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Hormone Symphony During Root Growth and Development

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Hormones regulate plant growth and development in response to external environmental stimuli via complex signal transduction pathways, which in turn form complex networks of interaction. Several classes of hormones have been reported, and their activity depends on their biosynthesis, transport, conjugation, accumulation in the vacuole, and degradation. However, the activity of a given hormone is also dependent on its interaction with other hormones. Indeed, there is a complex crosstalk between hormones that regulates their biosynthesis, transport, and/or signaling functionality, although some hormones have overlapping or opposite functions. The plant root is a particularly useful system in which to study the complex role of plant hormones in the plastic control of plant development. Physiological, cellular, and molecular genetic approaches have been used to study the role of plant hormones in root meristem homeostasis. In this review, we discuss recent findings on the synthesis, signaling, transport of hormones and role during root development and examine the role of hormone crosstalk in maintaining homeostasis in the apical root meristem. *Developmental Dynamics 241:1867–1885, 2012.* © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Normal cell growth and morphogenesis result from the concerted modulation of cell proliferation and cell elongation, which in turn respond and feed back to a complex combination of environmental and endogenous stimuli. Hormones are key endogenous stimuli in plant development that affect plant growth in small concentrations. Thus far, eight different plant hormones have been identified and isolated: auxins, gibberellins, cytokinins, ethylene, abscisic acid, brassinosteroids, strigolactones, and jasmonic acid (Santner et al., 2009; Santner and Estelle, 2009; Wolters and Jurgens, 2009). Plant hormones are small, naturally occurring substances with very diverse chemical natures and structures. These compounds regulate plant growth and development in response to external environmental stimuli via complex signal transduction pathways, which in turn exhibit feedback regulation of networks controlling cell differentiation and proliferation (Santner et al., 2009; Santner and Estelle, 2009; Wolters and Jurgens, 2009; Depuydt and Hardtke, 2011).

The activity of a given hormone depends on its biosynthesis, transport, conjugation, accumulation in the vacuole, and degradation. All hormones regulate several processes independently, and recent studies indicate that there is a complex crosstalk between hormones that regulates their biosynthesis, transport, and/or signaling functionality, although some hormones have overlapping or opposite functions (Benková and Hejatko, 2009; Galinha et al., 2009; Santner et al., 2009; Santner and Estelle, 2009; Wolters and Jurgens, 2009).

The size of meristems results from the balance between cell proliferation

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Fig. 1. Longitudinal confocal section of Arabidopsis root tip showing two of the three root zones. The proliferation zone (MZ) includes the stem cell niche and the zone in which cells divide actively. The elongation zone (EZ) is the region in which cells stop dividing and elongate. When elongation terminates, the cells attain their final fates. E, epidermis; C, cortex; En, endodermis; St, stele; Col, columella.

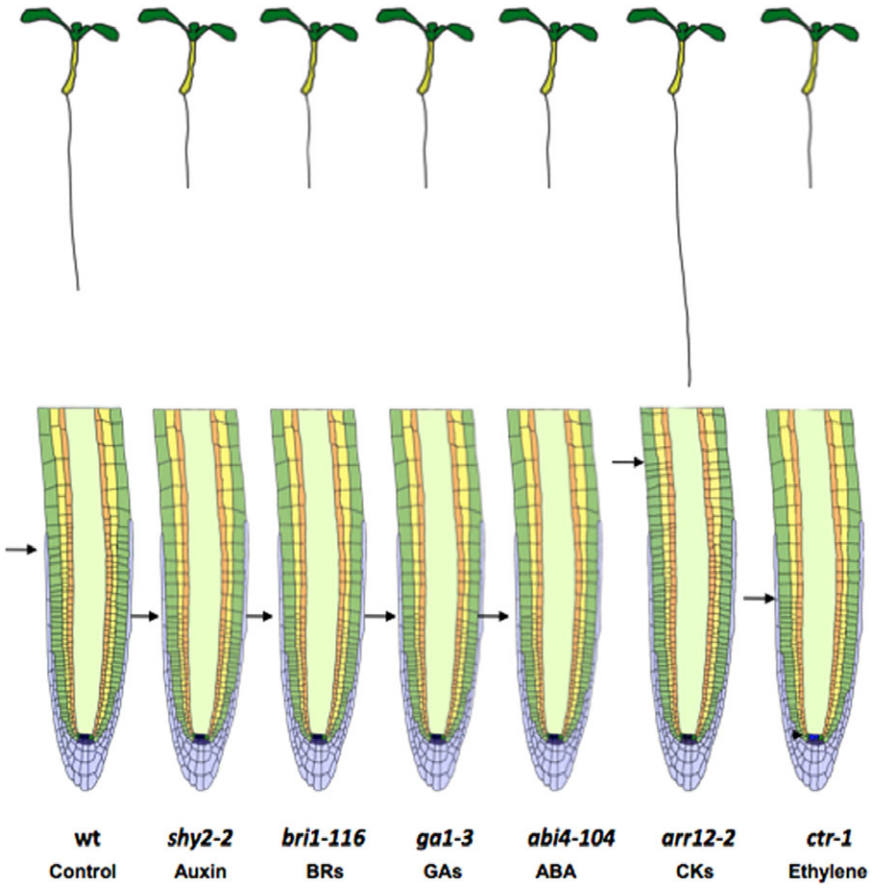

Fig. 2. Schematic representations of mutant root phenotypes for hormone pathways components. Loss- or gain-of-function mutants (top) and meristem sizes (bottom) are shown. The black arrows indicate the boundary between proliferation and elongation zones. Repression of auxin, Brassinosteroids (BRs), and Gibberelins (GAs) signaling causes short root phenotypes and a reduction in meristem size as observed in *shy2-2* gain-of-function and *bri1-116* loss-of-function mutants that repress auxin signaling (Dello Ioio et al., 2008b) and BR signaling (Gonzalez-Garcia et al., 2011), respectively; the same root growth phenotype is observed in *ga1-3* (GA) and *abi4-104* (Abscisic Acid; ABA) -deficient mutants (Achard et al., 2009; Cui et al., 2012). However, *arr12-2* loss-of-function mutants that repress Cytokinins (CKs) signaling have longer roots and meristems (Dello Ioio et al., 2007). The constitutive triple response *ctr-1* mutants exhibit enhanced ethylene signaling and short roots with smaller meristems as well as ectopic QC cell division (Ortega-Martinez et al., 2007; Negi et al., 2008; Thomann et al., 2009).

and differentiation rates. Meristem size regulation, which is clearly affected by plant hormones, is fundamental for normal development (Dharmasiri et al., 2005; Dello Ioio et al., 2007, 2008a; Benková and Hejatko, 2009; Galinha et al., 2009; Ubeda-Tomas et al., 2009). The root meristem is a particularly useful system in which to study such balance as the result, among others, of the complex role of plant hormones in the plastic control of plant development and physiology; both molecular genetic and cellular approaches have been used to study the role of plant hormones in root meristem homeostasis (Dharmasiri et al., 2005; Dello Ioio et al., 2007, 2008a; Benková and Hejatko, 2009; Galinha et al., 2009; Ubeda-Tomas et al., 2009). However, an integrated view of the independent and concerted action of all plant hormones in root meristem homeostasis has not been provided in previous reviews (Dello Ioio et al., 2007, 2008a; Benková and Hejatko, 2009; Galinha et al., 2009).

