Casting the Net—Connecting Auxin Signaling to the Plant Genome

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Auxin represents one of the most potent and most versatile hormonal signals in the plant kingdom. Built on a simple core of only a few dedicated components, the auxin signaling system plays important roles for diverse aspects of plant development, physiology, and defense. Key to the diversity of context-dependent functional outputs generated by cells in response to this small molecule are gene duplication events and sub-functionalization of signaling components on the one hand, and a deep embedding of the auxin signaling system into complex regulatory networks on the other hand. Together, these evolutionary innovations provide the mechanisms to allow each cell to display a highly specific auxin response that suits its individual requirements. In this review, we discuss the regulatory networks connecting auxin with a large number of diverse pathways at all relevant levels of the signaling system ranging from biosynthesis to transcriptional response.

As sessile organisms, plants are exposed to a continuously changing environment, which is shaped by a plethora of abiotic and biotic parameters. To cope with these challenges, plants have evolved regulatory networks that allow them to constantly adapt their growth and developmental program to the current conditions. Given the decentralized nature of cellular decision making in plants, these networks need to fulfill a surprisingly large number of sometimes conflicting functions. First, they need to be able to integrate a substantial amount of information into a stable cellular program. For example, a plant may encounter a windy and cold, but very bright, day in spring with the soil moist and nutrients available in abundance. In this hypothetical environment, a plant finds excellent conditions for growth on the one hand with water and nutrient availability near the optimum, as well as enough light to drive a maximum of photosynthesis. On the other hand, UV irradiation, low temperatures, and wind impose substantial stress on the individual. To complicate matters for finding the optimal developmental solution, the opposing inputs mostly affect different parts of the plant, requiring tight communication between roots, leaves, and stems. Here, the plant encounters a second challenge, namely, the system-wide coupling of cell behavior. Whereas in the above example uni-

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form cell behavior across the entire plant likely is beneficial, there are cases, such as localized attack by herbivores or partial shading, where strictly local responses are required. A third challenge for the discussed regulatory networks is that they need to be deeply embedded into the developmental and metabolic programs, both for environmental sensing and for modulating growth and physiology. Last, the decision making has to be aware of temporal components to allow the plant to prepare for certain conditions expected in the future, based on previous exposures.

In this review, we will focus on regulatory networks that have evolved around the auxin signaling system, which plays key roles in diverse aspects of plant development, physiology, and defense. The most abundant and best-characterized auxin, indole acetic acid (IAA), is a small metabolite with similarity to tryptophan and able to move throughout the plant body in the phloem or by active and highly polar cell–cell transport (Okada et al. 1991; Gälweiler et al. 1998; Müller et al. 1998; Palme and Gälweiler 1999; Reinhardt et al. 2003; Petrášek et al. 2006; Tanaka et al. 2006; Adamowski and Friml 2015). The core auxin perception and signaling system is relatively simple, consisting of only three dedicated intracellular components: receptor (Dharmasiri et al. 2005; Kepinski and Leyser 2005), transcriptional executor (Ulmasov et al. 1997a; Hardtke and Berleth 1998), and inhibitor protein (Ulmasov et al. 1997b; Rouse et al. 1998; Hamann et al. 2002), which are coupled to the proteasome system (Gray et al. 2001). However, the pathway has evolved by gene duplication, and in many plants all components are represented by multiple copies with diverse expression patterns and biochemical properties (Vernoux et al. 2011; Weijers and Wagner 2016; Kato et al. 2020), giving rise to an enormous range in direct cellular responses to auxin through combinatorial logic. Importantly, the medium- and long-term auxin response is further shaped by intricate connections of this core auxin-sensing pathway with a dazzling array of signaling systems through transcriptional cross regulation, protein modification, or chromatin remodeling.

CONTROL OF AUXIN HOMEOSTASIS AND TRANSPORT

Many of the biological effects of auxin appear highly localized, such as organ initiation or tropic responses, and it follows that the hormone must be able to act with high spatiotemporal specificity. Indeed, it has turned out that local accumulation of active auxin is tightly regulated at multiple levels including biosynthesis, transport, as well as conjugation and degradation of this small metabolite. Since genetic analysis had suggested that auxin transport would suffice to create local effects, localized auxin biosynthesis, inactivation, or sensing was thought to play only a minor role until recently (Cheng et al. 2006, 2007; Stepanova et al. 2008; Tao et al. 2008; Brumos et al. 2018). However, with the elucidation of auxin anabolic and catabolic pathways and the expression patterns of the underlying genes, it became clear that this level of control is more important than previously recognized. Not only do many auxin metabolic genes exhibit highly specific spatiotemporal expression patterns, they also respond dynamically to a variety of stimuli, lending strong support to the importance of complex gene regulatory networks controlling auxin homeostasis.

