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Asymmetric cell division in plant development[oo]

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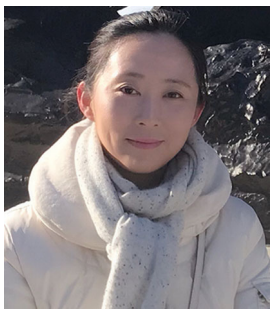

Juan Dong

ABSTRACT

Asymmetric cell division (ACD) is a fundamental process that generates new cell types during development in eukaryotic species. In plant development, post-embryonic organogenesis driven by ACD is universal and more important than in animals, in which organ pattern is preset during embryogenesis. Thus, plant development provides a powerful system to study molecular mechanisms underlying ACD. During the past decade, tremendous progress has been made in our understanding of the key components and mechanisms involved in this important process in plants. Here, we present an overview of how ACD is determined and regulated in multiple biological processes in plant development and compare their conservation and specificity among different model cell systems. We also summarize the molecular roles and mechanisms of the phytohormones in the regulation of plant ACD. Finally, we conclude with the overarching paradigms and principles that govern plant ACD and consider how new technologies can be exploited to fill the knowledge gaps and make new advances in the field.

Keywords: asymmetric cell division, peptide signaling, phytohormonal signaling, polarity proteins, plant development, transcription factors

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INTRODUCTION

Asymmetric cell division (ACD), specifying two daughter cells with distinct cell fates, provides a common mechanism for generating new cell types in the development of multicellular organisms (Abrash and Bergmann, 2009). Restricted by the rigid cell walls, the plant cells are immobile, thus particularly requiring precisely organized ACD events in time and space to ensure new cell types are properly generated and patterned during growth and development.

Using *Arabidopsis* as a primary model system, the molecular mechanisms underlying plant ACD have been well studied in several developmental contexts, such as embryogenesis, root apical meristem (RAM) initiation and development, lateral root (LR) initiation, and stomatal development (Petricka et al., 2009; Pillitteri et al., 2016). Although specific regulators and processes during ACD are divergent in different plant tissues and species, major cellular events and working themes are shared by different ACD systems. For example, the four major steps of an ACD are generally identified as (i) specification of the initial cell population; (ii) intrinsic and/or extrinsic cues-driven cell polarization; (iii) nuclear positioning and cell-plate formation; and (iv) daughter-cell fate differentiation (De Smet and Beeckman, 2011; Yi and Goshima, 2022). As in the other metazoan ACD systems, plant ACDs also require both intrinsic and extrinsic cue-based mechanisms to specify daughter-cell fates and these mechanisms often interplay and are regulated in a precisely

controlled spatiotemporal manner (Horvitz and Herskowitz, 1992; Ten Hove and Heidstra, 2008).

Key to a typical ACD is the production of two daughters with distinct daughter-cell fates, while the self-renewal capacity in one daughter cell (stem cell) is often maintained in some of the ACD systems, for example, the RAM and the stomatal lineage cells. Here, using a few ACD model systems in plants, we discuss how differential daughter-cell fates can be specified by the unequal activity of transcription factors (TFs), by polarized proteins and dynamic cell signaling, and/or by extracellular molecules that trigger differential signal transduction, and so forth. While the core molecular components and machinery are progressively revealed in these model systems, we incorporate knowledge obtained in the phytohormone field and draw attention to the cellular and subcellular regulation of the phytohormones associated with cell division, cell expansion, and cell-fate determination in plant ACD. Although, an important aspect of plant ACD is the asymmetric placement of the cell-division plane, which is not heavily discussed in this review. We refer our readers to a few recently published reviews (Rasmussen and Bellinger, 2018; Livanos and Müller, 2019; Müller, 2019; Yi and Goshima, 2022).

CELL SYSTEMS FOR STUDYING ACD IN PLANTS

Early studies in plant ACD showed that the first zygotic division in fucoid algae and the formation of the male germ lines in flowering plants are representative examples of divisionally physical asymmetry coupled to the asymmetric cell fates (Bisgrove and Kropf, 2008; De Smet and Beeckman, 2011). However, not all ACD systems display morphological asymmetry during cell division, but they commonly produce daughter cells with distinct cell fates. Below we summarize the major cell systems that have been heavily studied for ACD in plants, the majority of which are based on studies in the dicotyledonous model plant *Arabidopsis*. The list below is not intended to be inclusive but reflects where major advances have been made during the past years. Other systems not heavily discussed, such as ACDs in shoot apical meristem (SAM), also provide significant insights into the molecular control of stem-cell identity, division potential, maintenance, and termination during organogenesis (see reviews of Groß-Hardt and Laux, 2003; Aichinger et al., 2012; Heidstra and Sabatini, 2014).

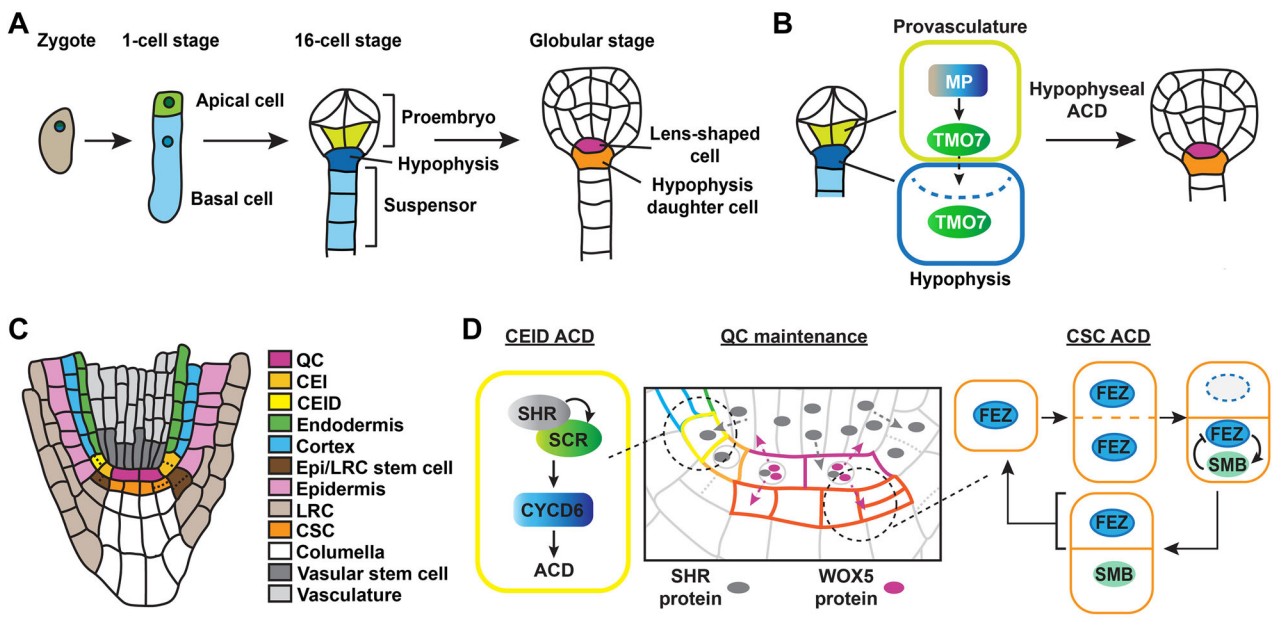

Figure 1. Plant asymmetric cell division (ACD) driven by asymmetric expression of transcription factors (TFs)
(A) ACD events during early embryogenesis generate (i) apical and basal lineages, (ii) inner and outer layers in the proembryo, and (iii) the lens-shaped quiescent center (QC) precursor (magenta). **(B)** The hypophyseal ACD is driven by the expression of TMO7 that is originally expressed in the upper provascular cells (light green) and diffused to the hypophysis (dark blue). The MP/ARF5 TF binds to the *TMO7* promoter to drive its expression. **(C)** Schematic shows a longitudinal section of a developing root apical meristem (RAM) with distinct cell types (differently colored). Future division planes in ACD are marked by dashed lines. **(D)** Key TFs are required for the QC maintenance (middle), and they are differentially expressed to specify daughter-cell fates in the ACD of CEID (left) and columella stem cell (CSC) (right), respectively. Middle: mobile TFs, SHR (gray ovals) and WOX5 (magenta ovals), have non-autonomous functions (arrows indicate protein movement) that are required for QC maintenance (middle). Left: the mobile TF SHR (gray ovals) diffuses from the vasculature tissue to the CEI and CEID, where it interacts with SCR to induce sequential ACDs by activating the expression of the cell-cycle gene *CYCD6*. Right: the CSC ACD is guided by the oscillating expression of FEZ that activates SMB to form a negative feedback loop to induce cell differentiation. The reappearance of FEZ in the apical daughter directs the next round of ACD.

Asymmetric cell divisions in the embryogenesis

Embryogenesis is the process involving the formation of an embryonic plant that initiates with a stereotypic ACD of the zygote, followed by more sophisticated changes in cell number, fate, and morphology (Figure 1A). As in animals, the zygotic ACD in *Arabidopsis* has been used as an important model for investigating the underlying molecular mechanisms. After fertilization, the asymmetric division of a longitudinally expanded zygote generates a smaller apical cell and a larger basal cell with distinct cell fates. The apical cell divides and develops into the majority of the proembryo. In contrast, the basal cell gives rise to the suspensor, an extraembryonic anchor. At late stages, oriented cell divisions in the proembryo are also necessary to create the formation of a three-dimensional embryo. For example, the divisions that enable the transition from the 8-cell to the 16-cell stage during embryogenesis override the geometrically defined division planes to generate unequal daughter cells and the inner/out cell layers (ten Hove et al., 2015). The RAM is initiated in the embryo at the globular stage by asymmetric division of the hypophysis cell (the uppermost cell of the suspensor) (Figure 1B). This asymmetric division generates an upper lens-shaped cell and a larger basal cell, which give rise to the quiescent center (QC), functions in maintaining root stem cells (van den Berg et al., 1997), and the columella root cap (Dolan et al., 1993), respectively.

Asymmetric cell divisions in the root development

Root apical meristem

In the *Arabidopsis* RAM, root stem cells adjacent to the QC divide asymmetrically to produce daughter cells with new identities (Figure 1C). There are four distinct classes of stem cells at the *Arabidopsis* root stem-cell niche (SCN) including the cortex/endodermal initials (CEIs), the epidermis/lateral root cap (Epi/LRC) stem cells, the columella stem cells (CSCs), and the vasculature stem cells (Petricka et al., 2009). (i) The CEI undergoes two rounds of successive ACDs to produce the cortical and endodermal cell layers in roots. The first ACD is anticlinal and generates a nonequivalent cortex/endodermal initial daughter (CEID) cell that further divides in a longitudinal orientation to produce the outer (cortex) and the inner (endodermis) layers of the root, respectively. (ii) The Epi/LRC stem cells, positioned adjacent to both QC and CEI, also undergo two rounds of successive ACDs to generate the epidermal cell layer and LRC. The first ACD is periclinal and produces a pair of inner and outer daughter cells. The inner daughter cell divides anticlinally to maintain the Epi/LRC stem cell and to generate an epidermal daughter cell, and the outer daughter cell undergoes several divisions to generate the LRC. (iii) The CSCs undergo anticlinal ACDs to generate a new set of CSCs and produce columella cells (Fisher and Sozzani, 2016). (iv) The vascular stem cells are located directly above the QC and divide consecutively along the longitudinal axes to generate the stele, including procambium, phloem, xylem, and so forth in the root (Figure 1C).

Lateral root initiation

In higher plants, the *de novo* formation of LRs is important for root architecture in responding to the changing environment. LRs initiate exclusively from the lateral root founder cells (LRFCs), a subset of mature pericycle cells adjacent to the xylem poles, named the xylem pole pericycle (XPP) cells. During LR initiation, LRFCs are specified by two neighboring pericycle cells whose nucleus migrate toward their common cell wall, then undergo two rounds of anticlinal asymmetric divisions to generate a single layer of lateral root primordium (LRP) consisting of short daughter cells flanked by long daughter cells (Malamy and Benfey, 1997). A subsequent round of periclinal division generates a two-layered LRP, which further leads to the formation of a dome-shaped LRP by organized cell expansion and division (von Wangenheim et al., 2016) and progressively acquires similar tissue organization as a primary root tip (Figure 5C). After emerging through the parent root epidermis, the apical meristem of an LR is activated to drive growth (Petricka et al., 2012).

Asymmetric cell divisions in stomatal development and patterning

Stomata are epidermal pores, each of which is surrounded by a pair of guard cells (GCs) that open and close to control the passage of CO_2, O_2, and water vapor between the external atmosphere and the internal tissues of a plant. Regardless of the two-cell or four-cell systems in dicots and monocots, respectively, the formation and patterning of stomatal complexes are tightly regulated by asymmetric and oriented cell divisions (Liu et al., 2009; Pillitteri and Torii, 2012). Here, we use maize (monocot) and *Arabidopsis* (dicot) as representatives to depict the stomatal developmental processes.

The four-cell systems

In grasses, such as maize and rice, each mature stomatal complex is composed of a pair of dumbbell-shaped GCs and two flanking subsidiary cells (SCs). The stomatal complexes are aligned linearly along the longitudinal axes of a leaf and the developmental progression of stomatal lineage is also well aligned with leaf growth and elongation (McKown and Bergmann, 2020; Nunes et al., 2020). In maize stomata development, a protodermal cell divides asymmetrically to produce a smaller guard mother cell (GMC) that divides and differentiates into GCs and a larger sister cell that differentiates into pavement cells (McKown and Bergmann, 2020). A developing GMC appears to provide physical/biochemical cues to recruit the neighboring cells on the two sides to become subsidiary mother cells (SMCs), a process manifested by directional nuclear migration toward the site in direct contact with the GMC (Figure 2D). The asymmetric divisions of SMCs produce highly specialized SCs that facilitate the more efficient function of stomatal GCs (Gray et al., 2020).