ROOT DEVELOPMENT

During embryogenesis, plant meristems are established and provide most of the post-embryonic cells that constitute the organs of plants throughout their life cycle. There are two main meristems: an aerial meristem at the growing tip of the shoot (shoot apical meristem; SAM) and an underground meristem at the root apex (root apical meristem; RAM). The *Arabidopsis thaliana* RAM contains a self-renewal stem-cell niche (SCN) with a central organizer termed the quiescent center (QC) because it comprises four cells with a very low division rate. The QC is surrounded by the stem (or initial) cells, which yield the cells of all the major tissues that compose the root. The initial cells divide asymmetrically with an intermediate proliferation rate. One of the daughter cells of each of the stem cells remains close to the QC and retains its stem cell identity,

TABLE 1. Summarized Characterization of Six Plant Hormones and Their Role During Root Development

HORMONE	Site of synthesis in the plant	Precursors	Conjugates (reversible storage)	Inactivation	Movement	Receptor and subcellular localization	Signal transduction components	DNA binding motif	Role in root development	Root mutant phenotype
AUXIN	In the shoot apical meristem and young leaves. In the roots along the meristem and, very importantly, in the QC.	Tryptophan and indole-3-glycerol phosphate.	Ester or amide linkages to sugars, amino acids, or peptides.	Oxindole-3-acetic acid.	Passive and active (influx carriers: AUX and LAX and efflux carriers: PIN and ABCB).	TIR-like and ABP1. Nuclear localization.	AUX/IAA and ARF.	5′-GTGCGC-3′	It has a central role in the establishment, organization and maintenance of the RAM, also affects root proliferation and elongation.	*shy2-2*, the triple mutant *tir1-1/afb2-1/afb3-1* and the quadruple *tir1-1/afb1-1/afb2-1/afb3-1* mutants have short roots.
CYTOKININ	Abundant in proliferating tissues, such as root and shoot apical meristems, young leaves, and immature seeds.	Adenine.	Cytokinins exist in plants not only as free bases but also in the form of nucleosides and nucleotides.	Depends on the activity of the CKX proteins.	Passive: tZ-type has been found on the xylem sap and iP-type in leaf exudates.	AHK2, AHK3 and AHK4. Plasma membrane localization.	AHP, A-ARR, B-ARR and CRF.	5′-(A/G)GGAT(T/C)-3′	Affects the rate of cell differentiation in the vascular tissues.	The triple mutant *ahk2/ahk3/ahk4* showed reduced root meristem. *ahk3* or (*ipt3/ipt5/ipt7*) have longer roots and meristems than *wt*.
GIBBERELLINS	In rapidly growing tissues such as the shoot and root tips, developing flowers and seeds.	Terpenoids.	GA-O-glucosyl ether or GA-glucosyl ester. There are many biosynthetic intermediates or catabolites.	2β-hydroxylation by GA 2-oxidases (GA2oxs).	Transport of intermediate pathway compounds between cells.	GID1a, GID1b and GID1c. Nuclear localization.	DELLA.	5′-TAACAAA/G-3′	Regulates root growth controlling cell proliferation and elongation (only in the endodermis).	Only one of the double mutant receptor combinations (*atgid1a/atgid1c*) shows a dwarf phenotype. *ga1-3* and *ga3ox1/ga3ox2* have smaller roots and root meristems.
BRASSINOSTEROIDS	In young aerial tissues, such as apical shoots, pollen and siliques.	Steroids.	Glycosylation and sterefication (myristate, palmitate and laurate).	25 and 26 hydroxylation.	Probably by short-distance that involves unknown carrier.	BRI1, BRL1 and BRL3. Plasma membrane localization.	BZR1 and BZR2/BES1.	5′-CGTG(T/C)G-3′ and 5′-CANNTG-3′	Affects root cell expansion and root cell division.	*bak1-1, dwf1-6, cbb3, bri1-116* mutants and *bak1-4/bkk1-1/serk1-8* triple mutant have short roots; *bri1-116* also has short meristems.
ETHYLENE	Leaves, roots, shoots and flowers.	Methionine.	N-malonyl-ACC.	Ethylene oxide.	Diffusion freely through membranes. The gas is distributed through intracellular spaces.	ETR1, ETR2, ERS1, ERS2, EIN4. Plasma membrane localization.	EIN2, EIN3.	5′-TAAGAGC CGCC-3′	Regulates root cell elongation and root hair differentiation. In the QC can promote cell division.	Mutants that increase the levels of ethylene as *ctr1-1* and *eto1-2* have short roots and QC ectopic cell division.
ABSCISIC ACID	In all tissues; in vascular parenchyma cells.	Zeaxanthin.	ABA-glucosyl esters (ABA-GE).	8′-OH-ABA.	Transported via xylem and phloem. Efflux by ABCG25 and iflux by ABCG40.	PYR and RCAR are soluble receptors.	ABI1 to ABI5 and ABFs.	ABREs (5′-ACGTGG/TC-3′) and CE1 (5′-CCACC-3′) or CE3 (5′-GCGTGTC-3′)	Regulates root elongation, quiescence and cell differentiation.	*abi4-104 mutant* has smaller roots. Several mutants are deficient in SCN differentiation such as *ba1-1, aba2-3, aba2-4, aba3-2, abi1-1, abi2-1, abi3-1 and abi5-5*.

whereas the other cell divides anticlinally, attains a maximum proliferation rate, and eventually elongates and differentiates into a specific root cell type (Dolan et al., 1993; van den Berg et al., 1995, 1997). After 4 to 6 division cycles in the meristematic or proliferation zone (MZ), the cells commence elongation and form the elongation zone (EZ) (V. Ivanov, personal communication; Bennett and Scheres, 2010). The cells then attain their ultimate fate in the differentiation zone (DZ). The Arabidopsis primary root has a simple radial structure of concentric cylinders of different cell types including (from outermost to innermost layer) a lateral root cap that extends as an outermost sheath of the root tip in the meristematic zone, epidermis, cortex, endodermis, and stele (pericycle and vasculature) (Dolan et al., 1993) (Fig. 1).

In this review, we examine recent findings on the synthesis, signaling, and transport of hormones that regulate homeostasis in the apical root meristem, and we review findings regarding the transcriptional activation of major genes involved in hormone pathways during root meristem development.

AUXIN

Auxin is involved at nearly all stages of plant growth and development in all organs (reviewed in (Woodward and Bartel, 2005; Benková and Hejatko, 2009; Galinha et al., 2009; Santner et al., 2009; Santner and Estelle, 2009; Wolters and Jurgens, 2009).

The most bioactive form of auxin in plants is indole-3-acetic acid (IAA), which is synthesized in Arabidopsis by tryptophan-dependent (TAM and IAN) and tryptophan-independent pathways (reviewed in Woodward and Bartel, 2005). Similar to most hormones, auxin can form inactive conjugates (Table 1) that may function in the storage of IAA, as intermediates in degradative processes or as protection against oxidative degradation; indeed, once IAA is oxidized to oxindole-3-acetic acid (OxIAA), it is broken down irreversibly (Ostin et al., 1998).

Auxin is mainly synthesized in young leaves and in the SAM, and it is transported to the root via the phloem (Ljung et al., 2001). However, recent studies have demonstrated that it is also synthesized in the root, and such synthesis is indispensable for maintaining the observed patterns of auxin gradients in the root meristem (Ljung et al., 2005; Ikeda et al., 2009; Petersson et al., 2009).

Auxin perception in plant cells begins when auxin binds to one of its multiple nuclear receptors including TRANSPORT INHIBITOR RESPONSE 1 (TIR1; Dharmasiri et al., 2005; Kepinski and Leyser, 2005), the TIR1-like proteins AUXIN SIGNALING F-BOX PROTEIN 1 to 5 (AFB1-AFB5; Dharmasiri et al., 2005; Parry et al., 2009), and the AUXIN BINDING PROTEIN (ABP1; Hertel et al., 1972; Jones, 1998). TIR1 and AFB1-AFB5 are F-box subunits of the ubiquitin ligase complex SCF^{TIR1}. Interaction with auxin does not appear to induce a conformational change in the complex; however, it does appear to stabilize the affinity of the receptors for AUX/IAA proteins, which are transcriptional repressors of *AUXIN RESPONSE FACTOR* (*ARF*) transcription factors. When AUX/IAA proteins interact with auxin receptors, the AUX/IAA proteins become ubiquitinated and targeted for degradation by the proteosome. This degradation effectively releases ARF proteins, which form dimers and regulate their target genes (reviewed in Calderon Villalobos et al., 2012). ARF family members bind to a sequence within the regulatory regions of target genes known as the AUXIN RESPONSE ELEMENT (ARE; 5′-TGTCTC-3′).

Auxin moves within Arabidopsis using two types of transport mechanisms. One of these mechanisms functions over long distances (termed long-range transport), is dependent on the phloem, and moves auxin mainly from the aerial part of the plant to the root. The other mechanism functions over short distances and is responsible for transport through plasma membranes via import-export mechanisms such as membrane diffusion, secretion, and receptor- or transporter-mediated systems (reviewed in Paponov et al., 2005; Petrásek and Friml, 2009; Vanneste and Friml, 2009). This cell-to-cell transport system complements vasculature translocation and is used mainly to load and unload substances from the phloem and to distribute short-range signals within tissues (Swarup et al., 2001; Marchant et al., 2002). When this short-range transport involves influx and efflux carriers that are distributed asymmetrically in the plasma membrane, it is referred to as polar auxin transport (PAT) and gives directionality to auxin distribution. PAT is dependent on influx carriers such as *AUXIN RESISTANCE 1* (*AUX1*) and *LIKE AUX* (*LAX*) family members as well as efflux transporters such as *PIN FORMED* (*PIN*) and *ATP-BINDING CASSETTE GROUP B* (*ABCB*/*MDRPGP*) family members (Bennett et al., 1996; Galweiler et al., 1998; Luschnig et al., 1998; Noh et al., 2001; Friml et al., 2002, 2003; Swarup et al., 2008; Verrier et al., 2008; Mravec et al., 2009).