Auxin (IAA) biosynthesis can follow both tryptophan (Trp)-dependent and -independent pathways, but currently only the Trp-dependent TAA-YUCCA pathway is well understood at the genetic and mechanistic level (Zhao 2018). To produce IAA from Trp, two sequential steps need to be carried out. The first step is catalyzed by enzymes encoded by members of the TRYPTOPHAN AMINOTRANSFERASE OF ARABIDOPSIS (TAA) gene family (Tao et al. 2008), whereas the second and rate-limiting step relies on flavin-containing monooxygenases encoded by the *YUCCA* (*YUC*) gene family (Zhao et al. 2001; Won et al. 2011). *YUC* genes show highly specific expression patterns and higher order *yucca* mutants show severe development defects (Cheng et al. 2006), lending support to the idea that levels of local auxin synthesis via the transcriptional regulation of *YUC*s is essential for the correct execution of developmental programs (Eklund et al. 2010; Cui et al. 2013;

Martínez-Fernández et al. 2014; Tang et al. 2017; Zhou et al. 2018; Blakeslee et al. 2019; Cao et al. 2019). An interesting example is the induction of *YUC* expression by the STYLISH (STY) transcription factor (TF) during fruit development (Eklund et al. 2010). *STY* expression is dependent on the activity of the AP2 TF DORNROESCHEN-LIKE (Eklund et al. 2011), which itself has been shown to act downstream of auxin signals (Cole et al. 2009), hinting at intricate feedforward connections. Similarly, in the root, auxin biosynthesis is controlled by the brassinosteroid (BR) signaling pathway via *TAA* and *YUC* genes in a cell-type-specific fashion, which in turn controls meristem development (Vragović et al. 2015). A subset of *YUC* genes have also been shown to be regulated at the epigenetic level. TFL2/LHP1 (Rizzardi et al. 2011), the HP1 homolog in plants, localizes to promoters of *YUC* genes and is required for their transcriptional activation. This interaction is functionally relevant, since in *tfl2/lhp1* mutants, the activity of the auxin output reporter DR5 is substantially reduced. In addition to these developmental inputs, altered *YUC* gene expression is also involved in the response to external stimuli, such as light (Li et al. 2012; Zhou et al. 2018), temperature (Sun et al. 2012), and biotic stress (Liu et al. 2016). For example, the growth responses downstream of shade perception and increase in ambient temperature are tightly connected and require direct binding of PHYTOCHROME INTERACTING FACTORS (PIFs) such as PIF4 and PIF7 to the promoters of *YUC* genes to increase local auxin biosynthesis (Hornitschek et al. 2012; Li et al. 2012; Hersch et al. 2014).

While the TAA-dependent step in the pathway does not appear to be rate limiting, *taa* mutants still exhibit substantial reduction in the levels of free IAA, along with obvious phenotypes (Stepanova et al. 2008). In line with the hypothesis that regulation of *TAA* genes is the primary mode of action to modulate auxin levels in response to environmental stimuli, *TAA* transcription has been shown to be under control of the phytohormones ethylene (Stepanova et al. 2008) and cytokinin (CK) (Yan et al. 2017), as well as light quality (Tao et al. 2008), high temperature (Franklin et al. 2011), or gravity (Cui et al. 2013). In addition to the transcriptional level, local auxin biosynthesis via TAA1 can also be regulated at the protein level by the switch of its enzymatic activity via T101 phosphorylation (Wang et al. 2020).

Acting downstream of auxin biosynthesis, IAA conjugation and degradation are also embedded into the regulatory networks underlying dynamic local auxin homeostasis. IAA conjugation to glutamic acid (IAA-Glu) or other amino acids, is the first step toward auxin degradation. The conjugating process is catalyzed by the Gretchen Hagen 3 (GH3) enzyme family, which are IAA-amido synthetases and first identified as auxin rapid-induced transcripts from soybean (Hagen and Guilfoyle 1985; Wright et al. 1987; Hagen et al. 1991). The feedback loop between auxin-induced increase in *GH3* mRNA accumulation and the conversion of IAA to inactive IAA-Glu by GH3 enzymatic activity provides a reset of local auxin levels. Importantly, the activation of *GH3* expression is also employed by other pathways, such as by CK signaling. In the root, the CK output TF ARABIDOPSIS RESPONSE REGULATOR 1 (ARR1) stimulates GH3.17, which transforms IAA into IAA-Glu in the lateral root cap, creating an auxin minimum defining the transition zone between cell division and cell differentiation in root meristem (Di Mambro et al. 2017, 2019). Unlike IAA-Asp or IAA-Glu, other IAA-amino acid conjugates can serve as a storage of IAA, such as IAA-Ala, and IAA-Leu, which can be hydrolyzed back to free IAA (Woodward and Bartel 2005). However, the oxidization of IAA into 2-oxoindole-3-acetic acid (OxIAA) is chemically irreversible, leading to the inactivation of IAA (Peer et al. 2013). The regulation of IAA oxidization was first revealed in a *dao* mutant (dioxygenase for auxin oxidation) in rice, which encodes a 2-oxoglutarate-dependent-Fe (II) dioxygenase, oxidizing free IAA into OxIAA (Zhao et al. 2013). Main defects of *dao* mutants in flowers and seeds highlight importance of auxin concentration in local contexts. Both *GH3* and *DAO* genes are induced by auxin, and inactivate auxin in a concentration-dependent manner, which serves as a dynamic feedback to maintain optimal auxin levels (Mellor

et al. 2016). In addition to regulatory conjugation of IAA, the abundance of its precursor IPA is also controlled by the formation of IPA-glucose (IPA-Glc), a reaction mediated by an UDP-glycosyltransferase (UGT76F1). This mechanism contributes significantly to auxin homeostasis via competing with YUC enzymes for the shared substrate IPA (Chen et al. 2020). Again, these steps are tightly integrated into the regulatory landscape and it has been shown that the environmental integrator PIF4 can bind to the promoter of both *YUC* and *UGT76F1* (Chen et al. 2020), suggesting a switch-like activity to tune growth to current conditions.

