic acid in plants. Nature **486**:228–232.

Fujii, H., Chinnusamy, V., Rodrigues, A., Rubio, S., Antoni, R., Park, S.Y., Cutler, S.R., Sheen, J., Rodriguez, P.L., and Zhu, J.K. (2009). In vitro reconstitution of an abscisic acid signalling pathway. Nature **462**:660–664.

Fukui, K., and Hayashi, K.I. (2018). Manipulation and sensing of auxin metabolism, transport and signaling. Plant Cell Physiol. **59**:1500–1510.

Galvan-Ampudia, C.S., Julkowska, M.M., Darwish, E., Gandullo, J., Korver, R.A., Brunoud, G., Haring, M.A., Munnik, T., Vernoux, T., and Testerink, C. (2013). Halotropism is a response of plant roots to avoid a saline environment. Curr. Biol. **23**:2044–2050.

Gampala, S.S., Kim, T.W., He, J.X., Tang, W., Deng, Z., Bai, M.Y., Guan, S., Lalonde, S., Sun, Y., Gendron, J.M., et al. (2007). An essential role for 14-3-3 proteins in brassinosteroid signal transduction in *Arabidopsis*. Dev. Cell **13**:177–189.

Ganguly, A., Lee, S.H., and Cho, H.T. (2012). Functional identification of the phosphorylation sites of *Arabidopsis* PIN-FORMED3 for its subcellular localization and biological role. Plant J. **71**:810–823.

Ganguly, A., Park, M., Kesawat, M.S., and Cho, H.T. (2014). Functional analysis of the hydrophilic loop in intracellular trafficking of *Arabidopsis* PIN-FORMED proteins. Plant Cell **26**:1570–1585.

Gao, Y., Zhang, Y., Zhang, D., Dai, X., Estelle, M., and Zhao, Y. (2015). Auxin binding protein 1 (ABP1) is not required for either auxin signaling or *Arabidopsis* development. Proc. Natl. Acad. Sci. U S A **112**:2275–2280.

Geiger, D., Scherzer, S., Mumm, P., Stange, A., Marten, I., Bauer, H., Ache, P., Matschi, S., Liese, A., Al-Rasheid, K.A.S., et al. (2009). Activity of guard cell anion channel SLAC1 is controlled by drought-stress signaling kinase-phosphatase pair. Proc. Natl. Acad. Sci. U S A **106**:21425–21430.

Geisler, M., Aryal, B., Di Donato, M., and Hao, P. (2017). A critical view on ABC transporters and their interacting partners in auxin transport. Plant Cell Physiol. **58**:1601–1604.

Geldner, N., Friml, J., Stierhof, Y.D., Jürgens, G., and Palme, K. (2001). Auxin transport inhibitors block PIN1 cycling and vesicle trafficking. Nature **413**:425–428.

Geldner, N., Anders, N., Wolters, H., Keicher, J., Kornberger, W., Muller, P., Delbarre, A., Ueda, T., Nakano, A., and Jürgens, G. (2003). The *Arabidopsis* GNOM ARF-GEF mediates endosomal recycling, auxin transport, and auxin-dependent plant growth. Cell **112**:219–230.

Glanc, M., Fendrych, M., and Friml, J. (2018). Mechanistic framework for cell-intrinsic re-establishment of PIN2 polarity after cell division. Nat. Plants **4**:1082–1088.

Grebe, M., Friml, J., Swarup, R., Sandberg, G., Terlou, M., Palme, K., Bennett, M.J., and Scheres, B. (2002). Cell polarity signaling in *Arabidopsis* involves a BFA-sensitive auxin influx pathway. Curr. Biol. **12**:329–334.

Grieneisen, V.A., Xu, J., Marée, A.F.M., Hogeweg, P., and Scheres, B. (2007). Auxin transport is sufficient to generate a maximum and gradient guiding root growth. Nature **449**:1008–1013.

Guo, H., and Ecker, J.R. (2003). Plant responses to ethylene gas are mediated by SCFEBF1/EBF2-dependent proteolysis of EIN3 transcription factor. Cell **115**:667–677.

Guo, X., Qin, Q., Yan, J., Niu, Y., Huang, B., Guan, L., Li, Y., Ren, D., Li, J., and Hou, S. (2015). Type-one protein phosphatase4 regulates pavement cell interdigitation by modulating PIN-FORMED1 polarity and trafficking in *Arabidopsis*. Plant Physiol. **167**:1058–1075.

Habets, M.E.J., and Offringa, R. (2014). PIN-driven polar auxin transport in plant developmental plasticity: a key target for environmental and endogenous signals. New Phytol. **203**:362–377.

Hacham, Y., Sela, A., Friedlander, L., and Savaldi-Goldstein, S. (2012). BRI1 activity in the root meristem involves post-transcriptional regulation of PIN auxin efflux carriers. Plant Signal. Behav. **7**:68–70.

Hall, B.P., Shakeel, S.N., and Schaller, G.E. (2007). Ethylene receptors: ethylene perception and signal transduction. J. Plant Growth Regul. **26**:118–130.

Han, H., Rakusova, H., Verstraeten, I., Zhang, Y., and Friml, J. (2020). SCFTIR1/AFB auxin signaling for bending termination during shoot gravitropism. Plant Physiol. https://doi.org/10.1104/pp.20.00212.

He, Y., Tang, R.H., Hao, Y., Stevens, R.D., Cook, C.W., Ahn, S.M., Jing, L., Yang, Z., Chen, L., Guo, F., et al. (2004). Nitric oxide represses the *Arabidopsis* floral transition. Science **305**:1968–1971.

Hedden, P., and Sponsel, V. (2015). A century of gibberellin research. J. Plant Growth Regul. **34**:740–760.

Henrichs, S., Wang, B., Fukao, Y., Zhu, J., Charrier, L., Bailly, A., Oehring, S.C., Linnert, M., Weiwad, M., Endler, A., et al. (2012). Regulation of ABCB1/PGP1-catalysed auxin transport by linker phosphorylation. EMBO J. **31**:2965–2980.

Hess, D.T., Matsumoto, A., Kim, S.O., Marshall, H.E., and Stamler, J.S. (2005). Protein S-nitrosylation: purview and parameters. Nat. Rev. Mol. Cell Biol. **6**:150–166.

Hill, K. (2015). Post-translational modifications of hormone-responsive transcription factors: the next level of regulation. J. Exp. Bot. **66**:4933–4945.

Hu, X., Neill, S.J., Tang, Z., and Cai, W. (2005). Nitric oxide mediates gravitropic bending in soybean roots. Plant Physiol. **137**:663–670.