PIN proteins mainly control the direction of auxin flux and the PIN family in Arabidopsis consists of eight members (Vieten et al., 2007; Zazímalová et al., 2007). The PIN proteins have a polar distribution in cell membranes, which causes a directed flux of auxin from one cell to another (Petrásek et al., 2006; Wisniewska et al., 2006; Mravec et al., 2008). Newly synthesized PIN proteins pass through the cell endomembrane system and are targeted to the apical, basal, or lateral plasma membrane (Feraru and Friml, 2008; Grunewald and Friml, 2010). Additionally, these proteins are continuously internalized by endocytosis from the plasma membrane and participate in constant cycles of endocytosis and exocytosis (Geldner et al., 2001; Marhavy et al., 2011).

AUXIN AND ROOT DEVELOPMENT

Auxin concentration varies among different plant tissues and organs, and such graded distribution is correlated with different cellular behaviors (Sabatini et al., 1999; Friml et al., 2002; Benková et al., 2003). In the root, graded auxin distribution is clearly associated with patterns of cell proliferation and elongation observed

along the apical-basal axis. High levels of auxin are found in the QC where there is little mitotic activity, intermediate auxin levels promote an intermediate level of mitotic activity in stem cells. Whereas in meristematic zone lower auxin levels are correlated with rapid cell proliferation, and the lowest levels of auxin are correlated with proliferation arrest and cell elongation/differentiation (Grieneisen et al., 2007). The *PLETHORA* (*PLT*) genes, which encode transcriptional regulators, have been postulated to be key components of the read-out mechanisms of auxin gradients. Indeed, the *PLT* genes that respond to auxin are also expressed along the RAM in a graded manner that resembles that of auxin (Aida et al., 2004; Galinha et al., 2007). Importantly, *PLT* genes, in conjunction with *SCARECROW* (*SCR*) and *SHORTROOT* (*SHR*) genes, are a fundamental part of the network that specifies the SCN (Helariutta et al., 2000; Sabatini et al., 2003; Azpeitia and Alvarez-Buylla, 2012; Aida et al., 2004). Auxin also regulates *WUSCHEL-RELATED HOMEOBOX 5* (*WOX5*), which is expressed in the QC and is necessary for maintaining the stem cells of the columella in an undifferentiated state (Ding and Friml, 2010; Sarkar et al., 2007).

The graded distribution of auxin along the root depends largely on the polar localization of its PIN transporters. At least five PIN proteins localize to the plasma membrane and create a "reflux" loop that controls auxin distribution in the growing root meristem (Blilou et al., 2005; Vieten et al., 2005). The PIN transporters appear to be functionally redundant, and only their multiple mutants show severe growth and differentiation defects (Blilou et al., 2005). These proteins localize to different areas of the root (Vieten et al., 2005) where they control the flux of recirculating auxin in the root meristem and could operate partially independently of auxin coming from the shoot (Blilou et al., 2005; Ljung et al., 2005; Vieten et al., 2005). The acropetal auxin flow in the stele toward the root tip seems to be maintained by PIN1, PIN3, PIN4, and PIN7; PIN4 then distributes this auxin to the columella where PIN3 and PIN7 redistribute it laterally to the lateral root cap and epidermis. PIN2, with the assistance of AUX1 and ABCB4, mediates basipetal auxin transport toward the elongation zone, whereas PIN1, PIN3, PIN4, and PIN7 recycle some auxin from the epidermis back to the vasculature. PIN2 transports auxin acropetally through the cortex cells (Blilou et al., 2005; Vieten et al., 2005). It has been shown that the modulation of PIN activity can independently affect meristem size, elongation rate, and final cell size (Blilou et al., 2005; Vieten et al., 2005).

Auxin also has a central role in the establishment, organization, and maintenance of the RAM (Reed et al., 1998; Sabatini et al., 1999; Benjamins et al., 2001; Friml et al., 2002; Lewis et al., 2007; Benjamins and Scheres, 2008). Mutants with defects in auxin activity fail to initiate roots and exhibit premature arrest of the root meristem and root stem cell function (Hardtke and Berleth, 1998). Exogenously applied auxin may have positive or negative effects on root growth depending on the concentration; the application of 0.1 nM IAA to wild-type Arabidopsis roots causes an increase in both meristem size (Dello Ioio et al., 2007) and root growth via modulation of the cellular response to gibberellins (see Root Cell Proliferation section in this review; Fu and Harberd, 2003).

In addition to its role in cell proliferation, auxin controls the transition from cell proliferation to cell differentiation in the root meristem via inhibition of the endoreduplication cycle (Ishida et al., 2010). Moreover, auxin also inhibits root cell elongation in non-stem cells at a concentration of 10^{-6} M, whereas at lower concentrations (10^{-10} M), root cell elongation is maintained (Evans et al., 1994).

When auxin transport is blocked, root regeneration (Sena et al., 2009) and lateral root formation are inhibited, root hair initiation and elongation are decreased (Quint et al., 2009), and the production of ectopic QC and stem cells is induced (Sabatini et al., 1999). Moreover, the triple *tir1-1/afb2-1/afb3-1* and quadruple *tir1-1/afb1-1/afb2-1/afb3-1* auxin receptor mutants exhibit various root phenotypes, with some plants displaying shortened roots whereas others entirely lack roots (Dharmasiri et al., 2005).

CYTOKININS

Cytokinins (CKs) play roles in many aspects of plant growth and development including apical dominance, the repression of leaf senescence, root cell differentiation, vascular tissue development, pathogen responses, nutrient mobilization, seed germination, and SAM maintenance (reviewed in Klee and Lanahan, 1995; Kieber, 2002). Many of these processes are controlled in coordination with other hormones, particularly auxin. Although CKs regulate many processes, they mainly function to control proliferation in the shoot and differentiation in the root (Ferreira and Kieber, 2005; Dello Ioio et al., 2007, 2008b; Kyozuka, 2007).

CKs are adenine derivatives that are abundant in proliferating tissues such as shoot apical meristems, young leaves, and immature seeds. Interestingly, one of the major regions in which cytokinin biosynthesis occurs is the columella of the root tip (reviewed in Aloni et al., 2004). CKs can act within the region where they are synthesized or they can move, e.g., from the root tip to the aerial tissues of the plant via the xylem (Takei et al., 2004; Hirose et al., 2008).

The synthesis of CK is initiated in a rate-limiting step catalyzed by *ATP/ADP-ISOPENTYL-TRANSFERASE* (*IPT*; Miyawaki et al., 2004; Takei et al., 2004), which transfers an isopentenyl group to an adenine nucleotide (iP nucleotide). In Arabidopsis, iP nucleotides are converted to tZ nucleotides by the cytochrome P450 monooxygenases CYP735A1 and CYP735A2 (Takei et al., 2004; Hirose et al., 2008). Inactive CK nucleotides such as iPRMP and tZRMP can be activated by *LONELY GUY* (*LOG*) proteins that directly convert these compounds to the bioactive freebase (Kyozuka, 2007), whereas most metabolic CK inactivation depends on the activity of the CYTOKININ OXIDASE/DEHYDROGENASE (CKX) protein family (Werner et al., 2001, 2003). All these genes and proteins are regulated differently, which suggests that they play important roles in coordinating cytokinins both spatially and

temporally during growth and development (Werner et al., 2003; Hirose et al., 2008; Frebort et al., 2011).

CKs are classified into 4 groups (isopentenyladenine (iP)-type, trans-zeatin-type (tZ-type), cis-zeatin-type, and aromatic cytokinins) according to the structure of their side chain. Although only the iP-type cytokinin (N^6-(Δ2-isopentenyl) adenine and its hydroxylated derivative trans-zeatin (tZ) are active in Arabidopsis, a variety of conjugates may form, which allows the plant to fine-tune the level of active hormone (Matsumoto-Kitano et al., 2008).