Whereas synthesis and breakdown only recently have emerged as important players in setting up local gradients of auxin, transport processes have attracted attention for many decades. Directed cell-to-cell transport of auxin has been demonstrated to lie at the heart of a plethora of developmental and adaptive processes, including tissue patterning, body polarity, organ specification, and tropisms. In line with the massive influence on many aspects of plant life, auxin transport is dynamically regulated both at the organismal, as well as the tissue level. One fundamental property influencing this process is the acidic environment found in the cell wall, the extracellular matrix of plants (Wolf et al. 2012), which dictates that auxin is partially protonated. This part of the auxin pool can passively diffuse across the plasma membrane (PM), while the rest is actively transported into cells by the influx carrier AUX1/LAX (Vanneste and Friml 2009; Swarup and Péret 2012) and the nitrate transporter NRT1.1 (Krouk et al. 2010).

The molecules responsible for the proton gradient between apoplast and cytoplasm are PM-localized H^+-ATPase proton pumps. Interestingly, the transport capacity of the pumps can be regulated by auxin itself and environmental cues, such as light (Kinoshita and Shimazaki 1999; Takahashi et al. 2012) and the mechanism for modulating H^+-ATPase activity is through protein modification. Both auxin and blue light activate pump activity via SMALL AUXIN UP RNA (SAUR) proteins (McClure and Guilfoyle 1987; Hagen and Guilfoyle 2002) that in turn inhibit type 2C protein phosphatase D (PP2C-D) enzymes, which usually inhibit H^+-ATPases (Leyser et al. 1996; Kinoshita and Shimazaki 1999; Takahashi et al. 2012; Spartz et al. 2014; Fendrych et al. 2016; Ren et al. 2018). The transcriptional regulation of SAUR proteins indeed represents a key component of the rapid auxin-induced changes in elongation growth that initiated auxin research more than 150 years ago (Darwin 1880). The SAUR H^+-ATPase module also has been shown to couple apoplast pH regulation with other phytohormones or environmental cues. For instance, BR signaling is able to induce phosphorylation of H^+-ATPase in hypocotyl elongation either through transcriptional activation of SAURs (Minami et al. 2019) or through a fast BR-regulated PM protein–protein interaction between the BR signaling receptor BRI1 and the H^+-ATPase (Fig. 1; Caesar et al. 2011; Miao et al. 2018). In addition, an alternative pathway based on a ligand-receptor system, involving RAPID ALKALINIZATION FACTOR (RALF) and the receptor-like kinase FERONIA, is able to elicit a transient apoplast alkalinization via inhibitory phosphorylation of H^+-ATPases (Haruta et al. 2014).

Because deprotonated IAA is essentially incapable of crossing the PM, auxin influx carriers AUXIN1/LIKE-AUX1 (AUX1/LAX) are required for its influx in cells (Swarup and Péret 2012). AUX1, the founder of the AUX1/LAX family, is an amino acid permease-like protein (Bennett et al. 1996) that functions as a H^+/IAA^- symporter (Yang et al. 2006). AUX/LAX family members in *Arabidopsis* are all proven functional auxin transporters (Péret et al. 2012) and are involved in a large variety of auxin-mediated developmental processes, such as AUX1 in root gravitropism, root hair development, and phyllotaxy (Bennett et al. 1996; Marchant et al. 1999, 2002); LAX2 in vascular development and quiescent center (QC) maintenance (Péret et al. 2012; Zhang et al. 2013); AUX1 and LAX3 redundant in lateral root initiation and apical hook formation (Hobbie and Estelle 1995; Vandenbussche et al. 2010; Péret et al. 2012); and AUX1, LAX1, and LAX2 redundant in leaf patterning and embryogenesis (Bainbridge et al. 2008; Robert et al. 2015). Specific expression patterns of those family members suggest that these