Hu, Y.F., Zhou, G., Na, X.F., Yang, L., Nan, W.B., Liu, X., Zhang, Y.Q., Li, J.L., and Bi, Y.R. (2013). Cadmium interferes with maintenance of auxin homeostasis in *Arabidopsis* seedlings. J. Plant Physiol. **170**:965–975.

Hua, J., and Meyerowitz, E.M. (1998). Ethylene responses are negatively regulated by a receptor gene family in *Arabidopsis thaliana*. Cell **94**:261–271.

Ischebeck, T., Werner, S., Krishnamoorthy, P., Lerche, J., Meijón, M., Stenzel, I., Löfke, C., Wiessner, T., Im, Y.J., Perera, I.Y., et al. (2013). Phosphatidylinositol 4,5-bisphosphate influences PIN polarization by controlling clathrin-mediated membrane trafficking in *Arabidopsis*. Plant Cell **25**:4894–4911.

Jásik, J., Bokor, B., Stuchlík, S., Mičieta, K., Turňa, J., and Schmelzer, E. (2016). Effects of auxins on PIN-FORMED2 (PIN2) dynamics are not mediated by inhibiting PIN2 endocytosis. Plant Physiol. **172**:1019–1031.

Jiang, L., Liu, X., Xiong, G., Liu, H., Chen, F., Wang, L., Meng, X., Liu, G., Yu, H., Yuan, Y., et al. (2013). DWARF 53 acts as a repressor of strigolactone signalling in rice. Nature **504**:401–405.

Jonsson, K., Boutté, Y., Singh, R.K., Gendre, D., and Bhalerao, R.P. (2017). Ethylene regulates differential growth via BIG ARF-GEF-dependent post-Golgi secretory trafficking in *Arabidopsis*. Plant Cell **29**:1039–1052.

Ju, C., Yoon, G.M., Shemansky, J.M., Lin, D.Y., Ying, Z.I., Chang, J., Garrett, W.M., Kessenbrock, M., Groth, G., Tucker, M.L., et al. (2012). CTR1 phosphorylates the central regulator EIN2 to control ethylene hormone signaling from the ER membrane to the nucleus in *Arabidopsis*. Proc. Natl. Acad. Sci. U S A **109**:19486–19491.

Julkowska, M.M., and Testerink, C. (2015). Tuning plant signaling and growth to survive salt. Trends Plant Sci. **20**:586–594.

Kania, U., Nodzyński, T., Lu, Q., Hicks, G.R., Nerinckx, W., Mishev, K., Peurois, F., Cherfils, J., De Rycke, R., Grones, P., et al. (2018). The inhibitor endosidin 4 targets SEC7 domain-type ARF GTPase exchange factors and interferes with subcellular trafficking in eukaryotes. Plant Cell **30**:2553–2572.

Keicher, J., Jaspert, N., Weckermann, K., Möller, C., Throm, C., Kintzi, A., and Oecking, C. (2017). *Arabidopsis* 14-3-3 epsilon members contribute to polarity of PIN auxin carrier and auxin transport-related development. eLife **6**:1–21.

Keshishian, E.A., and Rashotte, A.M. (2015). Plant cytokinin signalling. Essays Biochem. **58**:13–27.

Khan, M.I.R., Fatma, M., Per, T.S., Anjum, N.A., and Khan, N.A. (2015). Salicylic acid-induced abiotic stress tolerance and underlying mechanisms in plants. Front. Plant Sci. **6**:1–17.

Kieber, J.J., and Schaller, G.E. (2018). Cytokinin signaling in plant development. Development **145**:1–7.

Kitakura, S., Vanneste, S., Robert, S., Löfke, C., Teichmann, T., Tanaka, H., and Friml, J. (2011). Clathrin mediates endocytosis and

polar distribution of PIN auxin transporters in *Arabidopsis*. Plant Cell **23**:1920–1931.

Kleine-Vehn, J., Dhonukshe, P., Swarup, R., Bennett, M., and Friml, J. (2006). Subcellular trafficking of the *Arabidopsis* auxin influx carrier AUX1 uses a novel pathway distinct from PIN1. Plant Cell **18**:3171–3181.

Korver, R.A., van den Berg, T., Meyer, A.J., Galvan-Ampudia, C.S., ten Tusscher, K.H.W.J., and Testerink, C. (2020). Halotropism requires phospholipase Dζ1-mediated modulation of cellular polarity of auxin transport carriers. Plant Cell Environ. **43**:143–158.

Le Bot, N., Tsai, M.C., Andrews, R.K., and Ahringer, J. (2003). TAC-1, a regulator of microtubule length in the *C. elegans* embryo. Curr. Biol. **6742**:10–12.

Lešková, A., Zvarĭ, K.M., Araya, T., and Giehl, R.F.H. (2020). Nickel toxicity targets cell wall-related processes and PIN2-mediated auxin transport to inhibit root elongation and gravitropic responses in *Arabidopsis*. Plant Cell Physiol **61**:519–535.

Lewis, D.R., Negi, S., Sukumar, P., and Muday, G.K. (2011). Ethylene inhibits lateral root development, increases IAA transport and expression of PIN3 and PIN7 auxin efflux carriers. Development **138**:3485–3495.

Leyser, O. (2009). The control of shoot branching: an example of plant information processing. Plant Cell Environ. **32**:694–703.

Li, G., and Xue, H.W. (2007). *Arabidopsis* PLDζ2 regulates vesicle trafficking and is required for auxin response. Plant Cell **19**:281–295.

Li, L., Xu, J., Xu, Z.H., and Xue, H.W. (2005). Brassinosteroids stimulate plant tropisms through modulation of polar auxin transport in Brassica and *Arabidopsis*. Plant Cell **17**:2738–2753.

Li, G., Song, H., Li, B., Kronzucker, H.J., and Shi, W. (2015). Auxin resistant1 and PIN-FORMED2 protect lateral root formation in *Arabidopsis* under iron stress. Plant Physiol. **169**:2608–2623.

Li, Z., Waadt, R., and Schroeder, J.I. (2016). Release of GTP exchange factor mediated down-regulation of abscisic acid signal transduction through ABA-induced rapid degradation of RopGEFs. PLoS Biol. **14**:1–27.

Li, Y., Li, Y., Liu, Y., Wu, Y., and Xie, Q. (2018). The sHSP22 heat shock protein requires the ABI1 protein phosphatase to modulate polar auxin transport and downstream responses. Plant Physiol. **176**:2406–2425.