CKs are transported through the vasculature in a compartmentalized way; the tZ-type has been observed in the xylem sap and the iP-type was found in leaf exudates (Hirose et al., 2007; Matsumoto-Kitano et al., 2008). Thus far, no differences in the physiological roles of these two types of CKs have been observed; however, the translocation of cytokinins is apparently mediated by subsets of purine permeases and nucleoside transporters (Gillissen et al., 2000; Burkle et al., 2003; Hirose et al., 2005).

In Arabidopsis, CKs are perceived by a two-component system that involves a histidine kinase receptor located in the plasma membrane that induces a phosphorylation cascade and subsequently activates transcription factors in the nucleus (Muller and Sheen, 2007). Three independent histidine kinase receptors (*AHK2, AHK3*, and *CRE1*/*WOL*/*AHK4*) bind to cytokinin, autophosphorylate, and subsequently transfer the phosphoryl group to a histidine phosphotransfer protein that translocates to the nucleus and phosphorylates ARABIDOPSIS RESPONSE REGULATORS (ARR). Type-B ARRs are positive regulators that initiate the transcription of CK-responsive genes; among the targets of type *B-ARR* genes are a group of negative regulators termed type-A *ARRs* (To et al., 2004). Type-A ARRs are repressors that lack a DNA-binding domain and predominantly localize to the nucleus; there, it is likely that they act in conjunction with other transcription factors to regulate genes (Argueso et al., 2010). Certain members of the AP2 family of transcription factors, renamed CYTOKININ RESPONSE FACTORS (CRFs), are upregulated by cytokinin through the two-component system pathway. CRFs are also activated by AHPs, and it was proposed that they mediate cytokinin-regulated gene expression in tandem with B-type ARRs (Rashotte et al., 2006). B-ARR proteins bind to a core sequence within the regulatory regions of their target genes (5′-(G/A)GGAT(T/C)-3′).

THE ROLE OF CYTOKININS IN ROOT MERISTEM DEVELOPMENT

CKs negatively regulate the size of the RAM and primarily affect the meristematic cell differentiation rate. Exogenously applied cytokinin reduces the root meristem size (Dello Ioio et al., 2007), and CK-deficient mutants (e.g., *arr12-2* or the biosynthetic triple mutant *ipt3*/*ipt5*/*ipt7*; see Fig. 2) as well as plants overexpressing CKX display longer roots with longer meristems (Werner et al., 2003). The application of cytokinins does not appear to alter SCN activity or meristematic cell proliferation in the root; CKs affect the cell differentiation rate only when applied to the vascular tissue at the MZ/EZ transition zone in the presence of auxin (Dello Ioio et al., 2007). Furthermore, using mutant analysis, it was shown that only the AHK3 receptor and the ARR1 and ARR12 transcription factors mediated this effect (Dello Ioio et al., 2007, 2008b). It is important to emphasize that root meristem size and root growth are mediated mainly by the interplay between cytokinin and auxin (see Root Cell Proliferation and Root Cell Elongation sections in this review).

As expected, the over-expression of CKX in Arabidopsis induces many developmental changes in the root including a larger root meristem, a thicker columella cell layer, enhanced radial expansion with additional cell files, an enhanced vascular system, increased root branching, and additional adventitious roots (Schmülling et al., 2003). Interestingly, studies on CK receptor mutants revealed a positive role for CK in the root meristem: the triple receptor mutant (*ahk2*/*ahk3*/*ahk4*) exhibits a strong reduction in shoot and root growth (Nishimura et al., 2004). These results imply that the root response to CK is not linear; a small reduction in cytokinin levels or signaling increases root growth, but reduction beyond a threshold results in decreased growth.

GIBBERELLINS

Gibberellins (GAs) are important regulators of diverse aspects of plant growth and development including seed germination, stem and root elongation, leaf expansion, flower and seed development, and the size of the RAM. GAs promote cell division in the proliferation zone but have no effect on SCN activity (Taiz and Zeiger, 2006), and although they form a large family, only a small number of GAs are biologically active (e.g., GA_1, GA_3, GA_4, and GA_7, with GA_4 being the most active GA in Arabidopsis; reviewed in Hedden and Phillips, 2000). Consequently, many of the other GAs are biosynthetic intermediates or catabolites of bioactive GAs, and the final concentration of biologically active GAs depends on biosynthesis, catabolism and metabolic deactivation (reviewed in Yamaguchi, 2008).

GAs are synthesized and act mainly in rapidly growing tissues such as the shoot and root tips as well as developing flowers and seeds (Silverstone et al., 1997). GAs are biosynthesized from geranylgeranyl diphosphate (GGDP), a common C20 precursor of diterpenoids, and bioactive GAs in plants are synthesized by three different classes of enzymes: terpene synthases (TPSs), cytochrome P450 monooxygenases (P450s), and 2-oxoglutarate–dependent dioxygenases (2ODDs). GAs are deactivated in several different ways; the best characterized of these is 2β-hydroxylation catalyzed by a class of 2ODDs, the GA 2-oxidases (GA2oxs). However, other deactivation reactions have been reported including epoxidation in *Oryza sativa* and methylation in Arabidopsis (reviewed in Yamaguchi, 2008).

Another level of GA biosynthesis regulation in Arabidopsis might depend on (1) the subcellular compartmentalization of the pathway, which is similar to the biosynthesis of ent-kaurene in proplastids, the

conversion of ent-kaurene to GA_{12} in the endoplasmic reticulum, and other reactions that take place in the cytoplasm (Spray et al., 1996; Aach et al., 1997; Helliwell et al., 2001; Itoh et al., 2001; Nelson et al., 2004; Appleford et al., 2006) or (2) the physical separation of early and late GA biosynthetic steps in flowers, roots, and developing seeds, suggesting the transport of intermediate pathway compounds between cells (Yamaguchi et al., 2001; Kaneko et al., 2002, 2003; Mitchum et al., 2006). GAs influence their own metabolism via a feedback mechanism: GA downregulates the expression of enzymes that participate in its biosynthesis and upregulates enzymes that inactivate GAs (reviewed by Bethke and Jones, 1998; Williams et al., 1998; Hedden and Phillips, 2000). Some of the target genes of GA signaling have an element in their regulatory regions that is characterized as a GA-responsive element (GARE; 5′-TAACAAA/G-3′; see Table 1).

The soluble GA receptor was first discovered in rice and since then has been observed in many other plants including Arabidopsis, which has three redundant *GIBBERELIN INSENSITIVE DWARF1* (*GID1*) receptors termed *AtGID1a, AtGID1b*, and *AtGID1c* (Nakajima et al., 2006). Bioactive GA binds to the *GID1* receptor with high affinity, whereas inactive GAs exhibit low or nonexistent affinity for this receptor. This interaction allows for the destruction of DELLA proteins, which are repressors of transcription factors that mediate GA responses (Pysh et al., 1999; Chandler et al., 2002; Cao et al., 2005). The GA-GID-DELLA complexes are thought to perform two roles that are important for GA action. First, they induce a conformational change in DELLA that provokes its recognition and degradation through the $SCF^{GID2/SLY1}$ proteasome pathway (Fu et al., 2002; McGinnis et al., 2003; Sasaki et al., 2003). Second, they sequester DELLA proteins, thus reducing their ability to interact with growth-promoting transcription factors (Ueguchi-Tanaka et al., 2005; Nakajima et al., 2006). Because only double mutant plants (*atgid1a/atgid1c*) show a dwarf phenotype (Suzuki et al., 2009), there is some redundancy among the receptors.

Arabidopsis has five genes that encode DELLA proteins (GAI, RGA, RGL1, RGL2, and RGL3). These proteins are part of the GRAS protein family and may restrict the growth of organs and affect proliferation by upregulating the cell cycle inhibitors Kip-related protein 2 (KRP2) and SIAMESE (SIM). Additionally, they may alter the elongation rate of differentiated cells (Silverstone et al., 2001; Ubeda-Tomas et al., 2008; Achard et al., 2009).

GIBBERELLIN AND ROOT MERISTEM DEVELOPMENT

GA promotes root development and regulates root growth by controlling cell proliferation and elongation through the degradation of DELLA proteins (Fu and Harberd, 2003; Ubeda-Tomas et al., 2008, 2009; Achard et al., 2009). A reduction in the endogenous GA levels, either via genetic or chemical approaches, results in plants with shorter roots and smaller root meristems compared with wild type (Achard et al., 2009; Ubeda-Tomas et al., 2009). The *gai* mutant has a stabilized DELLA that cannot be marked for degradation, and affects cell elongation only when it is expressed in the RAM endodermis. However, the restriction of endodermal cell expansion affects the extension of all other cell files and thus affects total root growth (Ubeda-Tomas et al., 2008). Additionally, this mutant illustrates that bioactive GAs promote cell proliferation by affecting cell production rate and meristem size without interfering with SCN specification or activity (Ubeda-Tomas et al., 2009). Moreover, biosynthetic mutants of GA (*ga1-3* and *ga3ox1/ga3ox2*) have shorter roots and a smaller root meristem size compared with wild-type plants (Fig. 2; Ubeda-Tomas et al., 2009).

