Paired Receptor and Coreceptor Kinases Perceive Extracellular Signals to Control Plant Development[1][OPEN]

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Cell-to-cell and cell-to-environment communications are essential for plant growth, development, and adaptation to various environmental conditions. Receptor-like protein kinases (RLKs) are critical plasma membrane-localized proteins transducing extracellular signals into the cell to coordinate cellular activities during these processes. ZmPK1, the first plant RLK isolated via screening a maize (*Zea mays*) root cDNA library, contains a transmembrane domain linking a cytoplasmic Ser/Thr protein kinase domain and an extracellular domain that is similar to the S-locus glycoproteins of *Brassica* (Walker and Zhang, 1990). Subsequently, a growing number of plant *RLK* genes were identified, such as *S-LOCUS RECEPTOR KINASE* from *Brassica oleracea* (Stein et al., 1991) as well as *ARABIDOPSIS RECEPTOR KINASE1* (Tobias et al., 1992) and *TRANSMEMBRANE KINASE1* from Arabidopsis (*Arabidopsis thaliana*; Chang et al., 1992). Since this class of plant protein kinases show structural similarity to the mammalian growth factor receptor protein kinases, but no corresponding ligands of these putative receptors were identified at the time, they were designated as RLKs (Walker, 1993, 1994). Xa21, an RLK conferring rice (*Oryza sativa*) pathogen recognition and response, was the first plant RLK with defined biological function (Song et al., 1995). Thereafter, bioinformatics analyses identified an RLK superfamily that contains more than 610 and 1,131 members in the genomes of Arabidopsis and rice, respectively (Shiu and Bleecker, 2001; Shiu et al., 2004). Among these, there are around 420 typical RLKs in Arabidopsis, and the rest were named receptor-like cytoplasmic kinase (RLCK) due to absence of the extracellular domain (Shiu and Bleecker, 2001). Henceforth, a broad avenue was opened for investigating the molecular mechanisms underlying cell signaling in response to various extracellular signals during plant growth and development.

In the past two decades, the biological functions of a number of RLKs have been revealed. Many of them mediate signals of canonical phytohormones or peptide hormones to control plant development. For example, BRASSINOSTEROID INSENSITIVE1 (BRI1) perceives brassinosteroids to regulate cell elongation and plant growth (Li and Chory, 1997; Clouse and Sasse, 1998; Wang et al., 2001). Sulfated peptide phytosulfokine (PSK) is perceived by PSK RECEPTOR1 (PSKR1) to regulate cell division and expansion (Matsubayashi and Sakagami, 1996; Matsubayashi et al., 2002, 2006). Some RLKs, including the *Catharanthus roseus* RLK1-LIKE (CrRLK1L) subfamily members FERONIA (FER), ANXUR1/2 (ANX1/2), and BUDDHA'S PAPER SEAL1/2 (BUPS1/2), regulate pollen tube-female gametophyte interactions during fertilization (Huck et al., 2003; Escobar-Restrepo et al., 2007; Boisson-Dernier et al., 2009; Miyazaki et al., 2009; Ge et al., 2017). In addition, RLKs are also involved in the recognition of molecular

ADVANCES

- Plants possess a superfamily of RLKs that control pivotal biological processes during plant growth and development.
- RLKs form receptor–coreceptor complexes to transduce external signals and regulate plant development.
- SERKs are indispensable coreceptors that function with ligand-binding RLK receptors to regulate various biological processes.
- CIKs are emerging as a group of coreceptors that determine cell fate during anther development and SAM maintenance.
- Some downstream signaling components have been identified in RLK-mediated signaling pathways.

[1]This work was supported by National Natural Science Foundation of China (grant nos. 31970339, 31770312, 31470380, 31530005, and 31720103902), the 111 Project (grant no. B16022), and the Fundamental Research Funds for the Central Universities (grant nos. lzujbky-2019-kb05 and lzujbky-2020-kb05).