Li, T., Yan, A., Bhatia, N., Altinok, A., Afik, E., Durand-Smet, P., Tarr, P.T., Schroeder, J.I., Heisler, M.G., and Meyerowitz, E.M. (2019). Calcium signals are necessary to establish auxin transporter polarity in a plant stem cell niche. Nat. Commun. **10**:1–9.

Li, Y., Wang, Y., Tan, S., Li, Z., Yuan, Z., Glanc, M., Domjan, D., Wang, K., Xuan, W., Guo, Y., et al. (2020). Root growth adaptation is mediated by PYLs ABA receptor-PP2A protein phosphatase complex. Adv. Sci. (Weinh). **7**:1901455.

Liu, X., and Hou, X. (2018). Antagonistic regulation of ABA and GA in metabolism and signaling pathways. Front. Plant Sci. **9**:1–7.

Liu, S.X., Kawai, K., Tyurin, V.A., Tyurina, Y.Y., Borisenko, G.G., Fabisiak, J.P., Quinn, P.J., Pitt, B.R., and Kagan, V.E. (2001). Nitric oxide-dependent pro-oxidant and pro-apoptotic effect of metallothioneins in HL-60 cells challenged with cupric nitrilotriacetate. Biochem. J. **354**:397–406.

Liu, L., Yan, Y., Zeng, M., Zhang, J., Hanes, M.A., Ahearn, G., McMahon, T.J., Dickfeld, T., Marshall, H.E., Que, L.G., et al. (2004). Essential roles of S-nitrosothiols in vascular homeostasis and endotoxic shock. Cell **116**:617–628.

Liu, P.P., Montgomery, T.A., Fahlgren, N., Kasschau, K.D., Nonogaki, H., and Carrington, J.C. (2007). Repression of AUXIN RESPONSE FACTOR10 by microRNA160 is critical for seed germination and post-germination stages. Plant J. **52**:133–146.

Liu, Q., Zhang, Y.C., Wang, C.Y., Luo, Y.C., Huang, Q.J., Chen, S.Y., Zhou, H., Qu, L.H., and Chen, Y.Q. (2009). Expression analysis of phytohormone-regulated microRNAs in rice, implying their regulation roles in plant hormone signaling. FEBS Lett. **583**:723–728.

Liu, Y., Dong, Q., Kita, D., Huang, J.B., Liu, G., Wu, X., Zhu, X., Cheung, A.Y., Wu, H.M., and Tao, L.Z. (2017a). RopGEF1 plays a critical role in polar auxin transport in early development. Plant Physiol. **175**:157–171.

Liu, J., Moore, S., Chen, C., and Lindsey, K. (2017b). Crosstalk complexities between auxin, cytokinin, and ethylene in *Arabidopsis* root development: from experiments to systems modeling, and back again. Mol. Plant **10**:1480–1496.

Locascio, A., Blázquez, M.A., and Alabadí, D. (2013). Dynamic regulation of cortical microtubule organization through prefoldin-DELLA interaction. Curr. Biol. **23**:804–809.

Löfke, C., Luschnig, C., and Kleine-Vehn, J. (2013a). Posttranslational modification and trafficking of PIN auxin efflux carriers. Mech. Dev. **130**:82–94.

Löfke, C., Zwiewka, M., Heilmann, I., Van Montagu, M.C.E., Teichmann, T., and Friml, J. (2013b). Asymmetric gibberellin signaling regulates vacuolar trafficking of PIN auxin transporters during root gravitropism. Proc. Natl. Acad. Sci. U S A **110**:3627–3632.

Lu, C., Chen, M.X., Liu, R., Zhang, L., Hou, X., Liu, S., Ding, X., Jiang, Y., Xu, J., Zhang, J., et al. (2019). Abscisic acid regulates auxin distribution to mediate maize lateral root development under salt stress. Front. Plant Sci. **10**:1–16.

Lumba, S., Holbrook-Smith, D., and McCourt, P. (2017). The perception of strigolactones in vascular plants. Nat. Chem. Biol. **13**:599–606.

Lundin, V.F., Srayko, M., Hyman, A.A., and Leroux, M.R. (2008). Efficient chaperone-mediated tubulin biogenesis is essential for cell division and cell migration in *C. elegans*. Dev. Biol. **313**:320–334.

Marhava, P., Aliaga Fandino, A.C., Koh, S.W.H., Jelínková, A., Kolb, M., Janacek, D.P., Breda, A.S., Cattaneo, P., Hammes, U.Z., Petrášek, J., et al. (2020). Plasma membrane domain patterning and self-reinforcing polarity in *Arabidopsis*. Dev. Cell **52**:223–235.e5.

Marhavý, P., Bielach, A., Abas, L., Abuzeineh, A., Duclercq, J., Tanaka, H., Pařezová, M., Petrášek, J., Friml, J., Kleine-Vehn, J., et al. (2011). Cytokinin modulates endocytic trafficking of PIN1 auxin efflux carrier to control plant organogenesis. Dev. Cell **21**:796–804.

Marhavý, P., Duclercq, J., Weller, B., Feraru, E., Bielach, A., Offringa, R., Friml, J., Schwechheimer, C., Murphy, A., and Benková, E. (2014). Cytokinin controls polarity of PIN1-dependent auxin transport during lateral root organogenesis. Curr. Biol. **24**:1031–1037.

Mazur, E., Kulik, I., Hajný, J., and Friml, J. (2020a). Auxin canalization and vascular tissue formation by TIR1/AFB-mediated auxin signaling in *Arabidopsis*. New Phytol. https://doi.org/10.1111/nph.16446.

Mazur, E., Gallei, M., Adamowski, M., Han, H., Robert, H.S., and Friml, J. (2020b). Clathrin-mediated trafficking and PIN trafficking are required for auxin canalization and vascular tissue formation in *Arabidopsis*. Plant Sci. **293**:110414.

Mei, Y., Jia, W.J., Chu, Y.J., and Xue, H.W. (2012). *Arabidopsis* phosphatidylinositol monophosphate 5-kinase 2 is involved in root gravitropism through regulation of polar auxin transport by affecting the cycling of PIN proteins. Cell Res. **22**:581–597.

Melcher, K., Zhou, X.E., and Xu, H.E. (2010). Thirsty plants and beyond: structural mechanisms of abscisic acid perception and signaling. Curr. Opin. Struct. Biol. **20**:722–729.