BRASSINOSTEROIDS

Brassinosteroids (BRs) are steroids that are essential for normal plant development and participate in the regulation of cell elongation, cell division, bending, reproductive and vascular development, photomorphogenesis, root development, and various stress responses (reviewed in Clouse and Sasse, 1998; Divi and Krishna, 2009). Over 70 types of BRs have been identified in plants, but Brassinolide (BL) has the highest biological activity among BRs (reviewed in Fujioka and Yokota, 2003; Bajguz, 2007). BRs also form conjugates with sugars and fatty acids (Bajguz and Tretyn, 2003); however, the relevance (biological or otherwise) of these conjugates remains unknown (see Table 1).

BRs are synthesized in the cytoplasm by the mevalonate and isoprenoid pathways and are used to generate cycloartenol, the primary precursor of plant sterols (reviewed in Clouse and Sasse, 1998; Divi and Krishna, 2009). Several genes have been implicated in BR biosynthesis including *DET2* (Fujioka et al., 1997, 2002), *DWFA, CPD* (Szekeres et al., 1996; Choe et al., 1998, 1999), and BR6ox (Shimada et al., 2001).

Information regarding the site of BR synthesis is limited. Nevertheless, based on expression analyses of genes involved in their synthesis and analyses of where they are accumulated, it has been suggested that BRs are most actively synthesized and likely used in young developing aerial tissues (e.g., apical shoots, pollen, and siliques) and roots. Interestingly, although BR synthesis is more active in root tissues compared with shoot tissues, the concentration of BRs is lower in roots, which likely occurs because BRs are catabolized more rapidly in the root than in the shoot (Friedrichsen et al., 2000; Bancos et al., 2002; Shimada et al., 2003).

BRs are detected by the membrane-bound receptor BRI1 (BRASSINOSTEROID INSENSITIVE 1), which is a member of the leucine-rich repeat receptor-like kinase (LRR-RLK) receptor family (Belkhadir and Chory, 2006; Shiu et al., 2004). There are three BRI1 homologs in Arabidopsis, and at least two of these (BRL1 and BRL3) bind to BRs and apparently mediate the cell-type-specific BR response in vascular tissues (Cano-Delgado et al., 2004). BRI1 homodimerizes, and it is not clear whether BRs stabilize BRI1 homodimers or cause a conformational change that favors homodimerization in a manner similar to auxin-induced TIR1-IAA protein dimerization (see Auxin section in this review; Kim and Wang,

2010). This homodimerization is not sufficient for the activation of BRI1, and the receptor must first associate with BRs and subsequently with co-receptors such as BAK1 (BRI1-Associated Receptor Kinase 1), SERK1, and BKK1 (Wang et al., 2008; Gou et al., 2012). When a BR binds to its receptor, BRI1 autophosphorylation is induced, BKI1 (BRI1 KINASE INHIBITOR 1) dissociates, and BRI1 associates with BAK1 (Wang and Chory, 2006; Wang et al., 2008). Both BRI1 and BAK1 are serine/threonine and tyrosine kinases, and their association increases their level of autophosphorylation and sequential trans-phosphorylation (Oh et al., 2009a,b, 2010, 2012; Jaillais et al., 2011). The BRI1-BAK1 phosphorylation cascade triggers a downstream signaling cascade that activates BZR1 and BZR2/BES1, two transcription factors that regulate the expression of hundreds of genes. BZR1 is a transcriptional repressor that is able to recognize the BR-response element (BRRE; CGTG(T/C)G), whereas BZR2/BES1-BIM is a transcriptional activator that is able to bind to the E-box element (CANNTG) of a BR-inducible promoter (Wang et al., 2002; He et al., 2005; Yin et al., 2005; Sun et al., 2010). Recent reports indicate that both BZR1 and BZR2/BES1-BIM can bind to BR-repressible and BR-inducible genes. Nevertheless, BRRE and E-box (CACGTG) sequences are highly enriched in BR-repressible genes, whereas the CATGTG motif is highly enriched in BR-inducible genes (Sun et al., 2010).

Another important protein involved in the BR signal transduction pathway is BIN2 (BRASSINOSTEROID INSENSITIVE 2; Kim and Wang, 2010). In the absence of BRs, this GSK3-like kinase phosphorylates and inactivates BZR2/BES1 and BZR1 via several mechanisms that include protein degradation and reduced DNA binding (He et al., 2002; Li et al., 2002; Peng et al., 2008). In the presence of BRs, the activated BRI1-BAK1 complex initiates a signal cascade that blocks the activity of BIN2. Recent studies suggest that BIN2 is also targeted for protein degradation in response to BR signaling through the protein phosphatase BSU1 (BRI1 SUPPRESSOR 1; Kim and Wang, 2010).

BRASSINOSTEROIDS AND ROOT MERISTEM DEVELOPMENT

The expression of genes involved in BR biosynthesis and the detection of BRs in root tissues (Friedrichsen et al., 2000; Bancos et al., 2002; Shimada et al., 2003) suggest that BRs play an important role in roots. In fact, BRs promote root growth as indicated by studies of BR-related mutants (e.g., *dwf1-6, cbb3, bri1-116*, and the *bak1-4/bkk1-1/serk1-8* triple mutant) that exhibit a short root phenotype (Li et al., 2002; Mussig et al., 2003; Mouchel et al., 2006; Hacham et al., 2011; Du et al., 2012) and the exogenous application of BRs at low concentrations that promotes root growth. However, as is the case for all hormones, high concentrations inhibit root growth (Mussig et al., 2003). Root growth inhibition in mutants with low levels of BRs (*bri1* mutants) revealed that BRs are required for the promotion of cell expansion and cell division in meristematic root cells (Fig. 2; Gonzalez-Garcia et al., 2011; Hacham et al., 2011). In this case, the size of the root meristem is controlled by BRI1 activation in epidermal cells (Fig. 3), where this gene induces signals that allow for communication with the inner cells. In turn, these signals may be controlled through BES1 and BZR1 (Hacham et al., 2011). The role of BRs in root growth has been further demonstrated by the short root phenotype of the *bak1-4/bkk1-1/serk1-8* triple mutant, in which BR signal transduction is blocked (Du et al., 2012).

The function of BRs in stem cells remains unknown; however, several studies have recently indicated that BR signaling might enhance cell division and participate in gene expression in QC cells. The specific expression of BRI1 in the epidermis and its absence in other cell types (QC, endodermis and stele) non-autonomously activates the expression of *AGL42*, a member of the MADS box gene family (Hacham et al., 2011) with an unknown function that is mainly expressed in the root QC. Additionally, the *WUSCHEL-RELATED HOMEOBOX 5* (*WOX5*), *SCR*, and *SHR* transcription factors, which are required for the maintenance of root stem cells, are also upregulated by BRs and downregulated in the absence of BR signaling (Gonzalez-Garcia et al., 2011; Du et al., 2012), although it is unclear whether these genes are direct targets of this hormone. The mechanism by which BRs are able to regulate various processes during root development is thus far largely unknown.

ETHYLENE

Ethylene is a volatile compound that is soluble in both aqueous and lipid environments and plays roles in the regulation of seed germination, cell elongation, fruit ripening, leaf senescence, resistance to pathogens, root and flower growth (Bleecker and Kende, 2000). Ethylene is synthesized in all plant organs, including leaves, roots, shoots, and flowers; however, the highest rates of ethylene synthesis are observed in meristematic, stressed, or ripening tissues (Lin et al., 2009).

S-adenosylmethionine (S-AdoMet) is a precursor in ethylene biosynthesis and is converted to ethylene by 1-CARBOXYLIC ACID (ACC) SYNTHASE (ACS) and ACC OXIDASE (Kende, 1993). In this pathway, the rate-limiting step is the conversion of S-AdoMet to ACC. In Arabidopsis, seven ACS genes have been characterized, and their transcription is differentially regulated during development and in response to stressful stimuli (Liang et al., 1992; Van der Straeten et al., 1992; Arteca and Arteca, 1999; Lin et al., 2009).