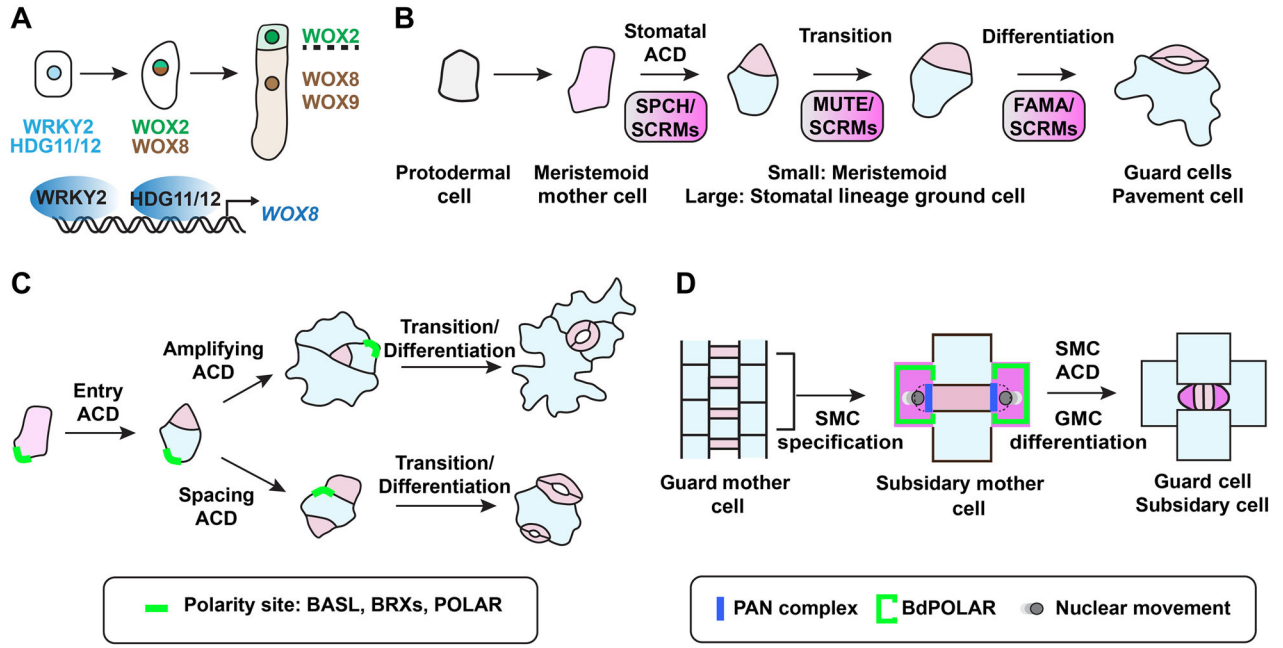

Figure 2. Intrinsic factors in the regulation of plant asymmetric cell division (ACD)

(A) Schematics depict the process of zygotic ACD and differentially expressed TFs. Before zygotic ACD, WRKY2 works together with HDG11 and HDG12 to induce zygote polarization by directly upregulating *WOX8* expression. Following the zygotic ACD, WOX2 and WOX8/9 are differentially inherited in apical and basal daughter cells, respectively. **(B)** Schematics of stomata development in *Arabidopsis* (dicot). Three bHLH TFs, SPCH, MUTE, and FAMA are consecutively required for stomatal initiation, transition, and differentiation through interacting with SCRM and SCRM2. **(C)** Schematics of stomatal ACDs for development and patterning in *Arabidopsis*. Amplifying ACDs occur in the meristemoid (M), and spacing ACDs occur in the stomatal lineage ground cell (SLGC). Stomatal ACD is guided by the polarity complex (green crescent) assembled by the scaffold proteins BASL, BRX members, and POLAR proteins. **(D)** Schematics of stomata development and subsidiary mother cell (SMC) ACD in monocots, such as maize or *Brachypodium*. The differentiation of the guard mother cell (GMC) is required for the specification of SMC (pink) and its subsequent ACD. Complementary polarized proteins, the PAN complex, and BdPOLAR, together with actin-mediated nuclear movement participate in the regulation of SMC ACD.

The two-cell systems

Two kidney-shaped GCs surrounding to form a stomatal pore are found in most plant species including mosses, ferns, gymnosperms, dicots, and some monocots. In contrast with the linear arrangement of stomata in grasses, the initiation of the stomatal precursors occurs randomly in young leaves of the dicot plant *Arabidopsis*. Shortly after germination, by an unknown mechanism, a subset of multipotent protodermal cells, called meristemoid mother cells (MMCs), is selected to divide and differentiate to start producing stomatal GCs. The asymmetric division of an MMC gives rise to two daughter cells with unequal sizes. The smaller, triangular-shaped daughter cell (meristemoid [M]) owns limited self-renewing capacity that allows a few rounds of ACDs prior to entering terminal differentiation. The larger daughter cell, called the stomatal lineage ground cell (SLGC), may divide one more time to produce more stomata or expand to become a pavement cell (Pillitteri and Torii, 2012). The spirally inward divisions of M favor the amplified production of pavement cells, whereas the SLGC division has to be reorientated by the pre-existed GC, thereby enforcing the one-cell-spacing rule so that the newly formed GCs are spatially separated from the existing ones (Figure 2C) (Herrmann and Torii, 2020; Guo et al., 2021b).

PRINCIPLES AND MECHANISMS DRIVING ACD IN PLANTS

Molecular mechanisms driving the specification of differential daughter-cell fates can be divided into two strategies, the intrinsic and the extrinsic mechanisms (Scheres and Benfey, 1999; Abrash and Bergmann, 2009). The intrinsic mechanisms involve the differential inheritance of determinants in the two daughter cells with specified fates, whereas extrinsic mechanisms require positional information and cell signaling events to drive two daughter cells to acquire distinct fates. However, during actual development, ACD events are often regulated by a combination of the two mechanisms.

Asymmetric cell fates: TFs on the move

Transcription factors play central roles in the initiation of ACD and the subsequent specification of daughter-cell fates (Simmons and Bergmann, 2016). Accordingly, the expression of TF themselves must be precisely controlled in a spatio-temporal manner in plant development and such regulation can be achieved at the transcriptional and/or the post-transcriptional levels (Strader et al., 2022). In particular, the immobile plant cells have evolved innovative modes of

cell-to-cell signal transduction, such as TFs moving between cells and functioning non-cell-autonomously to regulate cell-type-specific gene expression and cell-fate specification (Wu and Gallagher, 2012; Long et al., 2015a).

The first TF shown to move was the maize homeodomain protein KNOTTED1 (KN1), which is located in the three top layers (L1, L2, and L3) of the SAM, while its messenger RNAs (mRNAs) are absent from the top layer (L1), suggesting that the KN1 proteins diffuse in the SAM and expand its functional domain to the epidermis (Jackson et al., 1994). How KN1 proteins are expanded to another cell layer was recently elucidated such that the mRNAs of *KN1* travel through the plasmodesmata to the epidermis, a process mediated by RIBOSOMAL RNA-PROCESSING PROTEIN 44A (AtRRP44A) (Kitagawa et al., 2022).

Upon origination of the RAM in embryogenesis, the mobile basic helix–loop–helix (bHLH) TF, TARGET OF MONOPTEROS7 (TMO7), is required for hypophyseal ACD and its expression is directly activated by MONOPTEROS/AUXIN RESPONSE FACTOR (MP/ARF5) (Figure 1B) (Schlereth et al., 2010). The loss-of-function *tmo7* or *mp* mutants produce aberrant hypophyseal division patterns (Schlereth et al., 2010; Lu et al., 2018). Interestingly, TMO7 proteins were observed to move out from the provascular cells, where MP/ARF5 protein is located, to the adjacent hypophysis possibly by interacting with an endosomal protein SHORT ROOT INTERACTING EMBRYONIC LETHAL (SIEL) (Koizumi et al., 2011; Lu et al., 2018). Thus, TMO7 functions as a cell-to-cell communicator from the provascular cell to initiate the hypophyseal ACD (Figure 1B). In addition, the QC-specific homeobox TF, WUSCHEL-RELATED HOMEOBOX 5 (WOX5), is required for maintaining the stem-cell identity of the neighboring cells through its movement out of the QC (Figure 1D) (Sarkar et al., 2007; Pi et al., 2015). Recent studies, however, have raised the possibility of WOX5 functioning mainly in the QC and an unidentified WOX5-dependent factor acting non-cell-autonomously to maintain RAM organization (Berckmans et al., 2020).

In the RAM, a well known example of a mobile TF driving the CEID ACD is the GRAS family member SHORT ROOT (SHR), which interacts with another GRAS protein SCARECROW (SCR) to specify the asymmetric CEI division and the subsequent CEID ACD to generate the cortical and endodermal layers in root radial patterning (Figure 1C, D) (Helariutta et al., 2000). The absence of *SHR* or *SCR* results in one single layer of ground tissue (Helariutta et al., 2000). The *SHR* mRNAs are transcribed in the vasculature tissue, while the proteins move outward to the adjacent cell layers, including QC, CEI, CEID, and endodermis, to induce the expression of *SCR* (Nakajima et al., 2001; Gallagher and Benfey, 2009). Once reaching the endodermis, the SHR movement is restricted by a positive feedback loop with SCR and the presence of two TFs from the BIRDS C2H2 zinc finger family, BALD IBIS (BIB) and JACKDAW (JKD), retains SHR in the nucleus (Cui et al., 2007; Welch et al., 2007; Long et al., 2015b). In the CEID, SHR and SCR directly upregulate the expression of the cell-cycle gene *CYCLIN D6 (CYCD6)* to induce asymmetric division (Sozzani et al., 2010). Beyond the

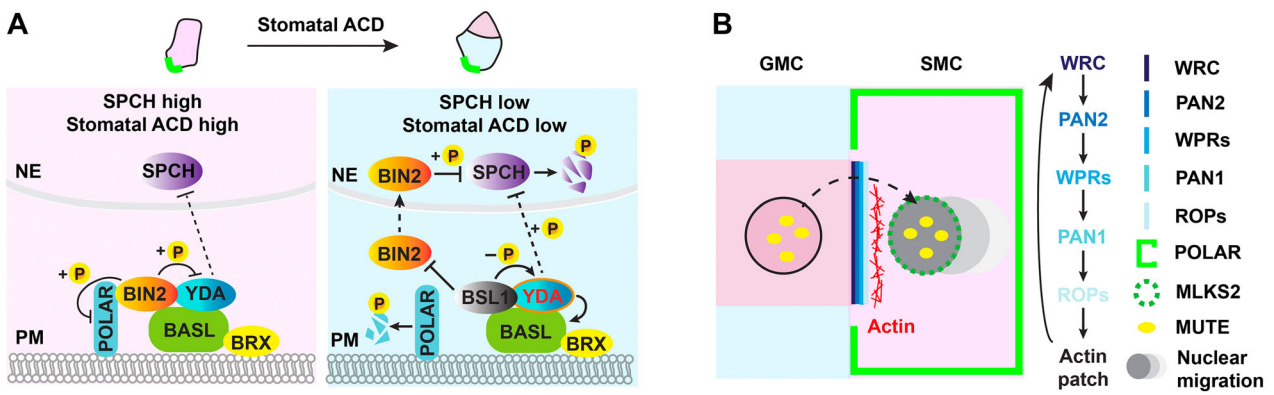

Figure 3. The dynamics of polarity proteins in regulating stomatal asymmetric cell division (ACD) in *Arabidopsis* and maize

(A) Diagrams show dynamically assembled polarity components in pre-mitotic (left) and post-mitotic (right) stomatal lineage cells expressing the polarity module (green crescent) in *Arabidopsis*. In the pre-mitotic cell (left), POLAR recruits the BIN2 kinase that suppresses the MAPKKK YDA's inhibition on SPCH, so that SPCH abundantly accumulates in the ACD precursor cell to drive cell division. In the post-mitotic cell, BASL recruits the BSL1 phosphatase that dislodges BIN2 from the polarity module and activates the YDA kinase, leading to highly suppressed SPCH activity and lowered cell division potential. Thus, the dynamically assembled polarity components differentially determine the high cell-division potential and restricted cell division at different stages during ACD. **(B)** Model for ACD of the subsidiary mother cell (SMC) in monocot stomatal development. Before the SMC ACD in maize, the SCAR/WAVE regulatory complex (WRC) (dark blue) is first assembled in the site of guard mother cell (GMC) contact, followed by sequential recruitment of PAN2, WPR proteins, PAN1 and ROP GTPases (light blue), that direct the actin patch formation and directional nuclear migration, ultimately leading to the asymmetric placement of the division plate. An outer nuclear membrane protein MLKS2 (dashed green oval) is required for the process of polarity complex-guided nuclear migration in maize. In addition, the transcription factor MUTE (yellow ovals), in both maize and *Brachypodium*, is originally expressed in the GMC, where it has an important role in inducing GMC symmetric division, and then moves to the adjacent SMC, where it directly upregulates the expression of *PAN1* and *PAN2*. In *Brachypodium*, BdPOLAR defines a polarity domain at the plasma membrane that is complementary to the PAN polarity and required for SMC ACD.

RAM, the movement of SHR also coordinates phloem development in *Arabidopsis* (Kim et al., 2020) and its homologues travel through multiple cell layers to direct anatomical complexity in the grassroots (Ortiz-Ramírez et al., 2021). The SHR movement largely relies on the coordinated activities of the microtubules, a type-14 kinesin KinG, and the endosomal protein SIEL (Koizumi et al., 2011; Wu and Gallagher, 2013; Spiegelman et al., 2018).

Another example of mobile TF specifying plant ACD is the bHLH MUTE in monocot stomatal development (Figure 3B). In the wheat-like grass *Brachypodium*, the specification of the SMC requires BdMUTE, whose function also contributes to the division and formation of GCs (Raissig et al., 2017). Similar phenotypes in *bdmute* were also observed in the maize *zmmute* mutant (Wang et al., 2019). In both monocot systems, *MUTE* transcription is restricted to the GMC, whereas MUTE protein is also identified in the adjacent SMCs. Interestingly, ZmMUTE initiates SMC ACD by directly activating the expression of *PANGLOSS1 (PAN1)* and *PAN2* (Wang et al., 2019), two key factors required for SMC polarization (Figure 2D) (Cartwright et al., 2009; Zhang et al., 2012).