Mellor, N., Vaughan-Hirsch, J., Kumpers, B.M.C., Help-Rinta-Rahko, H., Miyashima, S., Mahonen, A.P., Campilho, A., King, J.R., and Bishopp, A. (2019). A core mechanism for specifying root vascular patterning can replicate the anatomical variation seen in diverse plant species. Development **146**:1–10.

Méndez-Bravo, A., Ruiz-Herrera, L.F., Cruz-Ramírez, A., Guzman, P., Martínez-Trujillo, M., Ortiz-Castro, R., and López-Bucio, J. (2019). CONSTITUTIVE TRIPLE RESPONSE1 and PIN2 act in a coordinate manner to support the indeterminate root growth and meristem cell proliferating activity in *Arabidopsis* seedlings. Plant Sci. **280**:175–186.

Michniewicz, M., Zago, M.K., Abas, L., Weijers, D., Schweighofer, A., Meskiene, I., Heisler, M.G., Ohno, C., Zhang, J., Huang, F., et al. (2007). Antagonistic regulation of PIN phosphorylation by PP2A and PINOID directs auxin flux. Cell **130**:1044–1056.

Mishev, K., Lu, Q., Denoo, B., Peurois, F., Dejonghe, W., Hullaert, J., De Rycke, R., Boeren, S., Bretou, M., De Munck, S., et al. (2018). Nonselective chemical inhibition of Sec7 domain-containing ARF GTPase exchange factors. Plant Cell **30**:2573–2593.

Moore, S., Zhang, X., Mudge, A., Rowe, J.H., Topping, J.F., Liu, J., and Lindsey, K. (2015). Spatiotemporal modelling of hormonal crosstalk explains the level and patterning of hormones and gene expression in *Arabidopsis thaliana* wild-type and mutant roots. New Phytol. **207**:1110–1122.

Moriwaki, T., Miyazawa, Y., Kobayashi, A., and Takahashi, H. (2013). Molecular mechanisms of hydrotropism in seedling roots of *Arabidopsis thaliana* (Brassicaceae). Am. J. Bot. **100**:25–34.

Muraro, D., Larrieu, A., Lucas, M., Chopard, J., Byrne, H., Godin, C., and King, J. (2016). A multi-scale model of the interplay between cell signalling and hormone transport in specifying the root meristem of *Arabidopsis thaliana*. J. Theor. Biol. **404**:182–205.

Nagawa, S., Xu, T., Lin, D., Dhonukshe, P., Zhang, X., Friml, J., Scheres, B., Fu, Y., and Yang, Z. (2012). ROP GTPase-dependent actin microfilaments promote PIN1 polarization by localized inhibition of clathrin-dependent endocytosis. PLoS Biol. **10**:e1001299.

Naramoto, S. (2017). Polar transport in plants mediated by membrane transporters: focus on mechanisms of polar auxin transport. Curr. Opin. Plant Biol. **40**:8–14.

Neill, S.J., Desikan, R., Clarke, A., Hurst, R.D., and Hancock, J.T. (2002). Hydrogen peroxide and nitric oxide as signalling molecules in plants. J. Exp. Bot. **53**:1237–1247.

Neill, S.J., Desikan, R., and Hancock, J.T. (2003). Nitric oxide signalling in plants. New Phytol. **159**:11–35.

Ni, M., Zhang, L., Shi, Y.F., et al. (2017). Excessive cellular S-nitrosothiol impairs endocytosis of auxin efflux transporter PIN2. Front. Plant Sci. **8**:1–11.

Okada, K., Ueda, J., Komaki, M.K., Bell, C.J., and Shimura, Y. (1991). Requirement of the auxin polar transport system in early stages of *Arabidopsis* floral bud formation. Plant Cell **3**:677–684.

Osugi, A., and Sakakibara, H. (2015). Q&A: how do plants respond to cytokinins and what is their importance? BMC Biol. **13**:102.

Overvoorde, P., Fukaki, H., and Beeckman, T. (2010). Auxin control of root development. Cold Spring Harb. Perspect. Biol. **2**:1–17.

Paciorek, T., Zažímalová, E., Ruthardt, N., Petrášek, J., Stierhof, Y.-D., Kleine-Vehn, J., Morris, D.A., Emans, N., Jürgens, G., Geldner, N., et al. (2005). Auxin inhibits endocytosis and promotes its own efflux from cells. Nature **435**:1251–1256.

Pan, X., Fang, L., Liu, J., Senay-Aras, B., Lin, W., Zheng, S., Zhang, T., Manor, U., Chen, W., and Yang, Z. (2019). Auxin-induced nanoclustering of membrane signaling complexes underlies cell polarity establishment in *Arabidopsis*. bioRxiv https://doi.org/10.1101/734665.

Paponov, I.A., Friz, T., Budnyk, V., Teale, W., Wüst, F., Paponov, M., Al-Babili, S., and Palme, K. (2019). Natural auxin does not inhibit brefeldin a induced PIN1 and PIN2 internalization in root cells. Front. Plant Sci. **10**:1–7.

París, R., Vazquez, M.M., Graziano, M., Terrile, M.C., Miller, N.D., Spalding, E.P., Otegui, M.S., and Casalongué, C.a. (2018). Distribution of endogenous NO regulates early gravitropic response and PIN2 localization in *Arabidopsis* roots. Front. Plant Sci. **9**:1–11.

Peres, A.L.G.L., Soares, J.S., Tavares, R.G., Righetto, G., Zullo, M.A.T., Mandava, N.B., and Menossi, M. (2019). Brassinosteroids, the sixth class of phytohormones: a molecular view from the discovery to hormonal interactions in plant development and stress adaptation. Int. J. Mol. Sci. **20**:331.

Péret, B., Swarup, K., Ferguson, A., Seth, M., Yang, Y., Dhondt, S., James, N., Casimiro, I., Perry, P., Syed, A., et al. (2012). AUX/LAX genes encode a family of auxin influx transporters that perform distinct functions during *Arabidopsis* development. Plant Cell **24**:2874–2885.

Pernisova, M., Prat, T., Grones, P., Harustiakova, D., Matonohova, M., Spichal, L., Nodzynski, T., Friml, J., and Hejatko, J. (2016). Cytokinins influence root gravitropism via differential regulation of auxin transporter expression and localization in *Arabidopsis*. New Phytol. **212**:497–509.

Petrášek, J., Mravec, J., Bouchard, R., Blakeslee, J.J., Abas, M., Seifertová, D., Wiśniewska, J., Tadele, Z., Kubeš, M., Čovanová, M., et al. (2006). PIN proteins perform a rate-limiting function in cellular auxin efflux. Science **312**:914 LP–918.