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[OPEN]Articles can be viewed without a subscription.

www.plantphysiol.org/cgi/doi/10.1104/pp.19.01343

pattern elicitors to regulate plant immune responses. For instance, FLAGELLIN-SENSING2 (FLS2) is required for the perception of bacterial flagellin (Gómez-Gómez and Boller, 2000). ELONGATION FACTOR-TU (EF-Tu) RECEPTOR (EFR) is required for the EF-Tu-triggered response (Zipfel et al., 2006). PEP1 RECEPTOR1 (PEPR1) and PEPR2 sense endogenous danger signal Pep peptides (Yamaguchi et al., 2006, 2010; Krol et al., 2010). In addition, CHITIN ELICITOR RECEPTOR KINASE1 specifically interacts with chitin oligomers (Miya et al., 2007; Wan et al., 2008). To date, only a small portion of RLKs have been functionally characterized.

Most functionally defined RLK receptors require a different RLK as a coreceptor to recognize diverse extracellular signals. BRI1-ASSOCIATED RECEPTOR KINASE1 (BAK1) was the first identified RLK coreceptor essential for brassinosteroid signaling (Li et al., 2002; Nam and Li, 2002). BAK1, also designated as SOMATIC EMBRYOGENESIS RECEPTOR-LIKE KINASE3 (SERK3), belongs to a small SERK subfamily that comprises five members in Arabidopsis (Hecht et al., 2001). *Daucus carota* SERK (DcSERK) was originally identified in carrot suspension cell cultures as a marker for competent and embryogenic cells during somatic embryogenesis (Schmidt et al., 1997). Arabidopsis SERKs were recently demonstrated to control stem cell division patterns during zygotic embryogenesis (Li et al., 2019). The extracellular domains of all five Arabidopsis SERKs contain five leucine-rich repeats (LRRs), which are relatively short compared with most known ligand-binding RLK receptors, such as BRI1 with 25 LRRs in its extracellular domain (Chinchilla et al., 2009). BAK1 and SERKs function as coreceptors that can directly interact with diverse ligand-binding RLK receptors to regulate a variety of biological processes (Li, 2010; Ma et al., 2016). For example, BAK1 is required by BRI1 to mediate brassinosteroid signaling (Li et al., 2002; Nam and Li, 2002). SERK1 and SERK2 are required for EXCESS MICROSPOROCYTES1 (EMS1)/EXTRA SPOROGENOUS CELLS (EXS)-regulated tapetum specification (Li et al., 2017). The pattern recognition receptors FLS2, EFR, and PEPR1/2 also recruit BAK1/SERKs as coreceptors to regulate plant immune responses (Chinchilla et al., 2007; Heese et al., 2007; Schulze et al., 2010; Roux et al., 2011; Antolín-Llovera et al., 2012; Böhm et al., 2014). More recently, CLV3 INSENSITIVE RECEPTOR KINASES (CIKs) were uncovered as another group of coreceptors that control anther cell specification and the homeostasis of the shoot apical meristem (SAM; Cui et al., 2018; Hu et al., 2018). Both SERK and CIK subfamilies belong to group II LRR-RLKs. Several recent studies revealed that a group of glycosylphosphatidylinositol (GPI)-anchored proteins, including LORELEI and its homologs LORELEI-like-GPI-anchored protein1 (LLG1), LLG2, and LLG3, are also required as coreceptors of CrRLK1L receptors FER, ANX1/2, and BUPS1/2 to control root growth, pollen cell wall integrity, and pollen tube reception (Li et al., 2015; Liu et al., 2016; Feng et al., 2019; Ge et al., 2019; Xiao et al., 2019). In this review, we focus on current advances in RLK-SERK and RLK-CIK complexes during plant growth and development.