Asymmetric cell fates: Differential segregation of TFs

Following the first asymmetric zygotic division, the cell-fate specification of the apical and basal lineages is determined by the differentially expressed WOX homeobox TFs, named WOX2, WOX8, and WOX9 (Figure 2A). WOX2 and WOX8 are initially co-expressed in both the egg cell and zygote (Haecker et al., 2004). After the zygotic division, WOX2 expression is restricted to the apical daughter cell, whereas WOX8 and WOX9 are expressed exclusively in the basal daughter cell (Figure 2A) (Breuninger et al., 2008). The loss-of-function *wox2* mutants display cell-division defects restricted to the apical lineages, whereas *wox8;wox9* double mutants display embryonic arrest and abnormal divisions in both the apical and basal lineages (Wu et al., 2007; Breuninger et al., 2008). How the specific expression of *WOX2* and *WOX8/9* is differentially segregated remains unknown, but the upstream TF WRKY2 activates the expression of *WOX8/9* in the zygote to promote zygote polarization (Figure 2A) (Ueda et al., 2011).

Two NAC domain TF family proteins, FEZ and SOMBRERO (SMB) antagonistically control the asymmetric division and differentiation of the columella and Epi/LRC stem cells by their dynamically asymmetric expression patterns (Figure 1D) (Bennett et al., 2014). The loss of *FEZ* leads to reduced columella and LRC layers, indicating that FEZ promotes stem-cell divisions. Conversely, the absence of *SMB* leads to an extra layer of stem cells, indicating that SMB is required to inhibit cell division and promote differentiation (Willemsen et al., 2008). FEZ is expressed in the columella and Epi/LRC stem cells but disappears from the apical daughter immediately following ACD. Until the beginning of the next round of ACD, FEZ expression reappears in the initial cells, forming an oscillating expression pattern (Willemsen et al., 2008). SMB, which is activated by FEZ, in turn downregulates FEZ in the daughter cell, thereby forming a negative feedback loop to repress daughter-cell division and promote differentiation (Figure 1D) (Willemsen et al., 2008). It remains mysterious how FEZ oscillates in the apical cell, but SMB is repressed there by the non-autonomous action of WOX5 derived from the QC (Bennett et al., 2014).

Another example of an unequally accumulated TF is the bHLH protein SPEECHLESS (SPCH), which is crucial for driving stomatal lineage initiation and the subsequent asymmetric division (Figure 2B) (MacAlister et al., 2006). *SPCH* mRNA is widely expressed in the young leaf, whereas SPCH protein is restricted to a subset of protodermal cells, many of which undergo entry ACD to generate two daughter cells, M and SLGC (MacAlister et al., 2006; Robinson et al., 2011). Following the entry ACD, diminished SPCH level in SLGC enables its differentiation into pavement cells, while stabilized SPCH in M enables its self-renewal by one to three rounds of amplifying divisions (MacAlister et al., 2006). The close relative of SPCH, MUTE, which is expressed exclusively in the late M, is required to terminate the amplifying divisions and promote the GMC identity (Pillitteri et al., 2007; Adrian et al., 2015). The transition from GMC to GC is mediated by the third bHLH TF, FAMA, which prevents extra symmetric divisions in GMC and induces the GC identity (Ohashi-Ito and Bergmann, 2006). Collectively, the cell-state transitions in stomatal development are precisely controlled by successive activities of these three bHLH TFs in coordination with two additional bHLH members, ICE1/SCREAM (SCRM) and SCRM2 by forming heterodimer TF complexes (Kanaoka et al., 2008).

Cell polarization: Establishing asymmetry at the cell cortex

Cell polarity, referring to the asymmetric distribution of biological molecules and structures within a cell, is a fundamental feature of all living organisms and regulates various aspects of cellular function (Yang, 2008; Yang et al., 2020). Cell polarity also plays a vital role in the regulation of ACD, including controlling cell division potential, determining division-plane orientation, specifying daughter-cell fates, and so forth (Nakamura and Grebe, 2018; Guo and Dong, 2022). Polarly distributed proteins, as an important feature of cell polarity, have been well recognized to regulate ACD during embryogenesis, stomatal development, root patterning, and so forth. Much knowledge has been gained through studies in stomatal development in the past years, therefore we elaborate on how polarized proteins function in stomatal ACD and expand to recently emerged polarity cell systems in plants.

Stomatal ACD in *Arabidopsis*

In *Arabidopsis*, BREAKING OF ASYMMETRY IN THE STOMATAL LINEAGE (BASL) is one of the first characterized eudicot-specific polarity proteins that function to control stomatal ACD (Figure 2C) (Dong et al., 2009). In the loss-of-

function *basl* mutants, proper stomatal patterning is disrupted due to defects in the asymmetric divisions (Dong et al., 2009). BASL protein is initially accumulated in the MMC nucleus and later polarized at a cortical crescent to direct asymmetric division orientation by regulating the microtubule-based nuclear movement (Muroyama et al., 2020; Gong et al., 2021a). After an entry ACD, the newly formed M is always generated distally to the peripheral BASL crescent that is inherited by the large daughter cell, SLGC. The initial polarization of BASL is random relative to the axes of a developing leaf, suggesting an intrinsic feature of BASL polarity, but it can be reorientated by extrinsic peptide ligand–receptor signaling cues (Dong et al., 2009). When ectopically expressed, BASL polarity appeared to align with the growth axis of plant cells and tissues (Mansfield et al., 2018; Chan et al., 2020).

A few other polarity proteins have been identified in *Arabidopsis* and, together with BASL, provide a scaffolding module to dynamically recruit key components for the polarity module to regulate many processes required for stomatal ACD (Figures 3A). The BREVIS RADIX (BRX) family proteins were identified by a yeast-two-hybrid screen for BASL interacting proteins (Rowe et al., 2019). Indeed, the BRX protein co-polarizes with BASL in the stomatal lineage cells. The loss-of-function *brx-q* (*brxC; brxl1;brxl2;brxl3*) mutants bear stomatal defects that are highly similar to those in *basl* mutants (Rowe et al., 2019). POLAR LOCALIZATION DURING ASYMMETRIC DIVISION AND REDISTRIBUTION (POLAR) is another BASL-dependent polarity protein in stomata lineage cells, but no evidence has yet supported their direct physical interaction (Pillitteri et al., 2011). POLAR's primary function was found to recruit the GSK3-like kinases to regulate stomatal ACD (Houbaert et al., 2018).

The polarity platform provided by BASL–BRX–POLAR is established and maintained before, during, and after mitosis, although each member may polarize slightly differently in space and time (Pillitteri et al., 2011; Gong et al., 2021c). However, the persistence of this platform in an ACD cell at both pre-mitotic and post-mitotic stages necessitates differential components and function of the polarity module to promote cell division and restrict cell division, respectively (Figures 3A). Research in recent years has suggested that the differential regulation of the polarity complex is ultimately connected to the bHLH SPCH master regulator in initiating stomatal ACD (Figure 3A) (MacAlister et al., 2006). The protein abundance of SPCH is strongly suppressed by MAPKs (MPK3 and MPK6)-mediated phosphorylation (Lampard et al., 2008). In a pre-mitotic ACD precursor cell, SPCH levels must be maintained at high levels to ensure a high division potential of the cell. Indeed, in these cells, POLAR recruits the GSK3-like family kinase, BRASSINOSTEROID INSENSITIVE2 (BIN2), to the cortical crescent to directly inhibit MAPKKK YODA (YDA) activity, thus releasing the suppression of MPK3/6 on SPCH and SPCH is maintained at high levels (Figures 3A) (Kim et al., 2012; Houbaert et al., 2018). After ACD, SPCH levels must be diminished in the daughter SLGC to allow the differentiation process. This transition is enabled by the precisely timed assembly of new signaling molecules in the polarity complex, i.e., BIN2 is dislodged by the BASL-mediated recruitment of BRI1 SUPPRESSOR1-LIKE1 (BSL1) phosphatase upon mitosis (Guo et al., 2021a). The dissociation of BIN2 from the cortical polarity site involves the negative feedback regulation on POLAR and the BSL1 phosphatase-dependent activity (Figures 3A) (Houbaert et al., 2018; Guo et al., 2021a). The timed recruitment of BSL1 upon mitosis is critical because BSL1 directly dephosphorylates YDA, another polarity protein recruited by BASL (Zhang et al., 2015b), to activate MAPK signaling and enforce the suppression of SPCH that is required for the daughter-cell differentiation. Thus, BSL1 functions as a molecular switch governing the transition from cell division to cell-fate differentiation during stomatal ACD (Guo et al., 2021b).

Stomatal subsidiary ACD in monocots

Given the fact that no BASL homologues have been found in monocots, the mechanisms for how a stomatal protodermal cell undergoes an ACD to produce a GMC remain unknown. More progress has been made in studying the SMC ACD in maize and *Brachypodium* (Figures 2D and 3B). In maize SMC division, the SCAR/WAVE regulatory complex (WRC), which activates the ARP2/3-mediated actin nucleation, is first polarized in the SMC at the membrane region of the GMC contact (Facette et al., 2015). Subsequently, PANGLOSS2 (PAN2), a catalytically inactive leucine-rich repeat receptor-like kinase (LRR-RLK), is recruited by WRC to polarize PAN1 and the Rho of Plants (ROP) GTPases (Facette et al., 2015). The polarization of these signaling molecules is followed by actin patch formation and the directional nuclear migration of the SMC, ultimately leading to the asymmetric placement of the SMC division plane (Sutimantanapi et al., 2014; Facette et al., 2015). The successive polarization events described above are probably oversimplified because the mutation combinations generated synergistic phenotypes, indicating that parallel or interconnected pathways may converge to regulate SMC ACD. Indeed, recent work has identified the WEB1/PMI2-RELATED (WPR) proteins as PAN2 physical interactors to interact with F-actin and promote SMC polarization (Figure 3B) (Nan et al., 2022). Whether WPRs are regulated by ROPs is unknown.

Conversely, directional nuclear migration is an important progress required for plant ACD. The BASL–BRX polarity module was recently reported to drive pre-mitotic nuclear migration with a microtubule-based mechanism to regulate ACD orientation in *Arabidopsis* (Muroyama et al., 2020; Muroyama et al., 2022). In *Zea mays*, an outer nuclear membrane protein MLKS2, as a component of the LINKER OF NUCLEOSKELETON AND CYTOSKELETON (LINC) complex, was found to link nuclear migration to SMC polarization and ACD (Ashraf et al., 2022). Interestingly, BdPOLAR was

identified to polarize to the distal membrane domain that is reciprocal to the proximal PAN1 polarity domain in the *Brachypodum* SMC (Figure 3B) (Zhang et al., 2022). Both polarity domains in the SMC are required for ACD, but BdPAN1 and BdPOLAR exhibit distinct roles in directing pre-mitotic nuclear migration and division-plane orientation, respectively (Zhang et al., 2022), inviting future investigations on the functional regulations between the complementary polarity domains, directional nuclear movement, and division-plane determination during the SMC ACD.

With much known about cell polarization and division orientation in the SMC ACD system, the major knowledge gap lies in if and how cell polarization regulates asymmetric cell fates, in particular, if and how the polarity complexes restrict BdMUTE to the smaller daughter cell to control the SC differentiation.

Broader impacts of polarity proteins in cell division and differentiation

Besides those in stomatal lineage cells, polarity proteins are repetitively found to regulate cell division and differentiation throughout plant development (Muroyama and Bergmann, 2019; Ramalho et al., 2022). In *Arabidopsis* root development, the BRX family proteins promote continuous protophloem differentiation by interacting with AGC-family kinase PROTEIN KINASE ASSOCIATED WITH BRX (PAX) at the rootward polarity site of developing protophloem sieve elements (PPSEs) (Marhava et al., 2018). PPSE differentiation is impaired in the absence of *BRX* or *PAX*. Like other AGC-type kinases, PAX activates the auxin efflux carriers PIN-mediated auxin transportation, whereas BRX strongly suppresses this stimulation. When the intracellular auxin level is below the threshold, BRX associates with the plasma membrane (Koh et al., 2021), co-polarizes with PAX and inhibits auxin efflux from PPSE. Conversely, increased auxin levels dissociate BRX from the plasma membrane, allowing the activation of PAX for auxin efflux. Thus, BRX and PAX constitute a polarized molecular rheostat that controls intracellular auxin homeostasis in developing PPSEs, thereby timing the PPSE differentiation (Marhava et al., 2018).

The other polarity proteins involved in directing cell-division orientation include the SOSEKI (SOK) membrane-associated proteins, and two transmembrane receptor kinases, IRK and KINASE ON THE INSIDE (KOIN). The SOK family proteins are deeply conserved in land plants and the *Arabidopsis* genome encodes five paralogs (*SOK1*–*SOK5*) (Yoshida et al., 2019). Each SOK protein shows distinct polar edge localization in multiple cell types of developing embryos and roots that locally interpret global polarity cues along the apical–basal and radial body axes (Yoshida et al., 2019). Polarization of SOK relies on protein polymerization and clustering mediated by the head-to-tail oligomerization of the DIX domain. This domain is highly conserved and also identified in DISHEVELLED (DVL), a central regulator of planar cell polarity in animals (Schwarz-Romond et al., 2007; van Dop et al., 2020). The DIX-dependent polymerization of SOK results in local enrichment of the membrane-associated effector protein ANGUSTIFOLIA (AN) (van Dop et al., 2020), which was found to regulate actin filament for nuclear positioning in the leaves (Iwabuchi et al., 2019). While ectopically expressing SOK1 in root meristem disrupts cell division orientation, the underlying mechanism remains unknown (Yoshida et al., 2019).

Two LRR-RLK pseudo-kinases, KOIN and INFLORESCENCE AND ROOT APICES RECEPTOR KINASE (IRK), show contrasting polar localization in the *Arabidopsis* root meristem (Campos et al., 2020; Rodriguez-Furlan et al., 2022). In the endodermis, IRK localizes to the outer domain, while KOIN accumulates in the inner domain of the plasma membrane (Rodriguez-Furlan et al., 2022). In *irk* or *koin* mutants, excessive cell divisions are produced in the ground tissue stem cells and endodermis, implying that IRK and KOIN perceive bi-directional cues to repress specific cell division and to coordinate patterning across the entire root meristem (Rodriguez-Furlan et al., 2022).