Platre, M.P., Bayle, V., Armengot, L., Bareille, J., del Mar Marquès-Bueno, M., Creff, A., Maneta-Peyret, L., Fiche, J.B., Nollmann, M., Miège, C., et al. (2019). Developmental control of plant Rho GTPase nano-organization by the lipid phosphatidylserine. Science **364**:57–62.

Prát, T., Hajný, J., Grunewald, W., Vasileva, M., Molnár, G., Tejos, R., Schmid, M., Sauer, M., and Friml, J. (2018). WRKY23 is a component of the transcriptional network mediating auxin feedback on PIN polarity. PLoS Genet. **14**:1–18.

Prusinkiewicz, P., Crawford, S., Smith, R.S., Ljung, K., Bennett, T., Ongaro, V., and Leyser, O. (2009). Control of bud activation by an auxin transport switch. Proc. Natl. Acad. Sci. U S A **106**:17431–17436.

Qiao, H., Shen, Z., Huang, S. -s. C., Schmitz, R.J., Urich, M.a., Briggs, S.P., and Ecker, J.R. (2012). Processing and subcellular trafficking of ER-tethered EIN2 control response to ethylene gas. Science **338**:390–393.

Rakusová, H., Abbas, M., Han, H., Song, S., Robert, H.S., and Friml, J. (2016). Termination of shoot gravitropic responses by auxin feedback on PIN3 polarity. Curr. Biol. **26**:3026–3032.

Retzer, K., Akhmanova, M., Konstantinova, N., Malínská, K., Leitner, J., Petrášek, J., and Luschnig, C. (2019). Brassinosteroid signaling delimits root gravitropism via sorting of the *Arabidopsis* PIN2 auxin transporter. Nat. Commun. **10**:5516.

Rigó, G., Ayaydin, F., Tietz, O., Zsigmond, L., Kovács, H., Páy, A., Salchert, K., Darula, Z., Medzihradszky, K.F., Szabados, L., et al. (2013). Inactivation of plasma membrane-localized CDPK-RELATED KINASE5 decelerates PIN2 exocytosis and root gravitropic response in *Arabidopsis*. Plant Cell **25**:1592–1608.

Rivas-San Vicente, M., and Plasencia, J. (2011). Salicylic acid beyond defence: its role in plant growth and development. J. Exp. Bot. **62**:3321–3338.

Robert, S., Kleine-Vehn, J., Barbez, E., Sauer, M., Paciorek, T., Baster, P., Vanneste, S., Zhang, J., Simon, S., Čovanová, M., et al. (2010). ABP1 mediates auxin inhibition of clathrin-dependent endocytosis in *Arabidopsis*. Cell **143**:111–121.

Romero-Puertas, M.C., Perazzolli, M., Zago, E.D., and Delledonne, M. (2004). Nitric oxide signalling functions in plant-pathogen interactions. Cell. Microbiol. **6**:795–803.

Rong, D., Luo, N., Mollet, J.C., Liu, X., and Yang, Z. (2016). Salicylic acid regulates pollen tip growth through an NPR3/NPR4-independent pathway. Mol. Plant **9**:1478–1491.

Rosquete, M.R., and Kleine-Vehn, J. (2013). Halotropism: turning down the salty date. Curr. Biol. **23**:927–929.

Rowe, J.H., Topping, J.F., Liu, J., and Lindsey, K. (2016). Abscisic acid regulates root growth under osmotic stress conditions via an interacting hormonal network with cytokinin, ethylene and auxin. New Phytol. **211**:225–239.

Ruzicka, K., Simásková, M., Duclercq, J., Petrásek, J., Zazímalová, E., Simon, S., Friml, J., Van Montagu, M.C.E., and Benková, E. (2009). Cytokinin regulates root meristem activity via modulation of the polar auxin transport. Proc. Natl. Acad. Sci. U S A **106**:4284–4289.

Růzicka, K., Ljung, K., Vanneste, S., Podhorská, R., Beeckman, T., Friml, J., and Benková, E. (2007). Ethylene regulates root growth through effects on auxin biosynthesis and transport-dependent auxin distribution. Plant Cell **19**:2197–2212.

Sachs, T. (1975). The induction of transport channels by auxin. Planta **127**:201–206.

Sachs, T. (1981). The control of the patterned differentiation of vascular tissues. Adv. Bot. Res. **9**:151–262.

Sachs, T. (1969). Polarity and the induction of organized vascular tissues. Ann. Bot. **33**:263–275.

Salanenka, Y., Verstraeten, I., Löfke, C., Tabata, K., Naramoto, S., Glanc, M., and Friml, J. (2018). Gibberellin DELLA signaling targets the retromer complex to redirect protein trafficking to the plasma membrane. Proc. Natl. Acad. Sci. U S A **115**:3716–3721.

Sánchez-Vicente, I., Fernández-Espinosa, M.G., Lorenzo, O., and Brouquisse, R. (2019). Nitric oxide molecular targets: reprogramming plant development upon stress. J. Exp. Bot. **70**:4441–4460.

Sauer, M., and Kleine-Vehn, J. (2019). PIN-FORMED and PIN-LIKES auxin transport facilitators. Development **146**:dev168088.

Sauer, M., Balla, J., Luschnig, C., Wiśniewska, J., Reinöhl, V., Friml, J., and Benková, E. (2006). Canalization of auxin flow by Aux/IAA-ARF-dependent feedback regulation of PIN polarity. Genes Dev. **20**:2902–2911.

Sengupta, R., and Holmgren, A. (2012). The role of thioredoxin in the regulation of cellular processes by S-nitrosylation. Biochim. Biophys. Acta **1820**:689–700.

Seo, D.H., Ahn, M.Y., Park, K.Y., Kim, E.Y., and Kim, W.T. (2016). The N-terminal und motif of the *Arabidopsis* U-box E3 ligase pub18 is critical for the negative regulation of aba-mediated stomatal movement and determines its ubiquitination specificity for exocyst subunit Exo70B1. Plant Cell **28**:2952–2973.

Shi, Y.F., Wang, D.L., Wang, C., Culler, A.H., Kreiser, M.A., Suresh, J., Cohen, J.D., Pan, J., Baker, B., and Liu, J.Z. (2015). Loss of GSNOR1 function leads to compromised auxin signaling and polar auxin transport. Mol. Plant **8**:1350–1365.

Shibasaki, K., Uemura, M., Tsurumi, S., and Rahman, A. (2009). Auxin response in *Arabidopsis* under cold stress: underlying molecular mechanisms. Plant Cell **21**:3823–3838.