The ethylene signaling pathway is complex and not fully understood; however, mutants affected in the ethylene triple response (i.e., inhibition of elongation growth of dark-grown seedlings, induction of stem swelling, and the closure of the apical hook) have been isolated. Five putative endoplasmatic reticulum (ER) membrane-bound ethylene receptors, all of which are His-kinase two-component regulators, have been described: ETHYLENE RESPONSE1 (ETR1), ETR2, ETHYLENE RESPONSE SENSOR1 (ERS1), ERS2, and ETHYLENE INSENSITIVE4 (EIN4) (Hua et al., 1995, 1998; Bleecker et al., 1998; Sakai et al., 1998). In the absence of ethylene, CONSTITUTIVE

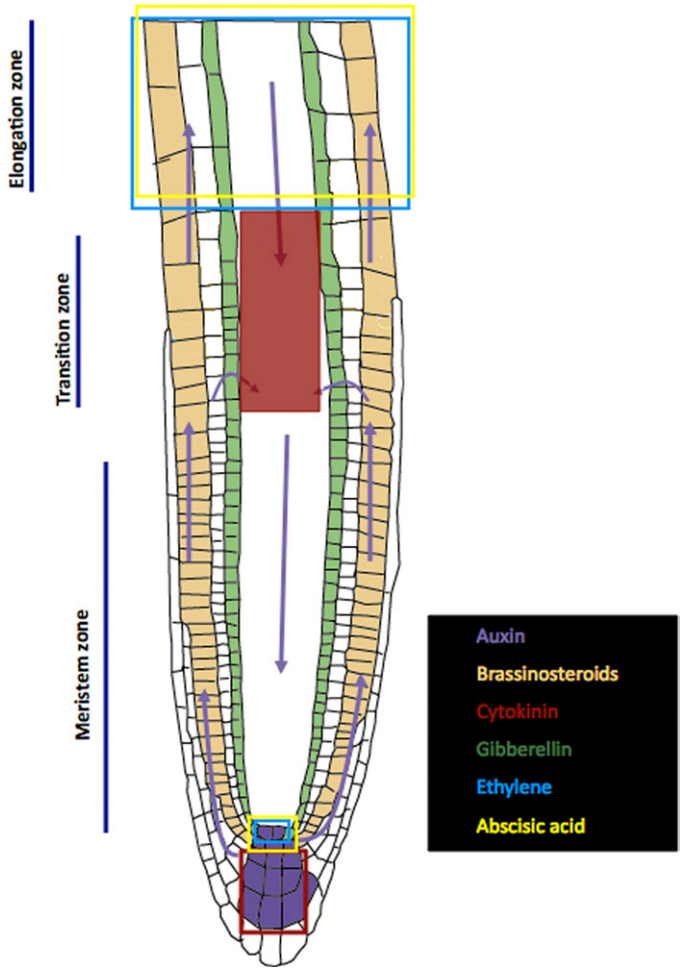

Fig. 3. Schematic representation of main tissue-specific concentration/function of different hormones in the root meristem. Auxin mainly accumulates in the stem and columella cells (purple color and arrows indicate auxin distribution). Brassinosteroids (BRs) mainly function in the epidermal cells to control meristem size (peach). Cytokinins (CKs) acts in the transition zone and columella cells (red). Gibberelins (GAs) acts in the endodermal cells to control meristem size and cell elongation (green). Ethylene accumulates in the QC and elongation zone (blue) and Abscisic Acid (ABA) functions in the elongation zone and QC cells (yellow).

TRIPLE RESPONSE 1 (CTR1) is active and represses ETHYLENE INSENSITIVE 2 (EIN2) as well as all the downstream components of the ethylene signaling pathway; CTR1 also localizes to the ER membrane. The transcription factor ETHYLENE INSENSITIVE 3 (EIN3) is constantly degraded through the action of EIN3 BINDING F-BOX 1 and 2 (EBF1 and EBF2) via the proteasome-mediated degradation pathway (Etheridge et al., 2005). Upon binding ethylene, the histidine-kinase domain of its receptor interacts with and inactivates CTR1, thus relieving the repression of downstream signaling. The newly activated EIN2 then promotes the activation of EIN3 and EIN3-like (EIL) transcription factors, which induces the expression of ETHYLENE RESPONSE FACTOR (ERF), which is another transcription factor implicated in the activation of a subset of ethylene response genes (reviewed in Bleecker and Kende, 2000). Ethylene also promotes the accumulation of EIN3 by repressing the action of EBF1 and EBF2 (Potuschak et al., 2003; Binder et al., 2007). It was previously thought that ethylene receptors only form homodimers to facilitate interaction with CTR1; however, all the ethylene receptors were recently shown to be capable of forming homo- and heterodimers in vitro in any combination, although their role in ethylene signaling has not yet been demonstrated (Lin et al., 2009).

The ethylene biosynthesis and signaling pathways are post-transcriptionally regulated. Some ACS isoforms and the transcription factor EIN3 are regulated by ubiquitin/26S proteasome-mediated degradation (Etheridge et al., 2005). Additionally, ETR1 gain-of-function and loss-of-function mutations affect the expression of ETR1 at the post-transcriptional level (Zhao et al., 2002).

ETHYLENE AND ROOT MERISTEM DEVELOPMENT

During root development, ethylene promotes root hair differentiation and inhibits cell elongation (Tanimoto et al., 1995; Pitts et al., 1998; Ruzicka et al., 2007). Ethylene also affects other aspects of root growth via the induction of certain genes involved in auxin biosynthesis including *ASA1/WE12/TIR7, ASB1/WE17* (alpha and beta subunits of ANTHRANILATE SYNTHASE), *TAA1/WE18* (TRYPTOPHAN AMINOTRANSFERASE), and *TARs* (*TAA1*-related genes) (Ruzicka et al., 2007; Swarup et al., 2007; Stepanova et al., 2008). The interaction between ethylene and auxin will be discussed in Root Cell Elongation section in this review.

Additionally, ethylene affects cell division in QC cells and is likely to be involved in root meristem maintenance. First, the high level of ethylene in *eto1* mutants promotes QC cell division independently of auxin and without interfering with QC cell fate, and, second, the constitutive activation of the ethylene response in *ctr* mutants generates additional QC cells and smaller root meristems (Fig. 2; Ortega-Martinez et al., 2007; Thomann et al., 2009).

ABSCISIC ACID (ABA)

Abscisic acid (ABA) is an isoprenoid hormone that is involved in the regulation of seed development and dormancy as well as plant responses to various environmental stresses, particularly stress due to water deficit. This hormone is present in all plant tissues from the apical bud to the root tip (reviewed in Finkelstein et al., 2002).

ABA is synthesized in nearly every cell that contains plastids; however, vascular tissues are likely to be the

main sites of ABA biosynthesis in non-stressed plants (Nambara and Marion-Poll, 2005). ABA is derived from the C_{15} compound farnesyl pyrophosphate or C_{40} carotenoids synthesized by the plastid 2C-methyl-D-erythritol-4-phosphate (MEP) pathway, and is predominantly found in vascular parenchyma cells (Nambara and Marion-Poll, 2005). Genes involved in ABA biosynthesis include a ZEAXANTHIN EPOXIDASE PROTEIN (ZEP), a 9-CIS-EPOXYCAROTENOID DIOXYGENASE (NCED), a SHORT-CHAIN ALCOHOL DEHYDROGENASE/REDUCTASE (SDR), and an ALDEHYDE OXIDASE (AAO). ABA is also synthesized indirectly through the cleavage of a C_{40} carotenoid precursor (reviewed in Xiong and Zhu, 2003). ABA is ubiquitous in vascular tissues and is transported via the xylem and phloem.

ABA may be inactivated by oxidation or by covalent conjugation with other molecules such as glucose to form ABA-glucose ester (ABA-GE). The three ABA hydroxylation pathways that oxidize ABA produce compounds that could carry out biological activities; however, hydroxylation triggers further inactivation steps (Nambara and Marion-Poll, 2005). It has also been shown that conjugation not only inactivates ABA but also causes an alteration in cellular distribution such that some conjugated ABA localizes in vacuoles and may serve as a storage form of the hormone. Moreover, these conjugates could be important for long-distance transport of ABA from the root to the shoot because ABA-GE has been found in high concentrations in the xylem sap (Verslues et al., 2007).