Extrinsic cues and signaling regulate plant ACD

As sessile organisms, plants have evolved unique mechanisms enabling them to react and flexibly adapt their developmental programs. Accordingly, the intrinsic mechanisms mediated by the polarity proteins and TFs discussed above can be regulated by extrinsic singling components, such as peptide ligands, receptor kinases, and others. Also, as the extrinsic cues and hormonal molecules often function in a range or form a gradient, we expand the discussion to the cells/regions beyond the ACD pairs, such as the SCN in the RAM.

ESF1 peptides in early embryo patterning

Core to the regulation of zygotic polarity and ACD is the canonical MAPK signaling cascade composed of the MAPKKK YDA, MAPKK 4 and 5, MAPK 3 and 6 (YDA–MKK4/5–MPK3/6) (Figure 4) (Lukowitz et al., 2004; Zhang et al., 2017). The *yda* or *mpk3;mpk6* mutants display reduced zygote elongation and symmetric cell division, resulting in two daughter cells both possessing an embryonic identity (Lukowitz et al., 2004; Zhang et al., 2017). In contrast, constitutively active YDA (YDA-CA) endows the apical daughter cell with suspensor-like characteristics (Lukowitz et al., 2004). Upstream of YDA is the EMBRYO-SURROUNDING FACTOR 1 (ESF1) peptides that are secreted from the endosperm cells, since the suspensor defects in *esf1*_RNAi embryos can be rescued by expressing *YDA-CA* (Costa et al., 2014). ESF1 peptides are presumptively recognized by the plasma membrane-localized SOMATIC EMBRYOGENESIS RECEPTOR KINASE (SERK) LRR–RLK receptor complexes, that are required for the activation of BRASSINOSTEROID SIGNALING KINASE (BSK) family members (Costa et al., 2014; Slane et al., 2014). Subsequently, BSK1 and BSK2 activate the YDA–MAPK signaling cascade in the zygote (Figure 4) (Neu et al., 2019). In addition, the *Brassicaceae*-specific membrane-associated protein SHORT SUSPENSOR (SSP/

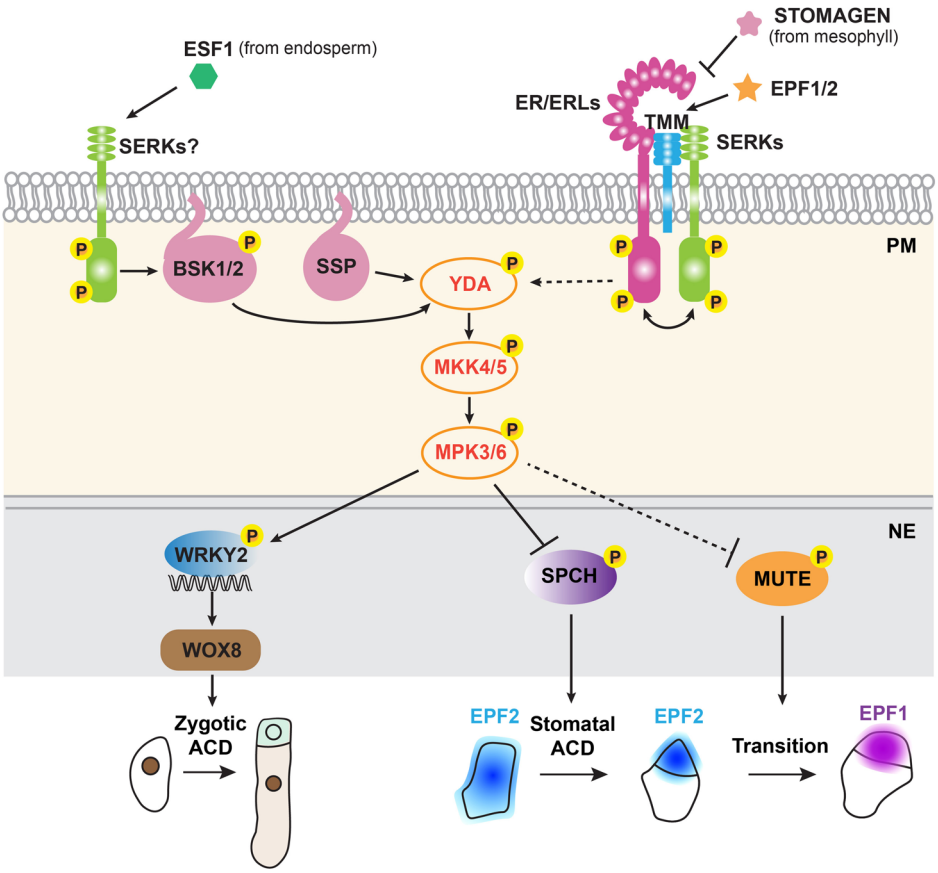

Figure 4. Extrinsic cue-mediated cell signaling regulates plant asymmetric cell division (ACD)
Schematics describe peptide ligand-mediated signal transduction that regulates zygotic and stomatal ACD, respectively. Zygotic ACD in *Arabidopsis* is triggered by the endosperm-derived ESF1 peptides that are likely to be perceived by the SERK receptor-like kinases at the cell surface. In the cytoplasm, membrane-associated BSK1/2 and SSP/BSK12 may directly activate the YDA–MKK4/5–MPK3/6 signaling pathway to stabilize WRKY2 protein that further directs the expression of *WOX8* to specify the basal cell lineage after a zygotic ACD. The YDA–MAPK cascade is shared by stomatal ACD for suppression of stomatal initiation. Upstream of YDA, the extracellular EPF family peptides, including the positive peptides EPF1/2 and negative peptides STOMAGEN, are perceived by the membrane receptor complex comprised of the ERECTA, TMM, and SERK proteins. Downstream of the YDA–MAPK signaling, the master transcription factor SPCH initiates stomatal ACD by inducing thousands of gene expressions, including the peptide ligand *EPF2*, and SPCH activity is directly suppressed by MPK3/6 activity for protein degradation. YDA–MAPK signaling may also suppress later developmental processes driven by MUTE (dashed line) that activates the expression of *EPF1* peptides in stomatal fate transition.

BSK12), which resembles a constitutively active version of BSK1, can directly activate YDA without involving the receptor complexes in the zygote (Neu et al., 2019). One of the direct targets of the YDA–MAPK signaling cascade in embryogenesis is WRKY2, which upregulates the expression of *WOX8* and *WOX9* (see above) by working together with two HD-ZIP IV family TFs, HOMEODOMAIN GLABROUS11 (HDG11) and HDG12 (Ueda et al., 2017).

CLAVATA3/EMBRYO-SURROUNDING REGION (CLE) peptides in RAM maintenance

The CLE family peptides play a vital role in shoot and root meristem maintenance (Willoughby and Nimchuk, 2021). In the SAM, the CLE family peptide *CLAVATA3 (CLV3)* is expressed in the stem cells *via* binding to the LRR-RLK member CLAVATA1 (CLV1) to restrict the expression of a homeobox TF, *WUSCHEL (WUS)*, within the organizing center (OC) (Brand et al., 2000). WUS is essential for maintaining the shoot stem-cell identity (Jha et al., 2020). Recently, the CLE40 peptides in differentiating cells function through the BAM1 (CLV1-family receptor) to promote *WUS* expression, thereby antagonistically to CLV3 maintaining SAM homeostasis (Schlegel et al., 2021). In the RAM, the CLE40 peptides promote the differentiation of CSCs through binding to CLV1 and the RLK member ARABIDOPSIS CRINKLY4 (ACR4) (Stahl et al., 2013). The *cle40, acr4*, and *clv1* single mutants display an increased number of CSC layers (Stahl et al., 2013). CLE40 peptides are expressed in and secreted from the columella cells, generating a declining ligand gradient toward the QC (Stahl et al., 2013). The CLE40 gradient is required for constraining *WOX5* expression to the QC (Richards et al., 2015). However, a recent study suggests that the regulation of CLE40 signaling to *WOX5* expression can be a secondary consequence of CLE40 in defining the QC identity (Berckmans et al., 2020). The other CLE ligands

participating in the regulation of RAM maintenance and LR development have been recently reviewed (Oh et al., 2018; Jourquin et al., 2020; Jeon et al., 2021).

EPIDERMAL PATTERNING FACTOR (EPF) peptides in stomatal development and patterning

The EPF family peptides have been well characterized in stomatal development (Figure 4) (Qi and Torii, 2018; Herrmann and Torii, 2020). Extracellular EPF1 and EPF2 ligands are perceived by three LRR-RLK members of the ERECTA family (ERf) (Shpak et al., 2005), including ERECTA (ER), ERECTA-LIKE 1 (ERL1), and ERL2, four members of the SERK co-receptors (Meng et al., 2015) and one LRR receptor-like protein (LRR-RLP), TOO MANY MOUTHS (TMM) (Nadeau and Sack, 2002). *EPF2* expression is restricted to stomatal lineage initial cells, i.e., MMCs, and early Ms (Hara et al., 2009; Hunt and Gray, 2009), whereas *EPF1* is expressed exclusively at later stages, including in late Ms, GMCs, and young GCs (Hara et al., 2007; Lee et al., 2012). The primary function of EPF2 is to inhibit the protodermal cells entering the stomatal lineage by binding to the ERf–TMM receptor complex that activates the downstream YDA–MKK4/5–MPK3/6 signaling cascade to degrade SPCH (Lampard et al., 2008; Horst et al., 2015; Lin et al., 2017). EPF1 functions as an inhibitor of stomatal differentiation by binding to the ERL1–TMM complex that eventually leads to the degradation of MUTE (Qi et al., 2017). Conversely, SPCH and MUTE promote the expression of *EPF2* and *ERL1* respectively, forming negative feedback loops to delicately regulate stomatal development patterning (Lau et al., 2014; Qi et al., 2017). In addition, EPF1 works as a paracrine signal secreted from late M, possibly imposing an attractive cue to facilitate the BASL polarity shift required for SLGC spacing divisions (Dong et al., 2009). Conversely, EPF-LIKE9 (EPFL9)/STOMAGEN, expressed in immature mesophyll cells, positively regulates stomatal development by competing with EPF2 and EPF1 for binding to the ER and ERL1 receptors, respectively, and repressing the MAPK signaling (Figure 4) (Sugano et al., 2010; Lee et al., 2015b). The other member, CHALLALH/EPFL6, is specifically expressed in the internal stem tissues, by preferentially acting through the ERL1 receptor, to confer regional specification of stomatal production in the stem epidermis (Abrash and Bergmann, 2010). Interestingly, a recent study reported that the CLE9/10 peptides suppress stomatal production through the HAESA-LIKE 1 (HSL1) receptor that recruits the SERK co-receptors to suppress SPCH levels, providing a signaling pathway in parallel to the EPF2-ERf module (Qian et al., 2018).

AUXIN SIGNALING IN THE REGULATION OF PLANT ACD

Phytohormones (auxin, cytokinin, gibberellic acid, brassinosteroids, ethylene, abscisic acid, salicylic acid, and jasmonic acid) play essential roles in nearly all aspects of plant development. Among them, auxin is a key regulator of cell division, elongation, and differentiation in various developmental contexts (Teale et al., 2006; Du et al., 2020). Auxin biosynthesis, transport, metabolism, and signaling have been intensively depicted by several recent reviews (Adamowski and Friml, 2015; Weijers and Wagner, 2016; Lv et al., 2019; Yu et al., 2022). Here, we focus on how auxin contributes to proper cell division and differentiation in plant ACDs (Figure 5).

Auxin synthesis and distribution

Plant organogenesis and growth pattern are highly dependent on differential auxin responses, the outcome of auxin homeostasis, transport, and signaling.

Auxin synthesis and flow during early embryogenesis

During embryogenesis of *Arabidopsis*, the auxin biosynthetic genes including the *TRYPTOPHAN AMINOTRANSFERASE OF ARABIDOPSIS* (*TAA*) family (3 members) and the *YUCCA* (*YUC*) family (11 members) display dynamic expression patterns and are required for asymmetric zygotic division (Figure 5A) (Robert et al., 2018). Prior to embryogenesis, *TAA1, YUC8*, and *YUC9* display a gradually increasing expression pattern in the integuments of the maternal tissue (ovule), which supplies auxin to the developing embryo (Robert et al., 2018). Accordingly, the loss-of-function *wei8;tar1* (*weak ethylene insensitive 8*, a recessive allele of *TAA1*) double mutants display aberrant embryonic division patterns due to the diminished maternal auxin source (Robert et al., 2018). During early embryogenesis, *YUC3, YUC4*, and *YUC9* are expressed in the suspensor cells before the globular stage, indicating their engagement in local auxin production in the basal cells (Figure 5A) (Robert et al., 2013). During the globular stage, *TAA1, YUC1, YUC4, YUC10*, and *YUC11* expression are restricted in the apical cells of the embryo, suggesting the establishment of a new auxin production site (Figure 5A) (Cheng et al., 2007; Stepanova et al., 2008). Accordingly, disruption of the basal auxin production in the single or double mutants of *yuc3, yuc4*, and/or *yuc9* resulted in defects of apical embryo patterning, whereas disruption of apical auxin production in the *yuc1;yuc4;yuc10;yuc11* quadruple mutants showed the disorganized basal patterning and post-embryonic organ formation (Robert et al., 2013).