Shinohara, N., Taylor, C., and Leyser, O. (2013). Strigolactone can promote or inhibit shoot branching by triggering rapid depletion of the auxin efflux protein PIN1 from the plasma membrane. PLoS Biol. **11**:e1001474.

Shkolnik-Inbar, D., and Bar-Zvi, D. (2010). ABI4 mediates abscisic acid and cytokinin inhibition of lateral root formation by reducing polar auxin transport in arabidopsis. Plant Cell **22**:3560–3573.

Sieberer, T., Seifert, G.J., Hauser, M.T., Grisafi, P., Fink, G.R., and Luschnig, C. (2000). Post-transcriptional control of the *Arabidopsis* auxin efflux carrier EIR1 requires AXR1. Curr. Biol. **10**:1595–1598.

Šimášková, M., O'Brien, J.A., Khan, M., Van Noorden, G., Ötvös, K., Vieten, A., De Clercq, I., Van Haperen, J.M.A., Cuesta, C., Hoyerová, K., et al. (2015). Cytokinin response factors regulate PIN-FORMED auxin transporters. Nat. Commun. **6**:8717.

Simon, M.L.A., Platre, M.P., Marquès-Bueno, M.M., Armengot, L., Stanislas, T., Bayle, V., Caillaud, M.C., and Jaillais, Y. (2016). A PtdIns(4)P-driven electrostatic field controls cell membrane identity and signalling in plants. Nat. Plants **2**:1–10.

Singh, G., Retzer, K., Vosolsobě, S., and Napier, R. (2018). Advances in understanding the mechanism of action of the auxin permease aux1. Int. J. Mol. Sci. **19**:9–11.

Skoog, F., and Miller, C.O. (1957). Chemical regulation of growth and organ formation in plant tissues cultured in vitro. Symp. Soc. Exp. Biol. **11**:118–130.

Soundappan, I., Bennett, T., Morffy, N., Liang, Y., Stanga, J.P., Abbas, A., Leyser, O., and Nelsona, D.C. (2015). SMAX1-LIKE/D53 family members enable distinct MAX2-dependent responses to strigolactones and karrikins in *Arabidopsis*. Plant Cell **27**:3143–3159.

Stepanova, A.N., and Alonso, J.M. (2009). Ethylene signaling and response: where different regulatory modules meet. Curr. Opin. Plant Biol. **12**:548–555.

Stirnberg, P., van De Sande, K., and Leyser, H.M.O. (2002). MAX1 and MAX2 control shoot lateral branching in *Arabidopsis*. Development **129**:1131–1141.

Stirnberg, P., Furner, I.J., and Ottoline Leyser, H.M. (2007). MAX2 participates in an SCF complex which acts locally at the node to suppress shoot branching. Plant J. **50**:80–94.

Street, I.H., Mathews, D.E., Yamburkenko, M.V., Sorooshzadeh, A., John, R.T., Swarup, R., Bennett, M.J., Kieber, J.J., and Schaller, G.E. (2016). Cytokinin acts through the auxin influx carrier AUX1 to regulate cell elongation in the root. Development **143**:3982–3993.

Sun, J., Xu, Y., Ye, S., Jiang, H., Chen, Q., Liu, F., Zhou, W., Chen, R., Li, X., Tietz, O., et al. (2009). *Arabidopsis* ASA1 is important for jasmonate-mediated regulation of auxin biosynthesis and transport during lateral root formation. Plant Cell **21**:1495–1511.

Sun, J., Chen, Q., Qi, L., Jiang, H., Li, S., Xu, Y., Liu, F., Zhou, W., Pan, J., Li, X., et al. (2011). Jasmonate modulates endocytosis and plasma membrane accumulation of the *Arabidopsis* pin2 protein. New Phytol. **191**:360–375.

Swarup, R., and Bhosale, R. (2019). Developmental roles of AUX1/LAX auxin influx carriers in plants. Front. Plant Sci. **10**:1–14.

Swarup, R., and Péret, B. (2012). AUX/LAX family of auxin influx carriers-An overview. Front. Plant Sci. **3**:1–11.

Swarup, R., Swarup, R., Marchant, A., Marchant, A., Ljung, K., Ljung, K., Sandberg, G., Sandberg, G., Palme, K., Palme, K., et al. (2001). Localization of the auxin permease AUX1suggests two functionally distinct hormone transport pathways operate in the *Arabidopsis* root apex Ranjan. Genes Dev. https://doi.org/10.1101/gad.210501.2648.

Swarup, R., Kargul, J., Marchant, A., Zadik, D., Rahman, A., Mills, R., Yemm, A., May, S., Williams, L., Millner, P., et al. (2004). Structure-function analysis of the presumptive *Arabidopsis* auxin permease AUX1. Plant Cell **16**:3069–3083.

Tada, Y., Spoel, S.H., Pajerowska-Mukhtar, K., Mou, Z., Song, J., Wang, C., Zuo, J., and Dong, X. (2009). Plant immunity requires conformational charges of NPR1 via S-nitrosylation and thioredoxins. Science **321**:952–957.

Tan, S., Abas, M., Verstraeten, I., Glanc, M., Molnár, G., Hajný, J., Lasák, P., Petřík, I., Russinova, E., Petrášek, J., et al. (2020).

Salicylic acid targets protein phosphatase 2A to attenuate growth in plants. Curr. Biol. **30**:381–395.e8.

Tanaka, H., Kitakura, S., De Rycke, R., De Groodt, R., and Friml, J. (2009). Fluorescence imaging-based screen identifies ARF GEF component of early endosomal trafficking. Curr. Biol. **19**:391–397.

Tanaka, H., Kitakura, S., Rakusová, H., Uemura, T., Feraru, M.I., de Rycke, R., Robert, S., Kakimoto, T., and Friml, J. (2013). Cell polarity and patterning by PIN trafficking through early endosomal compartments in *Arabidopsis thaliana*. PLoS Genet. **9**:e1003540.

Tejos, R., Sauer, M., Vanneste, S., Palacios-Gomez, M., Li, H., Heilmann, M., van Wijk, R., Vermeer, J.E.M., Heilmann, I., Munnik, T., et al. (2014). Bipolar plasma membrane distribution of phosphoinositides and their requirement for auxin-mediated cell polarity and patterning in *Arabidopsis*. Plant Cell **26**:2114–2128.

Testerink, C., and Munnik, T. (2011). Molecular, cellular, and physiological responses to phosphatidic acid formation in plants. J. Exp. Bot. **62**:2349–2361.