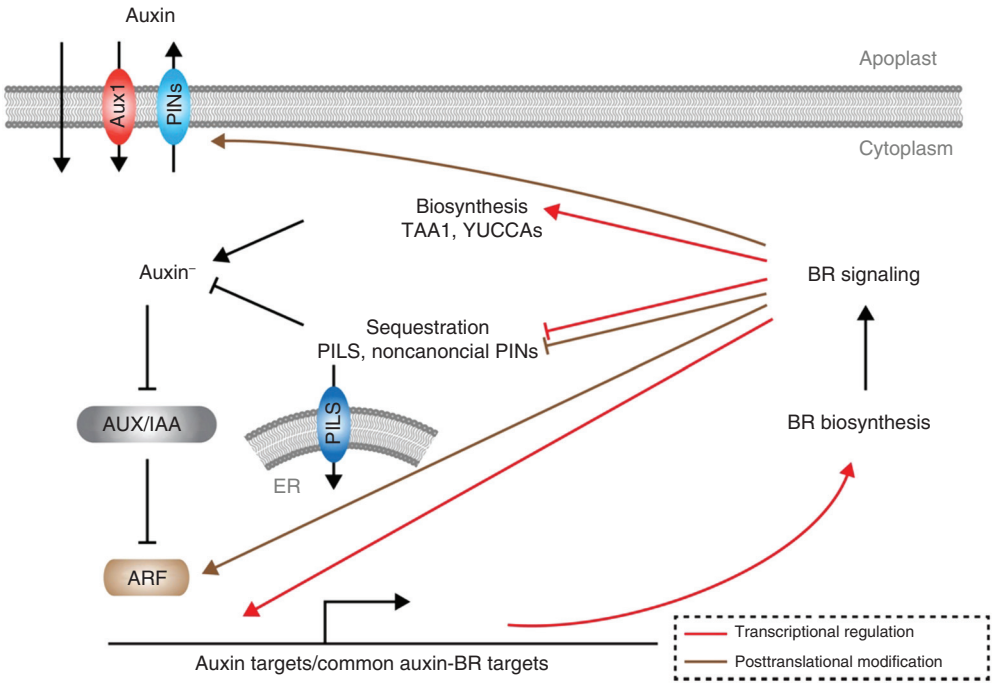

Figure 1. Regulatory network connecting auxin and brassinosteroid signaling. (ER) Endoplasmic reticulum, (BR) brassinosteroid.

genes are part of an intricate regulatory network and linked to developmental programs; however, most of the underlying mechanistic details still remain to be elucidated. Two examples of transcriptional control of *AUX1/LAX* genes show the prominent connection to hormone signaling: CK treatment promotes the binding of B-type ARR 1 and 12 TFs to the promoter of *LAX2* and causes QC cell division (Zhang et al. 2013). Once again highlighting the significance of feedback regulation in the auxin network, *LAX3* expression has shown to be activated by direct promoter binding of the nuclear auxin signaling module ARF7-LBD29 (Porco et al. 2016).

Once inside the cell, auxin is largely present as ionic IAA^- and therefore cannot exit the cell by diffusion. Hence, directional transport of auxin depends on two classes of auxin efflux carrier proteins, namely, the ATP-binding cassette of the B subfamily (ABCB) (Geisler et al. 2017) and PIN-FORMED (PIN) families (Okada et al. 1991; Gälweiler et al. 1998; Wisniewska et al. 2006; Adamowski and Friml 2015). A third class of transporters, PIN-like proteins (PILS) (Barbez et al. 2012), together with noncanonical PIN proteins (Bennett et al. 2014), regulate the intracellular auxin homeostasis by importing the hormone to the endoplasmic reticulum (ER). Since auxin mostly acts in the nucleus, this mechanism helps to create local response minima by exploiting the ER as auxin sink (Mravec et al. 2009; Barbez et al. 2012; Béziat et al. 2017; Feraru et al. 2019; Sun et al. 2020).

As the dominant directional auxin efflux carriers, PIN protein families are polarly localized at the PM and PIN localization predicts auxin flux direction (Petrášek et al. 2006; Vanneste and Friml 2009). Analysis of expression patterns and mutant phenotypes of *PIN* genes demonstrated that PINs are the major determinants of local auxin accumulation (Vieten et al. 2007). Polar localization of PINs on the PM is dependent on controlled exo- and endocytosis (Geldner et al. 2001; Paciorek et al. 2005; Kleine-Vehn et al. 2011) and posttranslational modi-

fication represents a major regulatory step in this context (Friml et al. 2004; Abas et al. 2006; Michniewicz et al. 2007; Kleine-Vehn et al. 2009; Leitner et al. 2012; Marhavý et al. 2014; Zourelidou et al. 2014; Weller et al. 2017; Grones et al. 2018; Marhava et al. 2018; Hajný et al. 2020).

Directional auxin transport represents an important module for the spatiotemporal regulation of cell behavior. Using this module, auxin feedbacks are integrated with developmental and environmental signals. For example, *PIN* gene expression and subsequent subcellular transport protein polarization is enhanced by auxin, which generates a powerful positive feedback loop that plays important roles in many developmental processes, such as phyllotaxis (Bhatia et al. 2016), leaf serrations (Bilsborough et al. 2011), canalization (Sauer et al. 2006; Hajný et al. 2020), lateral root initiation (Chen et al. 2015; Wang et al. 2015), and meristem maintenance (Krogan et al. 2016). This mechanism is based on the transcriptional activation of auxin pathway genes, including *PINs* (Paponov et al. 2008), which is dependent on auxin nuclear signaling and auxin concentration (Vieten et al. 2005). At the molecular level, ARFs can bind to the promoters of *PIN* genes in a variety of tissues (Chen et al. 2015; Krogan et al. 2016; Simonini et al. 2017) and are responsible for the reinforcement of auxin signaling and auxin transport (Sauer et al. 2006; Bilsborough et al. 2011; Chen et al. 2015; Bhatia et al. 2016; Krogan et al. 2016; Weijers 2016). For example, a small number of MP/ARF5-positive cells at the periphery of the shoot apical meristem (SAM) promote polarization of PIN1 protein in neighboring cells toward the MP/ARF5-expressing cells, thereby further enhancing auxin influx into the founder cells, which eventually will give rise to a new organ primordium (Bhatia et al. 2016). Similarly, during the early steps of early lateral root formation, ARF7 activates *PIN3* expression via direct binding to its promoter. Interestingly, ARF7 also activates expression of the MYB TF FOUR LIPS (FLP), which further enhances *PIN3* expression. This feedforward regulation helps sustain *PIN3* expression and likely makes the system more robust against initial auxin fluctuations (Chen et al. 2015). Another prominent example is the *Arabidopsis* fruit, where highly specific auxin accumulation patterns are achieved by intricate spatiotemporal control of *PIN* gene activity and PIN protein localization. First, auxin signaling output is switched from a bilateral to a radial pattern by the direct promotion of *PIN1* and *PIN3* expression through bHLH TFs of the HECATE clade, which likely act together with the SPATULA (SPT) bHLH factor (Schuster et al. 2015). Importantly, at the fruit tip, auxin transporters need to switch to an apolar localization to allow for accumulation of auxin in these cells and this transition is dependent on transcriptional repression of *PINOID* (*PID*) by the INDIHISCENT (IND)/SPT module (Moubayidin and Østergaard 2014). A similar process is required to pattern the valve margins to support seed dispersal. Here, *IND* directly represses *PID* and activates the related *WAG2* kinase to promote PIN3 delocalization, leading to a local minimum of auxin accumulation, which in turn is the signal for valve margin development (Sorefan et al. 2009). Another important example is the differential deployment of the auxin-PIN1-CUC2 module during leaf development in *Arabidopsis thaliana* and *Cardamine hirsuta*, which provides the substrate for leaf shape variations during evolution (Kierzkowski et al. 2019).