Directional auxin flow is mediated by both influx carriers, the AUXIN RESISTANT/LIKE AUX (AUX/LAX) family proteins, and efflux carriers, the PIN-FORMED (PIN) family proteins. During embryogenesis, directional auxin transport is enforced by the dynamic activity of the PINs (Figure 5A) (Friml et al., 2003; Blilou et al., 2005). The *pin1;pin3;pin4;pin7* quadruple mutants exhibit similar embryonic defects to those in *yuc* mutants (Blilou et al., 2005). After the first asymmetric zygotic division, PIN7 is specifically localized to the apical side of the suspensor cells, driving the auxin flows from the integuments to the proembryo (Figure 5A), where auxin is sensed and transduced to downstream signaling pathways that determine the cell-division orientation and

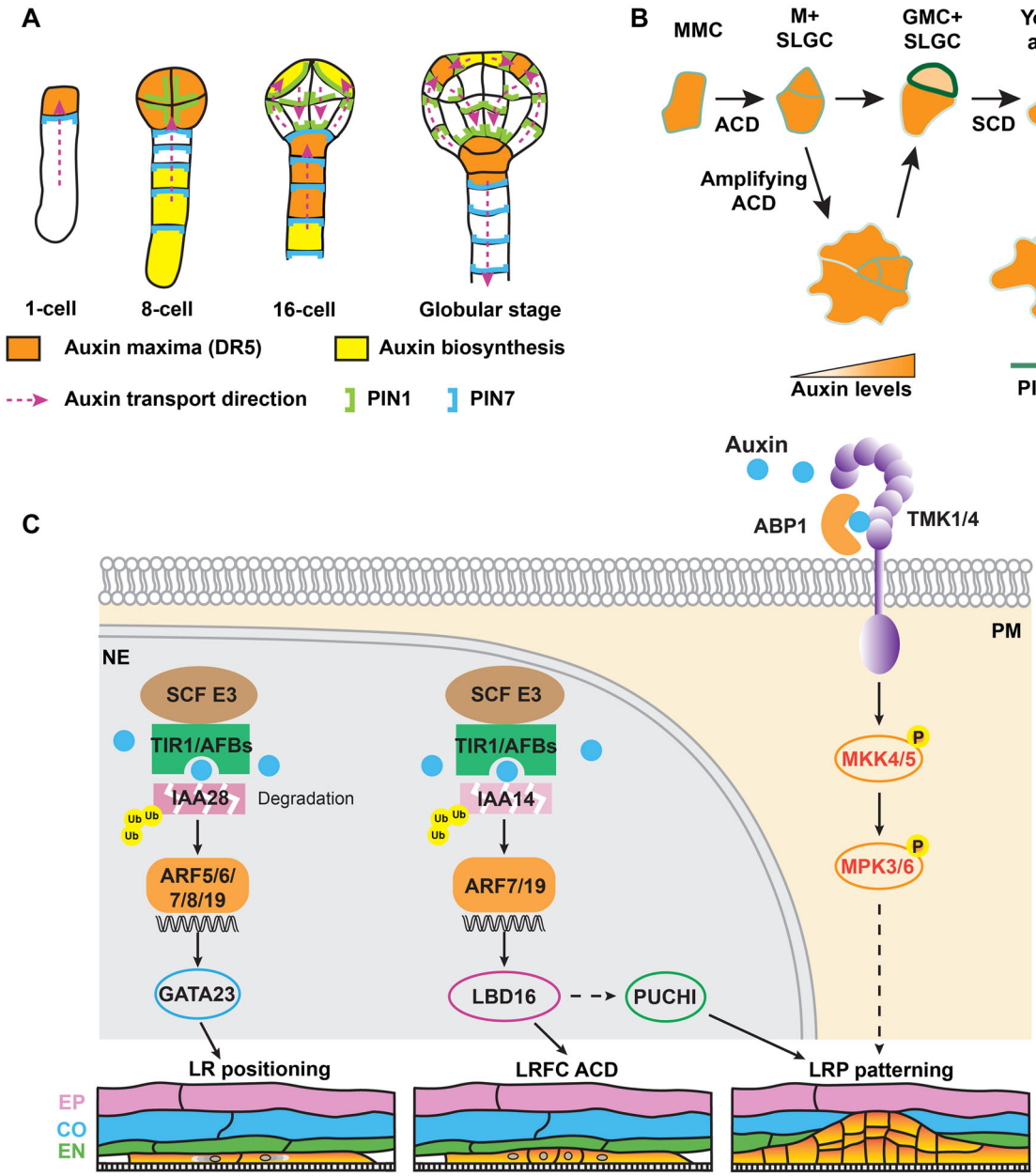

Figure 5. Auxin biosynthesis, transportation, and signaling regulate plant asymmetric cell division (ACD)
(A) The combined activity of local auxin biosynthesis (yellow cells) and directional transportation (magenta arrows) generates dynamic auxin maxima (orange cells) during early embryogenesis in *Arabidopsis*. The directional auxin transportation is mainly driven by the differentially polarized PIN1 and PIN7 as depicted. **(B)** An auxin depletion (light orange) presages stomatal differentiation. This process is coordinated by the elevated expression of the efflux transporter PIN3 (green lines) in meristemoids (Ms) and guard mother cells (GMCs) that undergo terminal differentiation. **(C)** The canonical auxin signaling mediated by the TIR1/AFB receptors regulates multiple stages in lateral root (LR) development. The LR positioning is specified by the release of IAA28-mediated suppression of ARF5/6/7/18/19 that activates the expression of *GATA23*. The LR initiation ACD is promoted by the release of IAA14-mediated suppression of ARF7/19 that activates the expression of *LBD16*. The ACD patterning during the lateral root primordium (LRP) formation is regulated by non-canonical auxin signaling mediated by cell-surface receptors, ABP1, and homologues, that partner with TMK1/4 receptor-like kinases. TMK1/4 directly activates MKK4/5 and MPK3/6 signaling to specify oriented cell divisions.

cell-fate specification (Friml et al., 2003). The mutation of *PIN7* leads to the filamentous embryo due to abnormal apical cell divisions (Friml et al., 2003). After the establishment of a new auxin production site in the apical cells of the globular embryo, PIN1 is polarized and localized to the basal membranes of the inner embryonic cells, while PIN7 is switched to the basal side of the suspensor cells (Friml et al., 2003). Collectively, the auxin flow is directed to move toward the base of the embryo to specify the formation of the hypophysis and to drive its division (Figure 5A) (Friml et al., 2003). Besides directional auxin efflux, the auxin influx determined by the dynamic expression of *AUX/LAX* is also

vital for the formation of the embryonic shoot and root apices (Robert et al., 2015).

Auxin maxima define the SCN in the RAM

The auxin maximum in the SCN of the RAM is maintained through the combination of auxin biosynthesis and directional auxin transport. In the QC, a high level of free auxin is generated partially *via* the locally expressed auxin biosynthetic genes, *YUC1* and *TAA1*, while suppressing the auxin conjugation gene, *SUPERROOT2 (SUR2)* (Brady et al., 2007; Tian et al., 2014). Moreover, the collective effect of cell-type-specific expression and distinct subcellular localization of PIN1, PIN2, PIN3, PIN4, and PIN7 gives rise to a unique pattern of auxin flow along the root tip, named "reflux loop," that maintains auxin maximum in the SCN and is required for root growth patterning (Blilou et al., 2005). Therefore, beyond the globular embryonic stage (when hypophysis undergoes ACD), the auxin distribution is required for the RAM activity *via* both localized auxin biosynthesis and directional auxin transport.

Auxin oscillation and LR initiation

Auxin participates in almost all stages of LR development. The specification of LRFCs (LR positioning), by which a subset of XPP cells is selected as LR initiation sites, displays an oscillation pattern (Roychoudhry and Kepinski, 2022). The oscillation pattern of LR positioning is an intrinsic feature and is driven by a so-called root "clock" (Perianez-Rodriguez et al., 2021), which was found to be reliant on auxin efflux from the LRC (Xuan et al., 2016, 2020). More specifically, in the outer LRC cells, the auxin precursor indole-3-butyric acid (IBA) is converted to indole-3-acetic acid (IAA), which is further transported to the LR initiation sites (De Rybel et al., 2012; Xuan et al., 2015). Additionally, the recurrent programmed cell death (PCD) of the most-distal LRC cells causes the release of auxin pulses to the neighboring stele cells that coincides with the periodicity of LR positioning (Xuan et al., 2016). The auxin influx carrier *AUX1*, which is widely expressed in multiple stages of LR development, mediates auxin transport from LRC to promote the specification of LRFCs (De Smet et al., 2007).

Auxin maxima and the LRFC ACD

High levels of auxin in the pericycle cells, driven by both YUC4-mediated auxin biosynthesis and AUX1-based auxin influx, enable the cell-fate transition to the LRFC (Laskowski et al., 2008; Tang et al., 2017). When the nuclear migration occurs in the two adjacent LRFCs, the auxin efflux carrier PIN3 is temporally induced and polarized to the inner membrane of endodermal cells overlaying the LRFCs, facilitating auxin reflux into the LRFCs to direct the following ACDs (Marhavý et al., 2013, 2016). The loss-of-function *pin3* mutants exhibit delayed progression in completing the first round of ACDs of LRFCs, resulting in increased numbers of LRFCs and reduced numbers of LRPs (Marhavý et al., 2013).

Asymmetric auxin flow in stomatal differentiation

During stomatal development, the auxin distribution pattern is also dynamically regulated (Figure 5B) (Le et al., 2014). Specifically, auxin levels, represented by both DII-VENUS and *DR5p*::VENUS reporters (Brunoud et al., 2012), peak in the early stage of Ms and decline during the late stage of Ms with the transition into the GMC fate. The auxin depletion is partially dependent on an elevated *PIN3* expression at the late stage of Ms (Le et al., 2014). Importantly, when auxin efflux is impeded in the *pin1;pin3;pin4;pin7*, or *pin2;pin3;pin4;pin7* mutants, or is blocked by auxin transport inhibitor (NPA), stomatal clusters appear, possibly due to the overaccumulation of auxin in the Ms (Le et al., 2014). The auxin biosynthesis- and signaling-deficient mutants also display overproduced stomata, implicating the essential roles of auxin in stomatal development (Balcerowicz et al., 2014; Zhang et al., 2014). Thus, well organized auxin biosynthesis and transport are required in stomatal development and patterning.

Auxin perception and signaling in the regulation of ACD

The output of positional information of auxin is reliant on its perception and signaling pathways including both TRANSPORT INHIBITOR RESPONSE 1/AUXIN SIGNALING F-BOX (TIR1/AFB) and TRANSMEMBRANE KINASE (TMK)-based mechanisms (Figure 5C) (Yu et al., 2022). Briefly, the nuclear auxin pathway involves auxin acting as a molecular glue to link TIR1/AFB F-box proteins with the AUXIN/INDOLEACETIC ACID (AUX/IAA) transcription repressors for proteolysis, therefore allowing the AUXIN RESPONSE FACTORS (ARF)-mediated transcription reprogramming (Lavy and Estelle, 2016; Leyser, 2017). At the cell surface, AUXIN BINDING PROTEIN 1 (ABP1) was first identified for its auxin binding activity and established to partner with TMK for its role in activating ROP GTPase (Xu et al., 2014), and ultrafast global phosphorylation (Friml et al., 2022). Members of the TMK family have been implicated in both cytosolic and nuclear processes in response to auxin (Cao et al., 2019).

Embryogenesis

Embryogenesis is highly dependent on auxin signaling that is mediated by the TF MP/ARF5, and its paired inhibitor BODENLOS/INDOLEACETIC ACID 12 (BDL/IAA12). Loss of *MP/ARF5* or expressing a malfunctional form of *BDL/IAA12* (stabilized expression) leads to aberrant ACD patterns in the proembryo and hypophysis (Schlereth et al., 2010; Rademacher et al., 2012). Elevated auxin levels in the lower half of the embryo promote the degradation of BDL/IAA12, which releases the inhibition of MP/ARF5, leading to direct upregulation of auxin transporters PIN1, AUX1 and LAX2 for hypophysis specification (Robert et al., 2015; Krogan et al., 2016). In this process, activated MP/ARF5 also promotes the expression of the mobile TFs, *WOX5* and *TMO7* (see above) (Schlereth et al., 2010).

Another important downstream gene controlled by MP/ARF5 during embryogenesis and ACD is *SOK1*, which encodes a cell polarity protein that displays polar localization in the apical membrane of specific inner cells at the globular stage, and in

the corners of the hypophysis during the transition to the heart stage (Yoshida et al., 2019). Misexpression of *SOK1* results in aberrant embryonic division patterns (Yoshida et al., 2019). Similarly, TIR1/AFB auxin receptors function redundantly to regulate embryo development. The quadruple *tir1;afb1;afb2;afb3* mutants display similar embryonic defects to those in either *mp/arf5* or *bdl/iaa12* mutants, indicating the essential roles of TIR1/AFB-mediated transcriptional signaling in the embryogenesis (Prigge et al., 2020).

The RAM and QC

Key TFs for the RAM maintenance, WOX5 and the AP2/ERF PLETHORA (PLT) family, are also controlled by auxin signaling (Figure 6A) (Sarkar et al., 2007; Mähönen et al., 2014). The regulation of *WOX5* expression by auxin is complex and delicate. In both the embryonic and post-embryonic root, *WOX5* expression is induced by auxin *via* the BDL/IAA12–MP/ARF5 signaling pathway (Sarkar et al., 2007; Möller et al., 2017). However, *WOX5* expression is downregulated by exogenous application of auxin *via* IAA17/AUXIN RESISTANT3 (AXR3)–ARF10/16 signaling pathway (Ding and Friml, 2010; Tian et al., 2014), indicating that auxin may restrict *WOX5* expression to the QC. Thus, auxin homeostasis is also important for stabilizing the RAM organization by fine tuning *WOX5* expression. In the QC, activated WOX5 induces the expression of *PLT1* to generate a PLT gradient with the peak in the QC to specify the root stem-cell identity (Ding and Friml, 2010; Mähönen et al., 2014). Accordingly, high levels of PLT in the QC maintain the root SCN; intermediate PLT levels outside of QC promote cell proliferation, and low PLT at the transition zone (TZ) promotes cell expansion and differentiation (Mähönen et al., 2014).