Testerink, C., Dekker, H.L., Lim, Z.Y., Johns, M.K., Holmes, A.B., De Koster, C.G., Ktistakis, N.T., and Munnik, T. (2004). Isolation and identification of phosphatidic acid targets from plants. Plant J. **39**:527–536.

Thaler, J.S., Humphrey, P.T., and Whiteman, N.K. (2012). Evolution of jasmonate and salicylate signal crosstalk. Trends Plant Sci. **17**:260–270.

Titapiwatanakun, B., Blakeslee, J.J., Bandyopadhyay, A., Yang, H., Mravec, J., Sauer, M., Cheng, Y., Adamec, J., Nagashima, A., Geisler, M., et al. (2009). ABCB19/PGP19 stabilises PIN1 in membrane microdomains in *Arabidopsis*. Plant J. **57**:27–44.

Tognetti, V.B., Bielach, A., and Hrtyan, M. (2017). Redox regulation at the site of primary growth: auxin, cytokinin and ROS crosstalk. Plant Cell Environ. **40**:2586–2605.

Ueguchi-Tanaka, M., Nakajima, M., Motoyuki, A., and Matsuoka, M. (2007). Gibberellin receptor and its role in gibberellin signaling in plants. Annu. Rev. Plant Biol. **58**:183–198.

Umezawa, T., Sugiyama, N., Mizoguchi, M., Hayashi, S., Myouga, F., Yamaguchi-Shinozaki, K., Ishihama, Y., Hirayama, T., and Shinozaki, K. (2009). Type 2C protein phosphatases directly regulate abscisic acid-activated protein kinases in *Arabidopsis*. Proc. Natl. Acad. Sci. U S A **106**:17588–17593.

van Berkel, K., de Boer, R.J., Scheres, B., and ten Tusscher, K. (2013). Polar auxin transport: models and mechanisms. Development **140**:2253–2268.

van den Berg, T., Korver, R.A., Testerink, C., and ten Tusscher, K.H.W.J. (2016). Modeling halotropism: a key role for root tip architecture and reflux loop remodeling in redistributing auxin. Development **143**:3350–3362.

Vandenbussche, F., Petrášek, J., Žádníková, P., Hoyerová, K., Pešek, B., Raz, V., Swarup, R., Bennett, M., Zažímolavá, E., Benkova, E., et al. (2010). The auxin influx carriers AUX1 and LAX3 are involved in auxin-ethylene interactions during apical hook development in *Arabidopsis thaliana* seedlings. Development **137**:597–606.

Vanneste, S., and Friml, J. (2009). Auxin: a trigger for change in plant development. Cell **136**:1005–1016.

Vanneste, S., and Friml, J. (2013). Calcium: the missing link in auxin action. Plants **2**:650–675.

Vanstraelen, M., and Benková, E. (2012). Hormonal interactions in the regulation of plant development. Annu. Rev. Cell Dev. Biol. **28**:463–487.

Verna, C., Ravichandran, S.J., Sawchuk, M., Linh, N.M., and Scarpella, E. (2019). Coordination of tissue cell polarity by auxin transport and signaling. eLife **1**:1–30.

Vernoux, T., Besnard, F., and Traas, J. (2010). Auxin at the shoot apical meristem. Cold Spring Harb. Perspect. Biol. **2**:1–15.

Vieten, A., Vanneste, S., Wiśniewska, J., Benková, E., Benjamins, R., Beeckman, T., Luschnig, C., and Friml, J. (2005). Functional redundancy of PIN proteins is accompanied by auxin-dependent cross-regulation of PIN expression. Development **132**:4521–4531.

Voß, U., Bishopp, A., Farcot, E., and Bennett, M.J. (2014). Modelling hormonal response and development. Trends Plant Sci. **19**:311–319.

Waldie, T., and Leyser, O. (2018). Cytokinin targets auxin transport to promote shoot branching. Plant Physiol. **177**:803–818.

Wang, C., Hu, T., Yan, X., Meng, T., Wang, Y., Wang, Q., Zhang, X., Gu, Y., Sánchez-Rodríguez, C., Gadeyne, A., et al. (2016). Differential regulation of clathrin and its adaptor proteins during membrane recruitment for endocytosis. Plant Physiol. **171**:215–229.

Wang, P., Shen, L., Guo, J., Jing, W., Qu, Y., Li, W., Bi, R., Xuan, W., Zhang, Q., and Zhang, W. (2019). Phosphatidic acid directly regulates pinoid-dependent phosphorylation and activation of the pin-formed2 auxin efflux transporter in response to salt stress. Plant Cell **31**:250–271.

Wasternack, C., and Song, S. (2017). Jasmonates: biosynthesis, metabolism, and signaling by proteins activating and repressing transcription. J. Exp. Bot. **68**:1303–1321.

Wei, Z., and Li, J. (2016). Brassinosteroids regulate root growth, development, and symbiosis. Mol. Plant **9**:86–100.

Weiss, D., and Ori, N. (2007). Mechanisms of cross talk between gibberellin and other hormones. Plant Physiol. **144**:1240–1246.

Wen, X., Zhang, C., Ji, Y., Zhao, Q., He, W., An, F., Jiang, L., and Guo, H. (2012). Activation of ethylene signaling is mediated by nuclear translocation of the cleaved EIN2 carboxyl terminus. Cell Res. **22**:1613–1616.

Wendehenne, D., Durner, J., and Klessig, D.F. (2004). Nitric oxide: a new player in plant signalling and defence responses. Curr. Opin. Plant Biol. **7**:449–455.

Willige, B.C., Isono, E., Richter, R., Zourelidou, M., and Schwechheimer, C. (2011). Gibberellin regulates PIN-formed abundance and is required for auxin transport–dependent growth and development in *Arabidopsis thaliana*. Plant Cell **23**:2184–2195.

Xu, W., Jia, L., Shi, W., Liang, J., Zhou, F., Li, Q., and Zhang, J. (2013). Abscisic acid accumulation modulates auxin transport in the root tip to enhance proton secretion for maintaining root growth under moderate water stress. New Phytol. **197**:139–150.

Xu, T., Dai, N., Chen, J., Nagawa, S., Cao, M., Li, H., Zhou, Z., Chen, X., de Rycke, R., Rakusová, H., et al. (2014). Cell surface ABP1-TMK auxin-sensing complex activates ROP GTPase signaling. Science **343**:1025–1029.

Yan, J., Zhang, C., Gu, M., Bai, Z., Zhang, W., Qi, T., Cheng, Z., Peng, W., Luo, H., Nan, F., et al. (2009). The *Arabidopsis* CORONATINE INSENSITIVE1 protein is a jasmonate receptor. Plant Cell **21**:2220–2236.