THE BRI1-SERK COMPLEX REGULATES BRASSINOSTEROID SIGNALING

Brassinosteroids are a group of phytohormones essential for cell elongation and plant growth (Clouse and Sasse, 1998). BRI1, a typical RLK containing an LRR-type extracellular domain, was first identified as a putative brassinosteroid receptor (Li and Chory, 1997). A number of later analyses demonstrated that BRI1 is indeed the receptor of brassinosteroids. For example, photoaffinity cross-linking analyses indicated that LRR22 and the 70-amino acid island domain between LRR21 and LRR22 in the extracellular domain of BRI1 are required for brassinosteroid perception (Kinoshita et al., 2005). Structural analysis further demonstrated that the island domain and LRR21 to LRR25 form a surface pocket in the interior of the superhelical BRI1 extracellular domain for brassinosteroid binding (Hothorn et al., 2011; She et al., 2011).

Although the physical interaction of brassinolide, the most active form of brassinosteroids, with BRI1 does not require the coreceptor BAK1 (Kinoshita et al., 2005), genetic results strongly demonstrated that BAK1 and SERKs are absolutely required for brassinosteroid signaling (Li et al., 2002; Gou et al., 2012). BRI1 and BAK1 interact and transphosphorylate each other in a brassinosteroid-dependent manner in planta (Li et al., 2002; Wang et al., 2005, 2008). The dark-grown *serk1 bak1 bkk1* triple mutant exhibits a typical deetiolation phenotype with opened cotyledons and deetiolated hypocotyls, which is similar to null *bri1* mutants. The phosphorylation levels of BRI1 in *serk1 bak1 bkk1* triple mutants cannot be induced upon exogenous application of brassinolide, indicating that phosphorylation and activation of BRI1 depend on functional BAK1 and SERKs. Consistent with the disruption of the brassinosteroid signaling, the downstream unphosphorylated active *bri1*-EMS-SUPPRESSOR1 (BES1) cannot be detected in the triple *serk* mutants with or without the treatment of exogenous brassinolide (Gou et al., 2012). Further structural analyses revealed that brassinosteroids act as molecular glue to mediate the physical interaction between the extracellular domains of BRI1 and BAK1. BAK1 is recruited to the interaction platform after the perception of brassinosteroids by BRI1 to stabilize the interaction and activate the downstream signaling pathway (Santiago et al., 2013; Sun et al., 2013). These results demonstrated that BAK1 and other SERK members function as essential coreceptors in BRI1-mediated brassinosteroid signaling (Fig. 1A). It was proposed that the interaction between BRI1 and BAK1 may stabilize the αC helix, which may be necessary for the activation of these two RLKs upon brassinosteroid binding (Moffett et al., 2017). Recent