Lateral root development

Lateral root development is controlled by both the TIR1/AFB-mediated auxin signaling in the nucleus and the TMK-mediated auxin pathway at the cell surface (Figure 5C) (Huang et al., 2019; Cavallari et al., 2021). It was shown that the TIR1/AFB-based transcriptional signaling is required for the proper *DR5* oscillation pattern and the subsequent LR positioning. In the XPP cells, the ARF TFs (ARF5, 6, 7, 8, and 19) and repressor IAA28 function downstream of TIR1/AFB to activate the expression of *GATA23* TF that specifies the LRFC identification (Figure 5C) (De Rybel et al., 2010). The loss of *ARF7* leads to aberrant *DR5* oscillation and irregular LR initiation sites (Moreno-Risueno et al., 2010). In addition to LR positioning, the TIR1/AFB-mediated transcriptional signaling also plays a vital role in LR initiation. Before the first ACD of LRFCs, accumulated auxin induces the expression of *LATERAL ORGAN BOUNDARIES-DOMAIN 16/ASYMMETRIC LEAVES2-LIKE 18* (*LBD16/ASL18*) TF *via* the SOLITARY ROOT (SLR)/IAA14–ARF7/ARF19-based auxin signaling module (Goh et al., 2019). LBD16/ASL18 and its downstream proteins are essential for the symmetry breaking of the LRFCs and subsequent ACDs (Figure 5C) (Goh et al., 2012). Furthermore, the LR-lacking phenotype of *arf7;arf19* double mutants can be restored by targeted expression of *LBD16/ASL18* to the XPP cells (Goh et al., 2012). After the first LRFC ACD, the AP2/EREBP-type TF, *PUCHI*, is induced by LBD16/ASL18 in an auxin-dependent manner and is essential for LRP patterning (Goh et al., 2019).

Moreover, TMK-mediated auxin signaling is also required for LRP patterning (Figure 5C) (Huang et al., 2019). TMK1 and TMK4 function redundantly to regulate cell expansion, division, and differentiation *via* mediating both transcriptional and non-transcriptional auxin signaling (Cao et al., 2019; Huang et al., 2019; Wang et al., 2020; Li et al., 2021; Lin et al., 2021; Friml et al., 2022). Interestingly, highly accumulated auxin at the LR initiation sites activates the MKK4/5 (MAPKKs)–MPK3/6 (MAPKs) signaling cascade through TMK1/4-mediated phosphorylation of MKK4/5 that directs cell-division orientation during LRP morphogenesis by an unknown mechanism (Huang et al., 2019), although MAPK signaling was suggested to impinge on mitotic microtubule organization and LRP division patterns (Smékalová et al., 2014; Huang et al., 2019).

Stomatal development

Stomatal development and patterning are also regulated by the TIR1/AFB-AUX/IAA-ARF-based auxin signaling module (Balcerowicz et al., 2014; Zhang et al., 2014). The loss of multiple *TIR1/AFB* genes or their downstream TF *MP/ARF5* gene leads to the formation of stomatal clusters and increased stomatal index. Similar phenotypic defects are also produced by stabilizing the ARF repressor BDL/IAA12 or AXR3/IAA17 (Balcerowicz et al., 2014; Le et al., 2014; Zhang et al., 2014). The working model depicts that, in mesophyll cells, free auxin promotes the interaction between TIR1/AFBs and BDL/IAA12, resulting in the degradation of BDL/IAA12 *via* the 26S proteasome to allow the transcriptional activity of MP/ARF5. Subsequentially, MP/ARF5 represses the expression of the *STOMAGEN/EPFL9* peptide *via* direct binding to its promoter, thus inhibiting stomatal development (Zhang et al., 2014). This study makes a linkage between auxin signaling and peptide signaling in the control of stomatal development. Moreover, light promotes stomatal development that is likely to be mediated through auxin signaling *via* AXR3/IAA17 that functions genetically upstream of the ERECTA receptor family and the YDA–MAPK signaling cascade (Balcerowicz et al., 2014).

BRASSINOSTEROID SIGNALING IN THE REGULATION OF PLANT ACD

The phytohormone brassinosteroids (BRs) coordinate plant growth and development by regulating cell expansion, division, and differentiation (Gudesblat and Russinova, 2011; Qi and Torii, 2018). Upon BR binding, the BRASSINOSTEROID INSENSITIVE 1 (BRI1) receptor is activated to recruit its co-receptor BRIASSOCIATED RECEPTOR KINASE (BAK1) and transduce signaling to the phosphatases BRI1

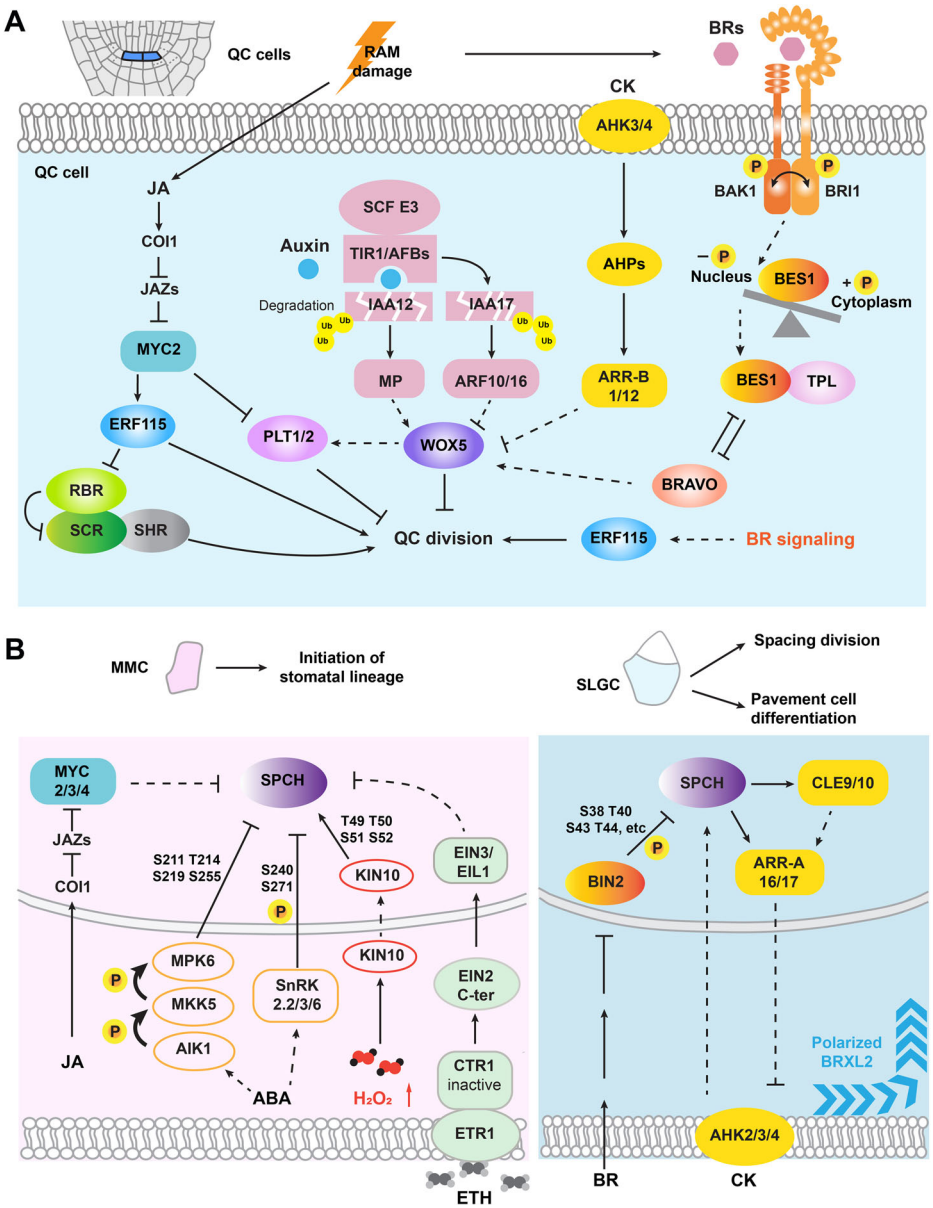

Figure 6. Phytohormonal signaling and crosstalk in the regulation of root apical meristem (RAM) and stomatal divisions

(A) The quiescent center (QC) division is fine tuned by phytohormonal signaling. *WOX5* expression is enriched in the QC cells to restrict cell division. The expression of *WOX5* can be both positively and negatively regulated by auxin-triggered activation of MP/ARF5 and ARF10/16, respectively. Cytokinin (CK) signaling suppresses the expression of *WOX5* by activating the ARR1/12 transcription factors (TFs). Brassinosteroids (BR) trigger the activity of the BRI1 and BAK1 receptors that eventually promote the nuclear partition of the BES1 TF in the QC cells, where BES1 interacts with the transcription co-repressor TPL to suppress the expression of *BRAVO/MYB56* that functions to restrict QC cell division. Following stress or damage, BR signaling is elevated, so that BES1-mediated suppression on BRAVO/MYB56 is strengthened to promote cell division for stem-cell replenishment. Upon wounding, jasmonic acid (JA) signaling induces the expression of *MYC2* and *ERF115* that releases the inhibition of RBR on SCR, so that elevated SCR functions together with SHR to promote cell division in the QC. **(B)** In *Arabidopsis*, the key TF SPCH in stomatal development is heavily regulated in pre-division (left) and post-division (right) cells. In meristemoid mother cells (MMCs) (pre-division cell, light pink), the SPCH protein is differentially phosphorylated by multiple kinases, including MPK6 and SnRK in the abscisic acid (ABA) signaling pathway, resulting in SPCH degradation. However, H_2O_2 signaling triggers the nuclear partition of the KIN10 kinase to phosphorylate SPCH for stabilization. Specific phosphorylation sites for SPCH are noted on each branch. JA signaling suppresses stomatal initiation through MYC2/3/4 that are likely to function through SPCH. Ethylene signaling suppresses stomatal initiation by an unknown mechanism (likely to be through SPCH), which also influences the polarization events represented by BRXL2 (blue arrowhead shapes in the SLGC). In the SLGCs that undergo pavement differentiation or spacing division (light blue), SPCH is phosphorylated by BIN2 kinase in the BR signaling pathway for protein degradation. CK signaling promotes *SPCH* expression that induces the expression of *CLE9/10* ligands and *ARR-A* TFs, both of which in turn suppress CK signaling. Thus, a locally reduced CK signaling is maintained in the SLGC.

SUPPRESSOR1/BSU-LIKEs (BSU1/BSLs), which inactivate the central repressor GSK3/SHAGGY-like kinase BIN2 *via* dephosphorylation and protein degradation, ultimately leading to the de-repression and nuclear localization of two key TFs, BRASSINAZOLE RESISTANT 1 (BZR1) and BRI1 EMS SUPPRESSOR1 (BES1), for BR responses (Figure 6A) (Kim and Russinova, 2020).

The QC and stem cells

The RAM maintenance is dependent on the BR homeostasis, as over-threshold or absence of BR leads to reduced RAM size (González-García et al., 2011). Levels of BR responses in the cell can be represented by differential nucleo-cytoplasmic partitioning of BZR1 and BES1, in that higher nuclear distribution of BES1/BZR1 stands for stronger BR responses and *vice versa* (Figure 6A) (Chaiwanon and Wang, 2015). In contrast with the auxin maximum in the root SCN, BZR1 and BES1 localize mainly in the cytoplasm, implicating that the low BR activity is associated with the maintenance of QC identity (Chaiwanon and Wang, 2015). In the elongation zone, BZR1 and BES1 accumulate mostly in the nucleus, indicating that high BR activity is associated with cell elongation and expansion (Chaiwanon and Wang, 2015). Indeed, the interplay between auxin and BR signaling regulates many aspects of plant growth and development, including RAM maintenance (Xuan and Beeckman, 2021).

BR signaling acts within the root SCN by downregulating massive QC-enriched genes to maintain stem-cell quiescence (Figure 6A) (Vilarrasa-Blasi et al., 2014; Chaiwanon and Wang, 2015). BES1 does so through physical interaction with TOPLESS (TPL), the Groucho/Tup1 transcriptional co-repressor, to suppress the gene expression (Espinosa-Ruiz et al., 2017). Among them, an R2R3-MYB TF *BRASSINOSTEROIDS AT VASCULAR AND ORGANIZING CENTER (BRAVO)/MYB56*, is a direct target of BES1 and specifically expressed in the QC, acting as a repressor of QC divisions. Upon environmental stresses, the division rate of QC is accelerated through BES1-dependent transcriptional and post-transcriptional inhibition of BRAVO, thus enabling the recovery of the root SCN upon damage (Vilarrasa-Blasi et al., 2014). Alternatively, under normal conditions, BRAVO is stable and represses the expression of *BES1* to maintain low cell-division frequency in the QC. Thus, the QC division activity is dynamically modulated by the antagonistic circuit composed of BES1-mediated BR signaling and its target BRAVO to respond to the changing environment. In addition, BRs also promote the expression of an ERF/AP2 TF *ETHYLENE RESPONSE FACTOR 115* (*ERF115*) (Heyman et al., 2013) that induces the expression of *PHYTOSULFOKINES 5 (PSK5)* peptides, providing another route to promote QC division (Heyman et al., 2016).

Stem-cell differentiation in the RAM

As auxin molecules, BRs also show sophisticated dosage-dependent regulation in plant development. For example, BRs when applied at different concentrations can contribute opposite effects to the differentiation of distal CSCs (González-García et al., 2011; Lee et al., 2015a). Low concentrations of BRs inhibit CSC differentiation, whereas high concentrations of BRs promote CSC differentiation (González-García et al., 2011; Lee et al., 2015a). The differential regulation of BRs can be explained by the distinct roles of the two key TFs, BZR1 and BES1. Mechanistically, the BR signaling-mediated promotion of CSC differentiation can be achieved through BES1-mediated regulation of *WOX5* expression (González-García et al., 2011), whereas the BR signaling-mediated repression of CSC differentiation is partly achieved through BZR1-dependent regulation of expression and localization of the PIN proteins in the RAM (Lee et al., 2015a).

In summary, the spatial–temporal distribution and signal transduction of BRs in the RAM plays a vital role in SCN maintenance through dynamic regulation of QC cell division and CSC differentiation in response to diverse environmental conditions.