Yang, H., and Murphy, A.S. (2009). Functional expression and characterization of *Arabidopsis* ABCB, AUX 1 and PIN auxin transporters in *Schizosaccharomyces pombe*. Plant J. **59**:179–191.

Yang, L., Zhang, J., He, J., Qin, Y., Hua, D., Duan, Y., Chen, Z., and Gong, Z. (2014). ABA-mediated ROS in mitochondria regulate root meristem activity by controlling PLETHORA expression in *Arabidopsis*. PLoS Genet. **10**:e1004791.

Ye, Y., Li, Z., and Xing, D. (2012). Sorting out the role of nitric oxide in cadmium-induced *Arabidopsis thaliana* programmed cell death. Plant Signal. Behav. **7**:20–22.

Yuan, H.M., Xu, H.H., Liu, W.C., and Lu, Y.T. (2013). Copper regulates primary root elongation through PIN1-mediated auxin redistribution. Plant Cell Physiol. **54**:766–778.

Yue, R., Tie, S., Sun, T., Zhang, L., Yang, Y., Qi, J., Yan, S., Han, X., Wang, H., and Shen, C. (2015). Genome-wide identification and expression profiling analysis of ZmPIN, ZmPILS, ZmLAX and ZmABCB auxin transporter gene families in maize (*Zea mays* L.) under various abiotic stresses. PLoS One **10**:1–23.

Žádníkova, P., Petrášek, J., Marhavý, P., Raz, V., Vandenbussche, F., Ding, Z., Schwarzerová, K., Morita, M.T., Tasaka, M., Hejatko, J., et al. (2010). Role of PIN-mediated auxin efflux in apical hook development of *Arabidopsis thaliana*. Development **137**:607–617.

Žádníková, P., Wabnik, K., Abuzeineh, A., Gallemi, M., Van Der Straeten, D., Smith, R.S., Inzé, D., Friml, J., Prusinkiewicz, P., and Benková, E. (2016). A model of differential growth-guided apical hook formation in plants. Plant Cell **28**:2464–2477.

Zegzouti, H., Li, W., Lorenz, T.C., Xie, M., Payne, C.T., Smith, K., Glenny, S., Payne, G.S., and Christensen, S.K. (2006). Structural and functional insights into the regulation of *Arabidopsis* AGC VIIIa kinases. J. Biol. Chem. **281**:35520–35530.

Zemlyanskaya, E.V., Omelyanchuk, N.a., Ubogoeva, E.V., and Mironova, V.V. (2018). Deciphering auxin-ethylene crosstalk at a systems level. Int. J. Mol. Sci. **19**:1–15.

Zhang, W., To, J.P.C., Cheng, C.Y., Eric Schaller, G., and Kieber, J.J. (2011). Type-A response regulators are required for proper root apical meristem function through post-transcriptional regulation of PIN auxin efflux carriers. Plant J. **68**:1–10.

Zhang, Y., Xiao, G., Wang, X., Zhang, X., and Friml, J. (2019). Evolution of fast root gravitropism in seed plants. Nat. Commun. **10**:4–13.

Zhang, X., Adamowski, M., Marhava, P., Tan, S., Zhang, Y., Rodriguez, L., Zwiewka, M., Pukyšová, V., Sánchez, A.S., Raxwal, V.K., et al. (2020a). *Arabidopsis* flippases cooperate with ARF GTPase exchange factors to regulate the trafficking and polarity of PIN auxin transporters. Plant Cell **12**. https://doi.org/10.1105/tpc.19.00869.

Zhang, X.P., Ma, C.X., Sun, L.R., and Hao, F.S. (2020b). Roles and mechanisms of Ca in regulating primary root growth of plants. Plant Signal. Behav. https://doi.org/10.1080/15592324.2020.1748283.

Zhao, Z., Andersen, S.U., Ljung, K., Dolezal, K., Miotk, A., Schultheiss, S.J., and Lohmann, J.U. (2010). Hormonal control of the shoot stem-cell niche. Nature **465**:1089–1092.

Zhao, S., Wu, Y., He, Y., Wang, Y., Xiao, J., Li, L., Wang, Y., Chen, X., Xiong, W., and Wu, Y. (2015). RopGEF2 is involved in ABA-suppression of seed germination and post-germination growth of *Arabidopsis*. Plant J. **84**:886–899.

Zhou, J.J., and Luo, J. (2018). The PIN-FORMED auxin efflux carriers in plants. Int. J. Mol. Sci. **19**:1–21.

Zhou, F., Lin, Q., Zhu, L., Ren, Y., Zhou, K., Shabek, N., Wu, F., Mao, H., Dong, W., Gan, L., et al. (2013). D14-SCF D3-dependent degradation of D53 regulates strigolactone signalling. Nature **504**:406–410.

Zhu, Q., Gallemí, M., Pospíšil, J., Žádníková, P., Strnad, M., and Benková, E. (2019). Root gravity response module guides differential growth determining both root bending and apical hook formation. Development https://doi.org/10.1242/dev.175919.

Zourelidou, M., Müller, I., Willige, B.C., Nill, C., Jikumaru, Y., Li, H., and Schwechheimer, C. (2009). The polarly localized D6 PROTEIN KINASE is required for efficient auxin transport in *Arabidopsis thaliana*. Development **136**:627–636.

Zourelidou, M., Absmanner, B., Weller, B., Barbosa, I.C.R., Willige, B.C., Fastner, A., Streit, V., Port, S.A., Colcombet, J., van Bentem, S.D.L.F., et al. (2014). Auxin efflux by PIN-FORMED proteins is activated by two different protein kinases, D6 PROTEIN KINASE and PINOID. eLife **2014**:1–25.

Zubo, Y.O., and Schaller, G.E. (2020). Role of the cytokinin-activated type-B response regulators in hormone crosstalk. Plants (Basel) **9**:166.

Zwiewka, M., Bilanovičová, V., Seifu, Y.W., and Nodzyński, T. (2019a). The nuts and bolts of PIN auxin efflux carriers. Front. Plant Sci. **10**:985.

Zwiewka, M., Bielach, A., Tamizhselvan, P., Madhavan, S., Ryad, E.E., Tan, S., Hrtyan, M., Dobrev, P., Vanková, R., Friml, J., et al. (2019b). Root adaptation to H_2O_2-induced oxidative stress by ARF-GEF BEN1- and cytoskeleton-mediated PIN2 trafficking. Plant Cell Physiol. **60**:255–273.