Recent biochemical and genetic approaches have uncovered several soluble ABA receptors including 14 proteins of the PYRABACTIN RESISTANCE/PYRABACTIN-LIKE or REGULATORY COMPONENTS OF ABA RECEPTOR family (collectively known as the PYR/PYL/RCAR family). Signaling commences when ABA binds to PYR/PYL/RCAR receptors, which promotes the inhibition of protein phosphatases of type 2C (PP2Cs). Because PP2Cs act as negative regulators of SnRK2, this inhibition allows for SnRK2 activation and subsequent phosphorylation of target proteins (Ma et al., 2009; Park et al., 2009). Several SnRK2 targets have been reported both at the plasma membrane and in the nucleus; these include ABA-responsive element binding factors (ABFs/AREBs) and the ion channels responsible for turgor-mediated stomatal closure (Melcher et al., 2010). SnRK2s also recognize ABA-responsive elements (ABRE) in the promoter regions of ABA-inducible genes. Six homologs of PP2C have been described (ABI1, ABI2, HAB1, HAB2, AHG1, and AHG3; Leung et al., 1997; Leonhardt et al., 2004; Saez et al., 2004; Yoshida et al., 2006; Nishimura et al., 2007), and several transcription factors (ABI3, ABI4, ABI5, and the ABFs) that regulate downstream ABA-inducible genes have also been characterized (reviewed in Finkelstein and Rock, 2002; Finkelstein et al., 2005; Fujita et al., 2005).

ABA AND ROOT DEVELOPMENT

ABA promotes root elongation in a dose-dependent manner when it is exogenously applied at 0.1 μM, whereas root growth is inhibited when the hormone is applied at concentrations above 1.0 μM (Ghassemian et al., 2000). This inhibition of the primary root requires *SnRK 2.2* and *SnRK 2.3* because mutations in these genes confer resistance to ABA (Fujii et al., 2007). It is likely that other ABA regulators are repressed during normal root development. For example, *SCR* inhibits *ABI4* (a transcription factor induced in response to ABA signaling) specifically in the endodermis. *scr-1* mutants have short roots and high levels of *ABI4*, and overexpression of ABI4 in the endodermis (where *SCR* is normally expressed) also yields shorter roots (Fig. 2). However, *abi4-104* loss-of-function mutants also have shorter roots, indicating that the expression level of ABI4 and the specific tissue where it is expressed have other root growth effects (Cui et al., 2012). ABA also acts as a root-to-shoot signal that controls the closure of stomata and affects root architecture in response to drought (Sharp, 2002; De Smet et al., 2003).

Additionally, ABA induces QC quiescence and suppresses cell differentiation in the SCN. Extra QC divisions were observed in mutants that are ABA-deficient (*aba1-1, aba2-3, aba2-4*, and *aba3-2*) or ABA-insensitive (*abi1-1, abi2-1, abi3-1*, and *abi5-1*). The inhibition of ABA biosynthesis also promotes stem cell differentiation (Zhang et al., 2010).

HORMONE CROSSTALK DURING ROOT DEVELOPMENT

For each plant hormone, knowledge regarding its metabolism, region of action, and function is important; however, hormones do not act independently of each other. In fact, hormone action depends on the relative concentrations of multiple hormones rather than only on their individual concentrations. Their signal transduction and biosynthetic pathways are interlinked, and this interdependence is known as hormone crosstalk. Thus, hormones form a complex network that underlies their net role during different developmental processes including root development.

The integrated role of plant hormones in the SCN as well as in cell proliferation, elongation, and departure from the RAM (i.e., entrance into the elongation and differentiation zones) will be discussed in the Root Cell Proliferation, Root Cell Elongation and Hormone crosstalk and SCN Patterning sections in this review.

ROOT CELL PROLIFERATION

The auxin/CK ratio is important for determining cell behavior along the apical-basal axis in the root because it maintains root meristem size and controls the transition from cell proliferation to cell elongation. A high level of auxin activity relative to CK action or concentration is required for the maintenance of cell proliferation, thus preventing cell expansion and differentiation. In contrast, relatively high levels of CK are important for the transition from the proliferative meristematic zone to the differentiation zone. In this antagonistic relationship, genes that are responsive to both hormones are cross-regulated. CK upregulates *SHORT HYPOCOTYL 2* (*SHY2*), which corresponds to

IAA3, an ARF repressor that decreases the expression of *PIN1, PIN3*, and *PIN7* (among other genes) in the vascular tissue of the transition zone (Dello Ioio et al., 2007, 2008b; Ruzicka et al., 2009; Moubayidin et al., 2010). Additionally, CK signaling negatively regulates PIN genes at the post-transcriptional level (Zhang et al., 2011). However, in the proliferation zone, auxin mediates the degradation of the SHY2 protein, which allows for PIN expression, proper auxin distribution, and normal cell division (Dello Ioio et al., 2007, 2008b). Auxin can inhibit CK metabolic inactivation by inducing CK oxidases, whereas CK locally promotes auxin synthesis (Zhou et al., 2011; Jones et al., 2010). Thus, CK not only represses polar auxin transport but also promotes local auxin biosynthesis in the proliferation zone (Zhou et al., 2011). However, the function of CK is complex, and although the overexpression of CKX in Arabidopsis leads to larger root meristems, CK receptor mutants exhibit short root phenotypes. GA indirectly promotes *PIN* expression by inhibiting ARR1, and GAs also target PIN proteins for vacuolar degradation (Moubayidin et al., 2010; Willige et al., 2011). The means by which these two processes are stabilized is not clear.

GA is also involved in RAM size regulation via its effects on the auxin/CK balance (Vanstraelen and Benková, 2012). In this balance, various downstream genes are regulated. Concurrently, auxin promotes GA synthesis (Frigerio et al., 2006) and enhances the degradation of RGA and GAI DELLA proteins (Fu and Harberd, 2003). Therefore, mutants that accumulate DELLAs typically have very small RAMs (Achard and Genschik, 2009; Ubeda-Tomas et al., 2009). Additionally, GA can act independently of the auxin-CK pathway and regulate cell proliferation and meristem size by downregulating the cell cycle inhibitor KRP2 via DELLA degradation (Achard and Genschik, 2009; Ubeda-Tomas et al., 2009).

BRs have also been implicated in the relationship between auxin and CK. *BREVIS RADIX* (*BRX*) is a putative transcriptional co-regulator that promotes root growth primarily by affecting meristem size (Mouchel et al., 2004). The *brx* mutant is deficient in BRs, and most of its auxin-responsive genes are globally impaired, which demonstrates the requirement for BRs in auxin-responsive transcription (Mouchel et al., 2006). In young roots, BRX is a direct target of ARF5/MONOPTEROS (MP), which transiently enhances *PIN3* expression to promote meristem growth. At later stages, cytokinin induction of *SHY2* in the vascular transition zone restricts *BRX* and *PIN3* expression, limiting meristem growth (Scacchi et al., 2010). Theoretical and experimental results suggest that BRX forms a complex with ARFs and that this interaction amplifies the transcriptional activity of ARFs. Alternatively, BRX may compete with Aux/IAA for interaction with ARFs (Scacchi et al., 2010; Sankar et al., 2011). It is unclear whether BRX/ARF complexes play a role in controlling meristem size because the BRI receptor is expressed in the epidermis and a BR-mediated signal has been demonstrated to originate from the epidermis (Gonzalez-Garcia et al., 2011; Hacham et al., 2011).

Taken together, these data indicate that cell proliferation and RAM size are regulated by the collective action of auxin, CKs, Gas, and BRs, all of which exhibit regulatory interdependency at the levels of biosynthesis, signaling, and transport.

JA and ABA also participates in root cell Proliferation antagonizing auxin. It has been documented that JA directly represses the expression of PLT or PIN, thus inhibiting RAM growth (Chen et al., 2011). However, a feedback mechanism occurs between these hormones. JA promotes auxin biosynthesis by inducing the expression of *ASA1*/*WE12*/*TIR7* (Stepanova et al., 2005; Sun et al., 2009), and auxin reduces JA signaling by upregulating the JAZ1 repressor (Grunewald et al., 2009). In addition, ABA and CK regulate ABI4, which in turn represses PIN1 expression (Shkolnik-Inbar and Bar-Zvi, 2011; Vanstraelen and Benková, 2012). A synergistic effect of ABA and auxin has also been reported. The exogenous application of ABA upregulates certain auxin response genes (e.g., *MP* and *PLT2*) (Zhang et al., 2010). Interestingly, unlike GA and BRs, ABA inhibits cell division via upregulation of *KRP1* (Wang et al., 1998).