Several other hormone pathways are integrated with auxin signaling at the level of the auxin transport machinery. For example, numerous studies have shown that CK signaling can interfere with polar auxin transport through direct transcriptional control of *PINs* (Pernisová et al. 2009; Ruzicka et al. 2009; Bishopp et al. 2011a,b; Xie et al. 2018), which has in some cases been shown to be mediated directly through B-ARR TFs. In addition, CK has been shown to interfere with auxin signaling–mediated reinforcement of *PIN* expression through modulating the expression of *SHY2*/*IAA3* (Dello Ioio et al. 2008). CK signaling can also influence PIN activity through posttranslational regulation (Marhavý et al. 2011, 2014; Zhang et al. 2011; Waldie and Leyser 2018), for example, by triggering depletion of PINs from specific polar membrane domains, thus enhancing polarity (Marhavý et al. 2011, 2014). A particularly in-

triguing example is on display during lateral root formation. Auxin signaling is involved in all stages of lateral root development, which is initiated by a local auxin response maximum in xylem pole pericycle cells near the root tip (Fukaki et al. 2002, 2005; Wilmoth et al. 2005; De Smet et al. 2007, 2010; Dubrovsky et al. 2008; Moreno-Risueno et al. 2010; Xuan et al. 2016). During further steps, auxin flux continues to be regulated in a complex and dynamic manner. For example, auxin itself induces expression of the auxin influx carriers *AUX1* and *LAX3* in the cells overlaying lateral root primordia. This, in turn, leads to auxin-mediated expression of cell wall remodeling enzymes, which helps to separate cells in the tissues that have to be crossed by the lateral root before emergence (Swarup et al. 2008). CK, on the other hand, negatively affects lateral root initiation and regulates expression and polarity of PIN proteins (Laplaze et al. 2007; Ruzicka et al. 2009; Marhavý et al. 2011, 2014; Bielach et al. 2012). Interestingly, CK produced in and around lateral root primordia forms an inhibitory field preventing the formation of further primordia and thus is important for the regulation of lateral root spacing (Chang et al. 2015). Besides CK, BRs (Retzer et al. 2019), strigolactones (Crawford et al. 2010; Shinohara et al. 2013), gibberellic acid (Willige et al. 2011; Löfke et al. 2013), and other phytohormones significantly influence polar auxin transport (reviewed in Semeradova et al. 2020).

CONTROL OF AUXIN SIGNALING

While the core auxin signaling system is simple and only consists of three basic modules, namely, receptor, inhibitor, and transcriptional output regulator, these elements have been multiplied by gene duplication events and co-opted in a multitude of regulatory programs. In *Arabidopsis*, there are six TIR1/AFB-like receptors, 29 Aux/IAA signaling inhibitors, and 23 ARF transcriptional regulators providing an extensive network for functional specification. Supporting the idea that diverse combinations of signaling components will result in context-dependent outputs, all members of the system display highly specific spatiotemporal expression patterns (Rademacher et al. 2011; Vernoux et al. 2011; Weijers and Wagner 2016; Kato et al. 2020). Recently, it was shown that activator *ARF* expression patterns are driven by a combination of constitutively open chromatin at their loci and the interaction of specific transcriptional repressors with the regulatory regions of individual ARF-encoding genes (Truskina et al. 2021). Importantly, because many WRKY regulators were found among the repressors, these findings suggest strong connectivity of activator ARFs to transcriptional inputs relaying environmental information. In addition, key components of developmental circuits, such as WUS, CUC2, and KNAT1, were found to bind to *ARF* promoters, supporting the view that ARFs may serve as central nodes integrating exogenous and endogenous signals.