Key regulators of BR signaling in stomatal development

Several studies have indicated that stomatal ACD is regulated by a few key components of the BR signaling pathway, that is the BIN2 GSK3-like kinases and the BSL Ser/Thr protein phosphatases, both of which appear to feed into the MAPK-mediated regulation of SPCH activity (Figure 3A) (Guo and Dong, 2022). More interestingly, both BIN2 kinase and BSL phosphatases show strikingly distinct regulation at the subcellular level. At the cell cortex, BIN2 interacts with the MAPKKK YDA to suppress MAPK signaling, therefore SPCH is stabilized, so that stomatal production is promoted by BIN2 (Kim et al., 2012). Conversely, when BIN2 is accumulated in the nucleus, it directly phosphorylates SPCH for degradation, therefore stomatal production is suppressed by BIN2 (Gudesblat et al., 2012). For the BSL phosphatases, at the cell cortex, the four family members (mainly BSL1) can directly dephosphorylate and activate the MAPKKK YDA to suppress SPCH, thereby suppressing stomatal differentiation (Guo et al., 2021a). However, in the nucleus, the BSL2/BSL3/BSU1 (mainly BSU1) directly dephosphorylates and inactivates MPK3/6 to stabilize SPCH, thereby promoting stomatal differentiation (Guo and Ding, and Dong, 2022). As discussed earlier, how BIN2 and BSL1 differentially regulate cell division in the pre-mitotic and post-mitotic stomatal linage cells, respectively, largely depends on their differential polarization timing (Guo et al., 2021b). Recently, it was shown that the BIN2 kinase activity is enhanced by the scaffold protein POLAR that is mainly polarized in the stomatal ACD precursor cells, raising the possibility that BR signaling is attenuated in the pre-mitotic cells (Kim et al., 2022). This notion is further supported by a lowered nuclear accumulation of BES1, indicating a lowered BR response in stomatal stem cells (Kim et al., 2022). However, whether and how BES1 or BZR1 driving BR responses regulate the stomatal division and/or fate need further investigation.

HORMONAL CROSSTALK IN THE REGULATION OF PLANT ACD

The RAM and QC

As discussed above, the interplay between auxin and BRs maintains RAM homeostasis. Cytokinins (CKs) are essential plant hormones that control numerous processes in plant development (Figure 6). Cytokinin signaling involves receptor-triggered phosphorylation relays and activation of the type B ARABIDOPSIS RESPONSE REGULATOR (ARR-B) TF family proteins for cellular responses (Kieber and Schaller, 2018). In the root tip, CK signaling regulates auxin distribution partially by regulating the expression levels of the PIN proteins. For example, ARR1/ARR-B-mediated CK signaling activates the transcriptional repressor SHY2/IAA3 in the auxin pathway to downregulate the expression of the auxin efflux carrier *PIN1, PIN3*, and *PIN7* genes (Dello Ioio et al., 2008), while ARR12 also participates in the downregulation of the *AUX1* and *LAX2* influx carrier genes (Zhang et al., 2013). Moreover, the type-A ARR negative regulators of CK signaling were found to regulate the PIN proteins at the post-transcriptional level (Zhang et al., 2011). In addition, CK signaling through ARR1 and ARR12 fine tune the expression of master TFs, *WOX5*, and *SCR*, to suppress cell division in the RAM (Figure 6A) (Dello Ioio et al., 2008; Zhang et al., 2013). Conversely, auxin signaling promotes the degradation of SHY2/IAA3 to sustain the activity of the *PIN* genes and division activity in the RAM (Dello Ioio et al., 2008). Therefore, CK and auxin signaling appears to antagonistically regulate the SCN division and differentiation, conferring the sustainability of the RAM in response to diverse environmental conditions.

Jasmonates (JAs) are lipid-derived stress hormones that can integrate environmental signaling to plant growth and development (Figure 6) (Huang et al., 2017). Jasmonate signaling initiates with the perception of JA-Ile (the biologically active form) by its receptor, the F-box CORONATINE INSENSITIVE 1 (COI1) protein, that triggers the degradation of the JASMONATE ZIM-DOMAIN (JAZ) repressors, leading to the activation of downstream TFs, e.g., MYC2/JASMONATE INSENSITIVE1 (JIN1), for JA responses (Ali and Baek, 2020). Jasmonate boosts LR development by promoting the expression of auxin biosynthesis genes (Cai et al., 2014). At the primary root tip, JA modulates the root SCN patterning through the key TF MYC2/JIN1 that represses the expression of *PLT1* and *PLT2* to ultimately promote QC cell division and CSC differentiation (Chen et al., 2011; Zhang et al., 2015a). Apart from this, upon wounding, JA signaling induces the expression of *ERF115*, then the ERF115 TF disturbs the physical interaction of RETINOBLASTOMA-RELATED (RBR), a key cell-cycle inhibitor, with SCR to release the suppression of SCR's function to promote QC divisions (Zhou et al., 2019). Thus, JA signaling plays an important role in a route that induces stem-cell activation and regeneration for the root to cope with adverse environments (Figure 6A).

Abscisic acid (ABA) is a key plant stress-signaling hormone that also contributes to plant growth and development under non-stressed conditions (Brookbank et al., 2021). Abscisic acid has been implicated in maintaining the QC quiescence and suppressing root stem-cell differentiation by regulating the gene expression of *PLT2, MP*, and *WOX5* (Zhang et al. 2010; Promchuea et al., 2017). Abscisic acid signaling was also found to reduce the expression levels of multiple PIN proteins in the root tips to alter auxin distribution and restrict QC division (Yuan et al., 2014; Promchuea et al., 2017; Xie et al., 2021). Although all these activities point to the crosstalk with auxin signaling, the mechanistic understanding of the processes regulated by ABA remains largely unknown.

Stomatal ACD

The bHLH TF SPCH that controls the initiation of stomatal lineage in *Arabidopsis* appeared to be one of the major targets regulated by phytohormone signals and these regulations occur at both the transcription and post-transcription levels (Figure 6B). It has been extensively shown that the SPCH protein activity and stability are dynamically regulated by phosphorylation and dephosphorylation. Among several established kinases and phosphatases upstream of SPCH, both the BIN2 GSK3-like kinase in the BR signaling pathway and the SNF1-related protein kinases (SnRK2.2/2.3/2.6) in the ABA signaling pathway phosphorylate SPCH at distinct sites for degradation (Gudesblat et al., 2012; Yang et al., 2022). Moreover, ABA activates the MKK5–MPK6 kinase cascade by enhancing the activity of a MAPKKK, named ABA-INSENSITIVE PROTEIN KINASE1 (AIK1)/MKKK20 (Li et al., 2017). In striking contrast, KIN10, the catalytic α-subunit of the energy sensor SnRK1, can directly phosphorylate SPCH at specific residues for stabilization (Thr49, Thr50, Ser51, and Ser52) (Han et al., 2020). More recently, it was shown that the KIN10-mediated stabilization of SPCH is enforced by a feedback regulation with H_2O_2 metabolism, so that elevated H_2O_2 in the Ms ensures the nuclear localization of KIN10 and high SPCH in the stomatal ACD precursor cells (Shi et al., 2022). Taken together, given the critical role of SPCH in specifying stomatal development, the emerging theme is that the phosphocodes of SPCH fine tune its protein stability and activity, so that stomatal developmental progression and production can be modulated to optimize plant growth in the changing environment.

At the transcription level, *SPCH* expression can be induced by either CK treatment or activating CK signaling in stomatal lineage cells (Figure 6B) (Vaten et al., 2018). Consistently, the defects of either CK biosynthesis (*ipt1;ipt3;ipt5;ipt7* and *ipt1;ipt3;ipt4;ipt5;ipt6;ipt7;ipt8*) or signaling (*ahk2;ahk3;cre1*) lead to reduced stomatal ACDs (Vaten et al., 2018). Conversely, the SPCH expression activates the production of factors that are repressive to CK

Table 1. Intrinsic and extrinsic singling components in the regulation of plant ACDs

System	Cell type	Component	Gene	Function	Reference(s)
Embryo	Zygote and proembryo	WOX homeobox TFs	*WOX2*	Expresses in the apical daughter cell and is required for the appropriate division pattern of apical zygotic lineages	Wu et al. (2007); Breuninger et al. (2008)
			WOX8/9	Expresses in the basal daughter cell and is required for the appropriate division pattern of both apical and basal zygotic lineages	Wu et al. (2007); Ueda et al. (2011)
		Zinc finger TF	*WRKY2*	Promotes the expression of *WOX8* and *WOX9*	Ueda et al. (2017)
		Polarity components	*SOK1/2/3/4/5*	Regulate embryonic cell division orientation	Yoshida et al. (2019)
		Peptides	*ESF1*	Are secreted from endosperm cells, and have been proposed to act upstream of YDA in embryogenesis	Costa et al. (2014)
		Downstream components of peptide signaling	*BSK1/2/12*	Activate YDA–MAPK signaling cascade in the zygote	Neu et al. (2019)
		MAPK signaling components	*YDA, MKK4/5, MPK3/6*	Is crucial for zygotic polarity building and subsequent ACDs	Lukowitz et al. (2004); Zhang et al. (2017)
	Hypophysis	bHLH TFs	*TMO7*	Is pivotal for hypophyseal ACD	Schlereth et al. (2010)
		Homeobox TF	*WOX5*	Is required for QC identity	Sarkar et al. (2007)
Primary root	QC, CEID, CSC and Epi/LRC stem cell	GRAS TFs	*SHR, SCR*	Promote asymmetric CEID divisions	Cui et al. (2007)
		BIRDS C2H2 zinc finger TFs	*BIB, JKD*	Restrict SHR movement to endodermis	Cui et al. (2007); Welch et al. (2007); Long et al. (2015b)
		Homeobox TF	*WOX5*	Specifically expressed in QC and is essential for root SCN maintenance	Pi et al. (2015)
		NAC domain TFs	*FEZ, SMB*	Antagonistically control the asymmetric divisions and differentiation of columella and Epi/LRC stem cells	Willemsen et al. (2008); Bennett et al. (2014)
		AP2-domain TFs	*PLT1/2*	Function in a dose-dependent manner, and are crucial for root SCN maintenance, stem-cell division and differentiation	Mähönen et al. (2014)
Primary root	QC, CEID, CSC and Epi/LRC stem cell	ERF/AP2 TF	*ERF115*	Promotes QC cell division	Heyman et al. (2013, 2016)
		R2R3-MYB TF	*BRAVO (MYB56)*	Is required to keep a low rate of QC cell division	Vilarrasa-Blasi et al. (2014)
		Polarity components	*BRX, PAX*	Fine tune PPSE differentiation through modulating PIN-mediated auxin efflux	Scacchi et al. (2009); Marhava et al. (2018)
			SOK1/2/3/5	Ectopically expressing SOK1 in root meristem disrupts cell division orientation	Yoshida et al. (2019)
			KOIN, IRK	Suppress ground tissue stem-cell divisions	Rodriguez-Furlan et al. (2022)
		Peptides	*CLE40*	Suppresses the divisions of CSCs *via* binding to CLV1 and ACR4	Stahl et al. (2013)
		Receptor	*CLV1, ACR4*	Suppresses the divisions of CSCs	Stahl et al. (2013)
Lateral root	LRFC	GATA zinc finger TF	*GATA23*	Is required for LRFC specification	De Rybel et al. (2010)
		Class I LBD TF	*LBD16 (ASL18)*	Is required for the symmetry breaking of LRFCs and subsequent ACDs	Goh et al. (2019)
		AP2/EREBP-type TF	*PUCHI*	Is essential for LRP patterning	Goh et al. (2019)
Stomatal lineage	MMC, M, SLGC	bHLH TFs	*SPCH*	Initiates stomatal ACDs	MacAlister et al. (2006); Robinson et al. (2011)

Continued

Table 1. Continued

System	Cell type	Component	Gene	Function	Reference(s)
			MUTE	Is required to terminate the M amplifying ACDs and acquire GMC fat	Pillitteri et al. (2007); Adrian et al. (2015)
			FAMA	Prevents extra symmetric divisions in GMC and induces the GC identity	Ohashi-Ito and Bergmann (2006)
			SCRM (ICE1), SCRM2	Work with SPHC, MUTE, and FAMA by forming heterodimer TF complexes	Kanaoka et al. (2008)
		Polarity components	*BASL*	Plays a pivotal role in directing stomatal ACDs and specifying daughter-cell fate	Zhang et al. (2015b); Gong et al. (2021a)
Stomatal lineage	MMC, M, SLGC	Polarity components	*BRX/ BRXL1/2/3/4*	Work as molecular partners of BASL, and redundantly regulate stomatal ACDs	Rowe et al. (2019)
			BIN2	Dynamically regulates SPCH activity during stomatal ACDs	Houbaert et al. (2018); Guo et al. (2021a)
			POLAR	Is required to regulate stomatal ACDs by recruiting BIN2	Pillitteri et al. (2011); Houbaert et al. (2018)
			BSL1	Suppresses stomatal ACDs and promotes daughter-cell fate determination	Guo et al. (2021b, 2022)
		Peptides	*EPF1*	Orients SLGC spacing ACDs, and inhibits stomatal differentiation by binding to the ERL1–TMM complex	Qi et al. (2017)
			EPF2	Represses stomatal ACDs *via* binding to the ER–TMM receptor complex	Hara et al. (2009); Hunt and Gray (2009); Horst et al. (2015)
			EPFL9 (STOMAGEN)	Promotes stomatal ACDs by competing with EPF2 and EPF1 for binding to their receptors	Sugano et al. (2010); Lee et al. (2015b)
			EPFL6 (CHALLALH)	Specifically expressed in the stem internal tissues, and is required to confer regional specification of stomatal production in the epidermis *via* binding to the ERL1 receptor	Abrash and Bergmann (2010)
			CLE9/10	Suppress stomatal production through the HSL1 receptor	Qian et al. (2018)
		Receptor	*ER*	Activates the downstream YDA–MKK4/5–MPK3/6 signaling cascade to degrade SPCH	Shpak et al. (2005); Lee et al. (2015b)
			ERL1	Activates the downstream YDA–MKK4/5–MPK3/6 signaling cascade to degrade MUTE	Shpak et al. (2005); Qi et al. (2017)
			ERL2	Prevents the fate transition from M to GMC	Shpak et al. (2005); Lin et al. (2017)
			HSL1	Recruits the SERK co-receptors to suppress SPCH levels	Qian et al. (2018)
Stomatal lineage	MMC, M, SLGC	Co-receptor	*TMM*	Works as a molecular partner of ER family proteins to regulate stomatal development and patterning	Nadeau and Sack (2002); Lin et al. (2017)
			SERK1/2/3/4	Redundantly regulate stomatal patterning	Meng et al. (2015); Qian et al. (2018)
		MAPK signaling components	*YDA, MKK4/5, MPK3/6*	Phosphorylate and de-stabilize SPCH to optimize stomatal patterning	Lampard et al. (2008); Guo et al. (2021a)
	SMC (monocots)	bHLH TFs	*MUTE*	Expresses in GMC but can move to adjacent SMC, and is crucial for the asymmetric division of SMC and the symmetric division of GMC	Raissig et al. (2017); Wang et al. (2019)

Continued

Table 1. Continued

System	Cell type	Component	Gene	Function	Reference(s)
		Polarity components	*PAN1/2*	Are pivotal for appropriate SMC division-plane positioning	Cartwright et al. (2009); Zhang et al. (2012)
			ROP GTPases	Are required for asymmetric SMC divisions	Facette et al. (2015)
			BRK1/2/3 (WRC)	Are required for PAN1/2 and ROPs polarization	Facette et al. (2015)
			WPRA1/2, WPRB1/2	Work downstream of PAN2 to direct SMC division-plane orientation through modulating actin filaments	Nan et al. (2022)
			BdPOLAR	Displays a distally polarized localization in SMCs, and is required for appropriate SMC division-plane positioning	Zhang et al. (2022)

Abbreviations: ACD, asymmetric cell division; TF, transcription factor. Primary root-related abbreviations: CEI, cortex/endodermal initial; CEID, cortex/endodermal initial daughter; CSC, columella stem cell; Epi/LRC, epidermis/lateral root cap; LRC, lateral root cap; OZ, oscillation zone; PPSE, protophloem sieve element; QC, quiescent center; RAM, root apical meristem; SCN, stem-cell niche; TZ, transition zone. Lateral root-related abbreviations: LR, lateral root; LRFC, lateral root founder cell; LRP: lateral root primordium. Stomatal lineage-related abbreviations: GC, guard cell; GMC, guard mother cell; M, meristemoid; MMC, meristemoid mother cell; SC (monocots), subsidiary cell; SLGC, stomatal lineage ground cell; SMC (monocots), subsidiary mother cell.