ROOT CELL ELONGATION

Auxin and GA pathways converge during root elongation and tissue differentiation; auxin is required for GA-induced degradation of RGA to mediate root elongation (Fu and Harberd, 2003). However, the GA-induced degradation of DELLA proteins is inhibited by ethylene (Achard et al., 2003). Thus, it is very interesting that certain regulatory effects of ethylene and auxin on growth are mediated via DELLA proteins (Achard et al., 2003; Fu and Harberd, 2003). DELLA proteins appear to be integrators of at least three different hormone pathways that orchestrate the response of the plant to different stimuli.

Auxin may induce BRs and, together or in parallel, these two hormones promote cell elongation (Hacham et al., 2011). However, BRs are known to stimulate the production of ethylene in roots (Mussig et al., 2003; Benková and Hejatko, 2009), indicating potential negative feedback regulation among these two hormones.

Auxin, GA, and BRs induce cell elongation; however, ethylene and auxin synergistically inhibit this process, and they reciprocally induce their biosynthesis and response. Ethylene stimulates auxin biosynthesis in root tips through the induction of *ASA1, ASB1, TAA1*, and *TAR* genes (Stepanova et al., 2005, 2008) and also stimulates basipetal auxin transport to the elongation zone, thus inhibiting cell elongation via regulation of polar auxin transporters (AUX1 and PIN2; Luschnig et al., 1998; Ruzicka et al., 2007; Swarup et al., 2007; Negi et al., 2008). However, elevated auxin levels lead to increased ethylene synthesis, which facilitates the inhibitory effect of ethylene on cell elongation (Swarup et al., 2007). Moreover, a whole-genome analysis revealed that auxin and ethylene function both independently and in concert, and the two hormones regulate each other at the levels of synthesis, transport, and signaling (Stepanova et al., 2007). CK also inhibits cell elongation, and this regulation depends on ETR1 and EIN2, two

components of the ethylene signaling pathway (Ruzicka et al., 2009; Kushwah et al., 2011). Interestingly, the repressive effect of ethylene on elongation does not affect the meristematic zone (Galinha et al., 2009).

Understanding how all these hormones pathways feed back and together underlie the modulation of cell proliferation and cell elongation/differentiation during root development will require integrative formal approaches (see "Theoretical approaches to the study of hormones in the root" section in this review).

HORMONE CROSSTALK AND SCN PATTERNING

As described above, several hormones affect SCN establishment and cellular patterning in the root. However, little is known about hormone crosstalk in the SCN. In fact, many of the hormone interactions observed in the proliferation and elongation zones (e.g., the synergistic relationship between auxin and BR at the signaling level) are not present in the SCN (Gonzalez-Garcia et al., 2011). Moreover, an effort to detect the interaction of ABA with ethylene in the regulation of the SCN indicated that ABA regulation is ethylene-independent (Zhang et al., 2010) even when ABA promotes ethylene biosynthesis (Ghassemian et al., 2000). There are only three documented examples of crosstalk in the SCN. The first of these is the induction of *MP* and *WOX5* expression by ABA, suggesting that auxin and ABA interact in the regulation of the SCN (Zhang et al., 2010). The second example is the auxin-mediated suppression of CK signaling during embryonic development, which determines the SCN of the primary root as a result of PIN-mediated auxin accumulation and the expression of *WOX5* and *PLT* (Friml et al., 2003; Weijers et al., 2006; Muller and Sheen, 2008). The third example is the upregulation of *TAA1* expression by ethylene in the QC (Stepanova et al., 2008). *TAA1* is an auxin biosynthesis gene that is also induced by CK and is necessary for maintaining proper auxin levels in the root. Contrary to these results, it has been reported that the effect of ethylene on QC cells is auxin independent, and it was suggested that auxin itself is not sufficient to induce cell division in the QC (Ortega-Martinez et al., 2007). Further experiments will be needed to clarify this apparent discrepancy.

Unraveling the means by which hormones communicate to regulate SCN maintenance, development, and patterning remains a challenge that needs to be addressed in future research. However, it is clear that hormone interactions at the levels of synthesis, metabolism, and distribution are being uncovered. Additionally, hormone interactions during the transcriptional or post-transcriptional regulation of key molecular components in signal transduction pathways and hormone interactions with many target genes in several developmental-specific contexts are slowly being clarified. Thus, a complex network of interactions and crosstalk between hormone pathways is emerging.

THEORETICAL APPROACHES TO THE STUDY OF HORMONES IN THE ROOT

Hormonal regulation is a complex process, and due to the non-linear nature of their interactions, hormones exhibit non-intuitive behaviors that necessitate theoretical and computational tools for their analysis. Some researchers have begun to use these tools, and auxin transport in the root has been the subject of theoretical analyses. An earlier study demonstrated that auxin transport mediated by PIN proteins is sufficient to robustly generate the auxin gradient observed along the root (Grieneisen et al., 2007), and a recent study illustrated how this mechanism, when coupled to the auxin-regulated PIN expression and degradation process, was able to recover the self-organizing properties of the auxin gradient observed in the root (Mironova et al., 2012), which is similar to what occurs during the root regeneration process (Sena et al., 2009).

Ethylene signaling has also been studied using theoretical tools. In this work, the communication channel conformed by the ethylene signal transduction pathway was studied in Arabidopsis root cells, and the Shannon entropy (H), or degree of uncertainty that the signal transduction pathway has during the decoding of the message received by ethylene receptors, was computed. These models showed that the amount of information managed by the root cells could be correlated with the frequency of the input signal. Indeed, it was shown that if one "master" gene (*ERF1*) and one "slave" gene (*HLS1*) are considered, then the total H is determined by the uncertainty associated with the expression of the "master" gene. Additionally, the H associated with *HLS1* expression determines the information content of the system that is related to the interaction of the antagonistic *ARF1,2* and *HLS1* genes (Diaz and Alvarez-Buylla, 2006, 2009).

Importantly, similar types of theoretical approximations have been used to formally evaluate the role of integrated hormone signaling pathways. The crosstalk between the auxin, ethylene, and CK signaling pathways was modeled using the same approximation as in Diaz and Alvarez-Buylla (2006). The model indicated how the *POLARIS* gene controls the ethylene-dependent regulation of auxin at the transport and biosynthesis levels, consequently regulating the auxin concentration at the root tip. This work also demonstrated how variations in the model parameters generate different auxin responses (Liu et al., 2010). The crosstalk between auxin and BRs was studied with a qualitative continuous approximation, which suggested the possible role of BRX in mediating communication between auxin and BRs (Sankar et al., 2011). Importantly, this hypothesis was experimentally verified (Scacchi et al., 2010). The crosstalk between auxin and CKs observed at the transition zone and the means by which auxin regulates the pattern and maintenance of the root SCN in conjunction with other transcription factors have also been studied with theoretical tools (Muraro et al., 2011; Azpeitia et al., 2010). This body of research has provided important clues about hormone function and highlights how the combined use of experimental and

theoretical approaches can improve our understanding of the crosstalk among hormones.

PERSPECTIVES

As data on plant hormone biosynthesis, metabolism, signal transduction pathways, transport, and overall function are uncovered, a complex network of interactions is revealed. However, we are still far from understanding how plant cells and whole plants dynamically integrate environmental and endogenous signals to control cell function and status (e.g., proliferative vs. elongating/differentiating). Previous views of hierarchical unidirectional pathways acting independently of each other are being discarded. Current knowledge regarding hormone pathways suggests that: (1) several hormones regulate genes in the signaling pathways of other hormones (Nemhauser et al., 2006); (2) proteosome protein degradation occurs in most hormone pathways (auxin, ethylene, BRs, and GAs); and (3) DELLA proteins function as central molecular components of a growth-repressing mechanism that integrates the action of most hormones (Achard et al., 2003, 2006).

Hormone pathways also converge in the regulation of common targets. Interestingly, however, transcriptomic analysis using GA, IAA, and BRs has suggested that the exogenous application of each hormone regulates a set of specific target genes independently (Nemhauser et al., 2006). This finding suggests that the direct targets of plant hormones may be specific; however, the same experiments suggest that different members of the same family are regulated by different hormones (Nemhauser et al., 2006).

We propose that integrative dynamic models such as those used to understand gene regulatory networks (Alvarez-Buylla et al., 2010) or single hormone signaling pathways (Diaz and Alvarez-Buylla, 2006, 2009) could be used to integrate and better understand the complex interactions that underlie hormone biosynthesis, metabolism, signaling, transport, and action, as well as their integrated role in cell proliferation and differentiation during root growth.

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