Another important aspect is that many components, most prominently the Aux/IAA auxin-response inhibitors, are transcriptionally activated by auxin (Abel et al. 1995), providing a potent feedback regulation in the network. Importantly, these interactions are mediated by ARF binding to promoters of *Aux/IAA* genes, which therefore have served as models to elucidate auxin output regulation (Krogan et al. 2014). One prominent example for a developmentally controlled input is the posttranscriptional control of *ARF3* mRNA accumulation by *trans*-acting siRNAs (ta-siRNA). Here, several gene-regulatory layers are superimposed to result in spatiotemporal refinement of *ARF3* and *ARF4* activity. First, the *TAS3* mRNA is transcribed, which is then targeted by *miR390* for phased processing into ta-siRNAs, which in turn target *ARF3* and *ARF4* transcripts for degradation. This intricate regulatory regime is required for a number of developmental contexts, including leaf development, lateral root growth, or developmental timing (Allen et al. 2005; Adenot et al. 2006; Fahlgren et al. 2006; Garcia et al. 2006; Marin et al. 2010).

In addition to their specific expression patterns, auxin signaling components exhibit divergent biochemical functions, which greatly contribute to the complexity of the resulting regulatory network. Most notably, ARF TFs, re-

sponsible for the transcriptional output of the system, show considerable sequence divergence and can functionally be grouped in those that have the potential to activate transcription (activator ARFs) and those that do not (repressor ARFs) (Mutte et al. 2018). The sequence divergence has also brought about specific DNA-binding behaviors and preferences for orientation and spacing of DNA-binding motifs, which together specify ARF-dependent gene regulatory output (Boer et al. 2014; Freire-Rios et al. 2020; Lanctot and Nemhauser 2020).

In addition to the transcriptional and biochemical level, specificity is also provided by the protein–protein interaction preferences between ARFs and Aux/IAAs, which in turn dictate the transcriptional output of the pathway (Vernoux et al. 2011; Weijers and Wagner 2016). As a rule of thumb, activator ARFs tend to show interactions with a large number of Aux/IAAs, whereas repressor ARFs do not (Vernoux et al. 2011). In addition to the complex dimerization patterns observed within the ARF-Aux/IAA universe, ARFs also directly interact with a number of other transcriptional regulators from diverse families, such as MYB, MADS-box, KANADI, RGA (GRAS), and bHLH (Shin et al. 2007; Varaud et al. 2011; Kelley et al. 2012; Smaczniak et al. 2012; Oh et al. 2014; José Ripoll et al. 2015). Importantly, MP interacts with the SWI/SNF chromatin-remodeling factors BRAHMA (BRM) and SPLAYED (SYD), which act to open chromatin at target loci. These positive regulators of gene expression compete with the binding of Aux/IAA proteins, which in turn interact with proteins of the TOPLESS family of transcriptional corepressors to repress target expression via histone deacetylation (Long et al. 2006; Szemenyei et al. 2008; Wu et al. 2015). Because auxin sensing triggers the degradation of Aux/IAAs, this represents a major switch for downstream gene activity. Another example for an inhibitory ARF interactor is the bHLH TF HECATE1, the activity of which seems to counteract the capacity of MP to drive auxin-dependent transcription in the periphery of the SAM (Gaillochet et al. 2017).

Recent studies have revealed that ARF6 forms a trimeric complex with PIF4 and the BR responsive TF BZR1 to integrate multiple cues into regulation of cell elongation. DNA binding of the three TFs to their common target loci is inhibited by DELLA proteins, thus GA signaling is required to release inhibition (Oh et al. 2014). BR and auxin signaling are connected at multiple levels in addition to convergence on target genes (Nemhauser et al. 2004). For example, auxin transcriptionally regulates BR biosynthesis and signaling (Chung et al. 2011; Yoshimitsu et al. 2011; Sakamoto et al. 2013; Zhang et al. 2015), whereas a BR input is wired into auxin signaling through interaction of the GSK3-like kinase BIN2, a BR signaling component, and ARFs (Fig. 1). BIN2 phosphorylates the (repressive) B-class ARF2, which decreases DNA binding of the TF, and thus enhances auxin response (Vert et al. 2008). BIN2 can also phosphorylate ARF7/19 to promote DNA binding by disturbing interaction with IAAs, thus enhancing auxin response. However, in this case, BIN2 does not seem to provide BR input but acts downstream of the signaling peptide TDIF (CLE41/44) and its receptor PXY (Cho et al. 2014).

It has recently emerged that posttranslational modification of ARFs seems to be a more general mechanism to mediate integration of inputs form other pathways. For example, ARF2 can also be phosphorylated in response to potassium stress (Zhao et al. 2016), whereas root branching toward water involves ARF7 SUMOylation. Here, SUMO negatively affects DNA binding activity and enhances interaction with IAA3, thus attenuating auxin signaling (Orosa-Puente et al. 2018).