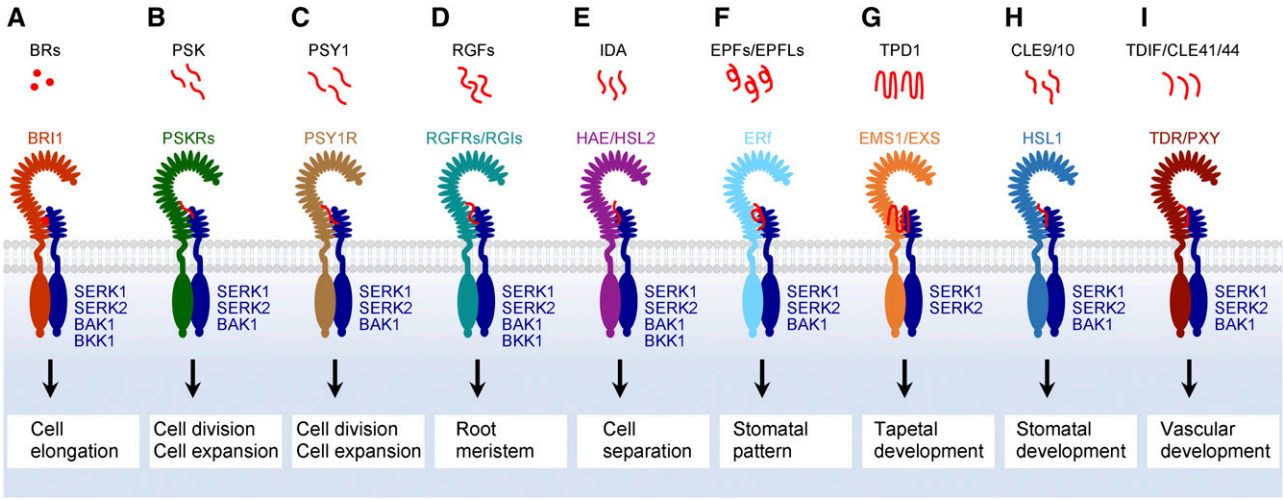

Figure 1. SERKs mediate a variety of signals to regulate plant growth and development. Extracellular signals, phytohormones or peptides, are perceived by RLK receptors with a large extracellular LRR domain. SERKs with a small extracellular LRR domain are recruited to form complete ligand-receptor-coreceptor complexes that transduce extracellular signals into intracellular responses for diverse biological functions. A, Phytohormone brassinosteroids (BRs) are perceived by the BRI1-SERK complex to regulate cell elongation. B and C, PSKR-SERK (B) and PSY1R-SERK (C) complexes perceive PSK and PSY1 peptides to control cell division and cell expansion, respectively. D, RGFs are perceived by the RGFR/RGI-SERK complex to regulate the root meristem. E, The HAE/HSL2-SERK complex senses IDA peptide to regulate cell separation processes. F, EPF/EPFL family peptides are perceived by the ERf-SERK complex to control the stomatal pattern. G, TPD1 peptide is perceived by the EMS1/EXS-SERK complex to specify tapetal cells. H, CLE9/10 is perceived by the HSL1-SERK complex to regulate stomatal development. I, The TDR/PXY-SERK complex perceives the TDIF/CLE41/44 peptide to regulate vascular development.

results demonstrated that the interaction between BRI1 and BAK1 is tightly regulated to appropriately transduce the brassinosteroid signal. For instance, BAK1-INTERACTING RECEPTOR-LIKE KINASE3 (BIR3), a member of LRR-RLK subgroup X, can directly interact with BRI1 and BAK1 in the absence of brassinosteroid to prevent the formation of the BRI1-BAK1 receptor complex, thereby negatively regulating brassinosteroid signaling (Imkampe et al., 2017; Großeholz et al., 2019). Consistent with this, structural analyses revealed that the elongated mutant of BAK1 contains a single amino acid substitution in the core of the SERK-BIR complex interface, which disrupts the interaction of BAK1 to BIRs, resulting in enhanced brassinosteroid signaling (Whippo and Hangarter, 2005; Hohmann et al., 2018a). By contrast, the immunophilin-like FK506-BINDING PROTEIN42/TWISTED DWARF1 promotes the interaction and phosphorylation of BRI1 and BAK1 in response to brassinosteroids (Chaiwanon et al., 2016; Zhao et al., 2016). The regulation of interaction and phosphorylation of the receptor and coreceptor provides an effective way to fine-tune early brassinosteroid signaling as well as integrate other external signals, such as phytohormones and pathogen stresses. Consistent with the vital and conserved functions of brassinosteroid signaling, homologous BRI1 and BAK1/SERKs have also been identified in crop plants, such as rice (Nakamura et al., 2006; Li et al., 2009; Park et al., 2011; Zhang et al., 2016a), maize (Kir et al., 2015), and tomato (*Solanum lycopersicum*; Bajwa et al., 2013; Peng and Kaloshian, 2014).