Table 2. Hormone signaling in the regulation of plant ACDs

System	Cell type	Component	Gene	Function	Reference(s)
Embryo	Zygote and proembryo	Auxin biosynthesis	*TAA1, YUC1/3/4/8/9/10/11*	Display dynamic expression patterns during embryogenesis, and are essential for establishing an apical–basal asymmetric division pattern	Robert et al. (2018)
		Auxin efflux carriers	*PIN1/3/4/7*	Are required for proper embryonic division pattern *via* dynamically directing auxin flows	Friml et al. (2003) Blilou et al. (2005)
		Auxin influx carriers	*AUX1, LAX1/2*	Are required for the formation of the embryonic shoot and root apex	Robert et al. (2015)
		Auxin receptor	*TIR1, AFB1/2/3*	Work redundantly to regulate embryo development	Prigge et al. (2020)
		AUX/IAAs	*BDL (IAA12)*	Is required for appropriate embryonic division pattern *via* repressing MP (AR5) activity	Schlereth et al. (2010); Rademacher et al. (2012)
		Auxin signaling TFs	*MP (ARF5)*	Is essential for appropriate embryonic division pattern	Schlereth et al. (2010); Rademacher et al. (2012); Krogan et al. (2016)
	Hypophysis	Auxin efflux carriers	*PIN1/7*	Are essential for hypophysis specification and subsequent hypophyseal ACD through directing auxin accumulation in the uppermost cell of the suspensor	Friml et al. (2003)
		Auxin influx carriers	*AUX1, LAX2*	Are required for hypophyseal ACD	Robert et al. (2015)
		AUX/IAAs	*BDL (IAA12)*	Is required for hypophyseal ACD *via* repressing MP (AR5) activity	Schlereth et al. (2010); Rademacher et al. (2012)
		Auxin signaling TFs	*MP (ARF5)*	Is required for hypophyseal ACD	Schlereth et al. (2010); Rademacher et al. (2012); Möller et al. (2017)

Continued

Table 2. Continued

System	Cell type	Component	Gene	Function	Reference(s)
Primary root	QC, CEID, CSC and	Auxin biosynthesis	*TAA1, YUC1*	Maintain high auxin level in root SCN	Brady et al. (2007); Tian et al. (2014)
	Epi/LRC stem cell	Auxin efflux carriers	*PIN1/2/3/4/7*	Promote auxin accumulation in root SCN through forming auxin reflux loop	Blilou et al. (2005)
Primary root	QC, CEID, CSC and	AUX/IAAs	*BDL (IAA12)*	Acts as a repressor of MP (ARF5)	Möller et al. (2017)
	Epi/LRC stem cell		*AXR3 (IAA17)*	Acts as a repressor of ARF10/16	Ding and Friml (2010); Tian et al. (2014)
		Auxin signaling TFs	*MP (ARF5)*	Is required for root SCN maintenance *via* inducing *WOX5* expression	Möller et al. (2017)
			ARF10/16	Are required for root SCN maintenance *via* downregulating *WOX5* expression	Ding and Friml (2010); Tian et al. (2014)
		BR signaling TFs	*BES1*	Promotes QC cell division through transcriptional and post-transcriptional inhibition of BRAVO	Chaiwanon and Wang (2015); Espinosa-Ruiz et al. (2017)
			BES1	Activates the distal CSCs differentiation *via* regulating *WOX5* expression	González-García et al. (2011)
			BZR1	Suppresses the distal CSCs differentiation partially by altering the expression and subcellular localization of PIN proteins	Lee et al. (2015a)
		CK response TFs (type B ARRs)	*ARR1/12*	Promotes QC cell division and CSCs differentiation by downregulating the expression of *WOX5 SCR, PIN1/3/7, AUX1* and *LAX2*	Moubayidin et al. (2013); Zhang et al. (2013)
		CK signaling repressor (type-A ARRs)	*ARR3/4/5/6/7/8/9/15*	Are required for post-transcriptional regulation of PIN efflux carriers in root tips	Zhang et al. (2011)
		JA signaling TF	*MYC2 (JIN1)*	Promotes QC cell division and CSCs differentiation through directly downregulating *PLT1/2* expression and upregulating *ERF115* expression	Chen et al. (2011); Zhou et al. (2019)
Lateral root	LRFC	Auxin biosynthesis	*YUC4*	Maintains auxin maximum in specified LRFCs	Tang et al. (2017)
		Auxin influx carriers	*AUX1*	Mediates the auxin transport from LRC, and is required for LRFC specification and subsequent ACDs	De Smet et al. (2007)
Lateral root	LRFC	Auxin efflux carriers	*PIN3*	Facilitates auxin transport into LRFCs for the subsequent ACDs	Marhavý et al. (2013, 2016)
		AUX/IAAs	*IAA28*	Is required for LRFC specification	De Rybel et al. (2010)
			SLR (IAA14)	Is required for LRFC ACDs through repressing *ARF7/19* activity	Goh et al. (2012, 2019)
		Auxin signaling TFs	*ARF5/6/7/8/19*	Play a crucial role in LRFC specification *via* upregulating *GATA23* expression	De Rybel et al. (2010); Moreno-Risueno et al. (2010)
			ARF7/19	Are crucial for LRFC ACDs *via* inducing *LBD16* expression	Goh et al. (2012, 2019)
		Non-canonical auxin signaling	*TMK1/4*	Are required for proper LRP division pattern through activating MKK4/5–MPK3/6 signaling cascade	Huang et al. (2019)
		MAPK signaling components	*MKK4/5, MPK3/6*	Are required for proper LRP division pattern	Huang et al. (2019)
Stomatal lineage	MMC, M, SLGC	Auxin efflux carriers	*PIN1/2/3/4/7*	Dynamically regulate auxin levels in stomatal lineage cells, and are required for proper stomatal patterning	Le et al. (2014)
		AUX/IAAs	*BDL (IAA12)*	Regulates stomatal development through repressing MP (ARF5) activity	Zhang et al. (2014)

Continued

Table 2. Continued

System	Cell type	Component	Gene	Function	Reference(s)
			AXR3 (IAA17)	Works genetically upstream of the YDA–MAPK signaling cascade to regulate stomatal differentiation in darkness	Balcerowicz et al. (2014)
		Auxin signaling TFs	*MP (ARF5)*	Suppresses stomatal development through downregulating *EPFL9 (STOMAGEN)* expression	Zhang et al. (2014)
		CK signaling TFs	*ARR16/17*	Repress CK response and SLGC spacing ACDs	Vaten et al. (2018)
		ABA signaling components	*SnRK2.2/ 2.3/2.6*	Directly phosphorylate SPCH and suppress stomatal ACDs	Yang et al. (2022)
			AIK1 (MKKK20)	Activates MKK5–MPK6 kinase cascade and suppresses stomatal ACDs	Li et al. (2017)
		ETH signaling components	*CTR1, EIN2, EIN3*	Regulates BRXL2 polarity and M amplifying ACDs	Gong et al. (2021b)
Stomatal lineage	MMC, M, SLGC	JA signaling components	*MYC2/3/4*	Repress *SPCH* expression and stomatal ACDs	Han et al. (2018)
		H_2O_2-scavenging enzyme	*APX1, CAT2*	Are required to regulate stomatal ACD through governing H_2O_2 level in stomatal lineage cells	Shi et al. (2022)
		H_2O_2 response component	*KIN10*	Phosphorylates and stabilizes SPCH when intracellular H_2O_2 is accumulated	Han et al. (2020); Shi et al. (2022)

Phytohormone-related abbreviations: ABA, abscisic acid; BR, brassinosteroid; CK, cytokinin; ETH, ethylene; IAA, indole-3-acetic acid; JA, jasmonic acid.

signaling, including two signaling peptides, CLE9 and CLE10, and two type-A ARRs (ARR16 and ARR17). This negative feedback between SPCH and CK signaling creates a lowered level of local CK signaling that is mainly linked to the SLGC and their specified spacing ACDs (Vaten et al., 2018). Besides CK, *SPCH* expression is also repressed by MYC2/3/4-mediated JA signaling (Han et al., 2018), but whether this regulation is direct or indirect needs more investigation.

The self-renewal capacity of stomatal lineage cells is recently linked to ethylene signaling and nutrient availability (Figure 6B) (Gong et al., 2021b). This connection was revealed through mutant screening for depolarized BRXL2-YFP in stomatal lineage cells and the causative mutation was identified with the Raf-like kinase *CONSTITUTIVE TRIPLE RESPONSE* (*CTR1*), a key repressive regulator in ethylene signaling. In *ctr1* mutants, the depolarized BRXL2 was eventually linked to the reduced self-renewal capacity of the Ms and, interestingly, the phenotypes can be complemented by the external application of glucose (Gong et al., 2021b). How ethylene signaling and nutrients antagonistically fine tune stomatal stem-cell divisions remains an intriguing question to be addressed in the future.

CONCLUSION AND PERSPECTIVES

Research in the past decade made significant progress toward uncovering components and molecular mechanisms underlying plant ACD in development. In summary, the generation of cell-type diversity involves shared mechanisms, including (i) differential expression of cell-fate determinants, (ii) cell polarity-driven unequal cell signaling and physiology, and (iii) extracellular cue-directed signal transduction. These regulators and their functions are summarized in Table 1. As anticipated, the phytohormones, either through components of one pathway or through crosstalk with the other pathway, participate in the regulation of plant ACD. We mainly use the root and stomatal systems to elaborate on their contribution (Table 2). In addition, environmental signals, such as light, temperature, and carbon dioxide, are also required to regulate plant ACD (see recent reviews by Qi and Torii, 2018; Lee and Bergmann, 2019), which we did not discuss in this review due to the space limit. Although the molecular components involved in different plant ACD systems are divergent, some strategies are shared, such as the spatiotemporal segregation of key TFs mediated by protein movement or cell-type-specific transcriptional and post-transcriptional regulations (Figure 1). It becomes clear that master TFs and polarity proteins act as central hubs to integrate peptide signaling and hormonal regulation, thereby cell-division patterns are optimized in response to various developmental and environmental cues. For example, SPCH, acting as a pivotal TF in initiating stomatal ACD, is differentially regulated for its stability and/or stability by "phosphocodes" to interpret signaling triggered by hormones or biochemical cues (Figure 6B). However, the mechanistic understanding behind the phosphocode-dependent regulation of SPCH activity remains lacking. Similarly, polarity proteins, such as BASL and POLAR, also undergo phosphorylation-based modification that are

required for their stability or degradation (Zhang et al., 2015b; Houbaert et al., 2018). Future studies on post-transcriptional modification of key TFs and polarity proteins will expand our understanding of the regulatory mechanism of plant ACD. Additionally, more progress has been made in the research of epigenetic regulation of stem-cell ACD (Alejo-Vinogradova et al., 2022) and the results hold the promise to uncover how key TFs are initially expressed in specific stem-cell populations. Using advanced single-cell RNA-sequencing (scRNA-seq) technologies, the spatiotemporal resolution of single-cell transcriptomics data started to reveal fine-grained models of stem-cell division and differentiation in *Arabidopsis* (Denyer et al., 2019; Zhang et al., 2019; Lopez-Anido et al., 2021). In the future, the wide use of scRNA-seq technologies in different plant species will provide a new avenue to study ACD at the evolutionary level. Indeed, two recent studies showed that scRNA-seq had been successfully applied in rice roots, providing a paradigm-shifting strategy toward mechanistically understanding plant development in crop species (Liu et al., 2021; Zhang et al., 2021). In addition, synthetic biology is rapidly emerging and has the potential to revolutionize many aspects of our lives. A deep understanding of the regulatory mechanism of plant ACD will help us to design synthetic genetic circuits, as has happened to eukaryotic cell lines and prokaryotic bacteria (Nielsen et al., 2016; Gao et al., 2018), so that plant development and patterning can be reprogrammed for improving food yield and quality and enhanced adaption to an ever-changing climate. Indeed, a recent study on the application of synthetic genetic circuits to engineer *Arabidopsis* root development opens new avenues to translate basic research into agricultural applications (Brophy et al., 2022).

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Y.Z. and J.D. wrote the manuscript. Y.Z., J.D., and T.X. revised the manuscript. All authors read and approved of its content.

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