CONTROL OF AUXIN OUTPUT

For auxin to be able to play so many divergent roles, the output of the signaling pathway needs to be tightly integrated with other regulatory programs. Importantly, since many activities are highly local, this also requires that the competence for specific auxin responses is limited to few cells by independent repression of downstream genes. Plant stem cell systems, or meristems, represent prominent examples for this scenario, since auxin plays essential, but highly specific roles in subsets of meristematic cells. In

the root meristem, auxin accumulates maximally in niche and stem cells and is required for the maintenance of both populations (Sabatini et al. 1999; Friml et al. 2002; Vanneste and Friml 2009); however, adjacent cells that are also exposed to high levels of auxin do not exhibit stem cell fate. In the shoot meristem, high auxin signaling output is excluded from niche and stem cells, but required for inducing differentiation in adjacent cells (Vernoux et al. 2011; Luo et al. 2018; Ma et al. 2019). And finally, auxin provides a locally restricted signal for the development of wood from the cambium, despite a substantially broader accumulation in this tissue (Brackmann et al. 2018). All of these cases have in common that auxin signaling interacts with regulatory modules controlled by WUSCHEL-RELATED HOMEOBOX (WOX) TFs. WUSCHEL (WUS) is a master regulator in shoot apical stem cells (Mayer et al. 1998; Leibfried et al. 2005; Busch et al. 2010; Yadav et al. 2013; Ma et al. 2019), whose family members play conserved functions in stem cell induction, organization, and maintenance, such as WOX5 in root QC cells (Sarkar et al. 2007), WOX4 in cambium stem cells (Brackmann et al. 2018), and root cambium organizer cells (Smetana et al. 2019), as well as other WOXs in embryonic stem cells (WOX2) (Zhang et al. 2017), leaf mediolateral axis cells (WOX1 and WOX3/PRS) (Nakata et al. 2012; Guan et al. 2017; Zhang et al. 2020), and de novo organogenesis (WOX11/12) (Liu et al. 2014). In the stem cambium, WOX4 promotes stem cell fate and is activated by ARF3/4, while it is repressed by ARF5/MP (Brackmann et al. 2018). These results showed that auxin not only is required to position the stem cells, but at the same time to define the fate of one of the derived cell lineages. In the SAM, auxin acts mainly as a local signal to trigger differentiation in the periphery; however, SAM treatments even with high doses and in the absence of auxin transport do not lead to stem cell termination (Reinhardt et al. 2003; Guenot et al. 2012). This robustness is conferred by the local activity of WUS in niche and stem cells by acting as a global repressor of auxin-dependent transcriptional activation (Ma et al. 2019). Interestingly, even in the shoot, stem cells require a basal level of auxin signaling, and it turns out that WUS acts as an auxin response rheostat via the promotion of histone deacetylation (Ma et al. 2019). The dependence of stem cells on low auxin signaling may be connected to the cross talk of auxin with CK (Fig. 2). In the SAM, auxin acts to repress the expression of type-A ARRs, negative feedback regulators of CK via direct binding of MP to ARR promoters, thereby synergizing with the activity of WUS (Leibfried et al. 2005; Zhao et al. 2010). Breaking this interaction may lead to reduced local CK signaling and hence a termination of the stem cell pool. Similarly, during embryonic stem cell initiation, WOX2 represses auxin signaling and in parallel activates CK, which shields the stem cells from differentiation (Zhang et al. 2017). Later, during the initiation of the root meristem, auxin induced expression of type-A ARRs, which in turn limits CK output in the hypophysis to the cells that will give rise to the QC (Müller and Sheen 2008). Along these lines, auxin signaling is required to restrict WOX5 expression to the QC of the mature root meristem, probably through microRNA *MIR169*-targeted ARF10 and ARF16 auxin-response factors (Ding and Friml 2010). Importantly, WOX5 expression and QC function depend on PLETHORA (PLT) proteins, AP2 TFs that play important roles in setting the balance between cell proliferation and differentiation in roots and shoots (Aida et al. 2004; Galinha et al. 2007; Cruz-Ramírez et al. 2013; Mähönen et al. 2014; Shimotohno et al. 2018). *PLT* expression, in turn, depends on auxin, and PLT proteins promote auxin biosynthesis and signaling, forming a positive feedback loop (Santuari et al. 2016). PLT proteins form a relatively stable and inert gradient that is generally aligned with the auxin-response gradient in the root meristem (Sabatini et al. 2003; Billou et al. 2005; Grieneisen et al. 2007), but uncouples developmental patterning from rapid auxin fluctuations (Mähönen et al. 2014), for example, those observed during growth adjustments and tropic responses (Shih et al. 2015; Fendrych et al. 2018; Harmer and Brooks 2018). This auxin-PLT module is antagonized by CK signaling to accomplish robust zonation of the longitudinal root meristem (Di Mambro et al. 2017; Salvi et al. 2020).

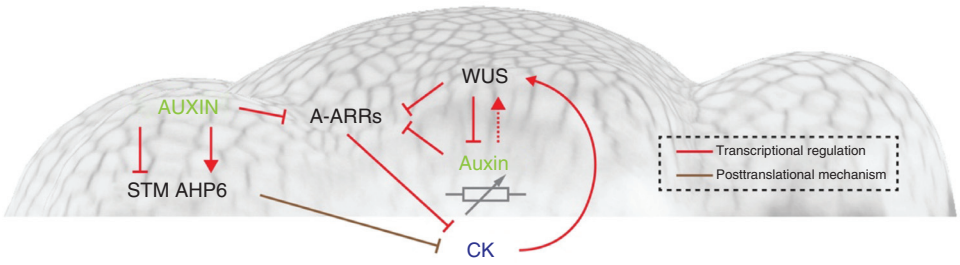

Figure 2. Regulatory network connecting auxin and cytokinin signaling in the shoot apical meristem (SAM). (CK) Cytokinin.

Several other regulators interact with auxin to coordinate developmental decisions. At the shoot apex, differentiation is repressed by the class I KNOX homeobox TF SHOOTMERISTEMLESS (STM), whose combined activity with WUS is required for stem cell fate (Lenhard et al. 2002). To allow differentiation at the periphery, STM expression is turned off in response to local PIN1-mediated auxin accumulation (Heisler et al. 2005) via histone deacetylation-mediated transcriptional silencing (Chung et al. 2019). This epigenetic reprogramming of the *STM* locus is achieved directly by ARF3/ARF4 and indirectly by MP through the intermediary regulator FILAMENTOUS FLOWER (FIL) (Chung et al. 2019). Interestingly, *STM* at the same time receives positive regulatory inputs by mechanical signals (Landrein et al. 2015), providing an important integration point, which likely serves to properly position organ primordia at the shoot apex. In parallel to this system, auxin signaling at the SAM interacts with an elaborate prepattern setup by the polarity factors KANADI (KAN) and REVOLUTA (REV), one of the HD-ZIP III TFs. While *REV* is expressed throughout a wide central domain, but excluded from the periphery due to the activity of the mobile miR165/166, KAN accumulation is restricted to the very periphery. Interestingly, both factors repress organ formation, directing maximal *PIN1* expression and auxin response to the boundary of their expression domains (Caggiano et al. 2017). This not only defines a competence zone for differentiation, but also prepatterns emerging organ primordia, because the cells in the specification field inherit the *REV*/*KAN* expression domains, which in turn will instruct dorsoventral patterning of leaves.

The developing vascular system of the root provides another great example for how auxin signaling is embedded into developmentally regulated transcriptional networks. In a first step, a local auxin maximum established by polar auxin transport confers provascular initial identity to some of the inner cells of the embryo at the early globular stage. MP plays a crucial role in the formation of vascular tissue and activates a suite of downstream TFs termed TARGET OF MONOPTEROS (TMO) (Hardtke and Berleth 1998; Schlereth et al. 2010). One of these, namely, the bHLH regulator TMO7, moves from the basal cell of the embryo proper to the topmost cell of the suspensor to trigger hypophysis development. In contrast, TMO5, another MP target in the embryo, acts cell-autonomously by dimerizing with LONESOME HIGHWAY, but holds the key to setting up the vascular CK signaling domain to promote periclinal cell divisions in both the embryo and the primary root (De Rybel et al. 2013, 2014; Ohashi-Ito et al. 2014). In xylem precursor cells, the TMO5/LHW complex promotes the expression of *LONELY GUY4* (*LOG4*) encoding for a rate-limiting enzyme in CK biosynthesis (De Rybel et al. 2014). Concomitantly, xylem precursor cells are desensitized against the CK they produce through auxin-induced expression of the CK signaling inhibitor AHP6 (Mähönen et al. 2006; Bishopp et al. 2011a; Ohashi-Ito et al. 2014). However, within the xylem axis, *AHP6* is only expressed in protoxylem precursor cells, due to the presence of auxin-induced HD-ZIP

III TFs in the central xylem cells (Carlsbecker et al. 2010; Bishopp et al. 2011a; Ursache et al. 2014). As these central cells are also largely insensitive toward CK, the existence of another, yet unidentified inhibitory factor besides AHP6 has been postulated. HD-ZIP III TFs also feed back on the auxin response as PHABULSOSA promotes the expression of both MP and the non-auxin-responsive *IAA20*, indicating an elaborate regulation of auxin signaling strength (Müller et al. 2016). Taken together, high auxin response in xylem precursor cells promotes the biosynthesis of CK and simultaneously cell autonomously interferes with CK signaling. Xylem precursor cell-derived CK thus acts non–cell autonomously in the adjacent procambial domain, where CK signaling promotes formative (periclinal) cell divisions (Mähönen et al. 2000, 2006). In addition, CK in the procambium, which is also derived from phloem transport cells, is required for the expression and subcellular localization of PIN proteins that direct auxin flow toward the xylem axis (Bishopp et al. 2011a,b). This intricate network is further stabilized by a group of DOF TFs called PEARs, which are induced in protophloem sieve-element precursor cells by CK. These factors move to neighboring procambial cells and promote cell division and in addition enhance HD-ZIP III expression, which in turn antagonize PEARs (Miyashima et al. 2019). Interestingly, the bilateral symmetry of the root vasculature, established through the mutually inhibitory interdigitation of auxin and CK signaling, also impacts on tissues outside of the stele (Andersen et al. 2018).

Later in development, during secondary root growth, MP and HD-ZIP III activities synergize to activate a canonical WOX organizer module, in this case built around WOX4. Importantly, vascular stem cell fate is induced non–cell autonomously in the procambial cell adjacent to the WOX4 expressing organizer cell, leading to a direct and indirect induction of xylem and phloem identity, respectively, via a common stem cell (Smetana et al. 2019). This elegant coupling of highly local auxin signaling, CK production, and mobile factors allow for a stepwise elaboration of a complex vascular system from a single inductive cell in the embryo.

Taken together, research in past decades has uncovered that the auxin signaling system is deeply embedded into a multitude of regulatory networks at all levels from biosynthesis to transcriptional output and from the organismal to the subcellular scale. This very embedding appears to be the mechanism allowing one small molecule to play so many and so different roles during plant life.

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