PSKR/PSY1R/RGI-SERK PAIRS PERCEIVE SULFATED PEPTIDES TO REGULATE CELL PROLIFERATION AND ROOT MERISTEM MAINTENANCE

Besides their roles in response to the canonical phytohormones, brassinosteroids, RLKs also mediate peptide hormones to regulate various processes in plant growth and development (Murphy et al., 2012; Hirakawa and Sawa, 2019). PSK is a posttranslationally sulfated pentapeptide that was identified from suspension cultures of *Asparagus officinalis* and rice and that can effectively promote cell proliferation at nanomolar concentrations (Matsubayashi and Sakagami, 1996; Matsubayashi et al., 1997). Preprophytosulfokine genes were identified in Arabidopsis and crop plants, such as rice, maize, and cotton (*Gossypium hirsutum*; Yang et al., 1999; Lorbiecke et al., 2005; Han et al., 2014; Sauter, 2015), suggesting that they possess conserved roles in regulating plant development. PSK acts as a non-cell-autonomous signal to promote growth, which is dependent on brassinosteroid biosynthesis and signaling (Hartmann et al., 2013). PSK signaling is also required for pollen tube growth and funicular pollen tube guidance in Arabidopsis and fiber elongation in cotton (Han et al., 2014; Stührwohldt et al., 2015). PSK is perceived at the plasma membrane by PSKR1, an LRR-RLK containing 21 LRRs and a 36-amino acid island between the 17th and 18th LRRs (Matsubayashi et al., 2002, 2006). When *PSKR1* and its closest paralog *PSKR2* were both knocked out, the double mutant exhibited significantly shortened roots that were insensitive to PSK, indicating

that the Arabidopsis genome possesses two PSK receptors to redundantly control cell proliferation (Amano et al., 2007). PSKR1 possesses kinase, guanylate cyclase, and Ca^{2+}/calmodulin-binding activities that are required for PSK signaling (Kwezi et al., 2011; Hartmann et al., 2014; Kaufmann et al., 2017). Biochemical analyses indicated that PSKR1 interacts with BAK1. PSK-induced root growth and protoplast expansion are extremely impaired in both *bak1-3* and *bak1-4* (Ladwig et al., 2015). In addition, both the *pskr1-3 pskr2-1* and *serk1-3 serk3-1 serk4-1* mutants produced increased numbers of metaxylem cell compared with the wild type, indicating that PSKR1/2 and BAK1/SERKs suppress xylem identity. RLP44, a receptor-like protein (RLP), functions as a scaffold to promote the interaction between PSKR1 and BAK1 (Holzwart et al., 2018). These results suggested that BAK1 may function as a coreceptor to transduce the PSK signal similar to that in BRI1-mediated brassinosteroid signaling. PSK can effectively induce PSKR1 to form a heterodimer with BAK1 and other SERKs. However, structural results showed that PSK is not directly involved in the PSKR-SERK interface, which is different from the interaction of BRI1 and BAK1. PSK binding allosterically induces PSKR-SERK interaction, in which the completely disordered island domain of free PSKR is well stabilized for the subsequent recruitment of a SERK as the coreceptor to form a stable PSKR-SERK complex (Fig. 1B; Wang et al., 2015).

PLANT PEPTIDE CONTAINING SULFATED TYROSINE1 (PSY1) is another 18-amino acid Tyr-sulfated glycopeptide identified from Arabidopsis suspension cell culture, which can significantly promote cellular proliferation and expansion. PSY1R, an LRR-RLK paralogous to PSKR1, is the receptor perceiving PSY1 (Amano et al., 2007). Since both PSK and PSY1 promote cell proliferation and the *pskr1 pskr2 psy1r* triple knockout mutant showed significantly decreased cell size and cell number, it was proposed that the paralogous receptors PSKR1/2 and PSY1R integrate two distinct growth-promoting peptide signals to redundantly control cellular proliferation and plant growth (Amano et al., 2007). A recent study revealed that PSY1R and BAK1/SERKs can interact with and mutually transphosphorylate each other, suggesting that BAK1 and SERKs may also function as coreceptors of PSY1R to transduce the PSY1 signal and promote plant growth (Oehlenschlæger et al., 2017). Genetic and structural results are still required to test whether BAK1 and SERKs are bona fide coreceptors of PSY1R (Fig. 1C).

A tyrosylprotein sulfotransferase (TPST) was identified in Arabidopsis that can catalyze Tyr sulfation of both PSY1 and PSK (Komori et al., 2009). *tpst* mutants displayed similar but more severe phenotypes compared with the *pskr1 pskr2 psy1r* triple mutant (Amano et al., 2007; Komori et al., 2009), leading to the identification of another group of Tyr-sulfated peptides named ROOT MERISTEM GROWTH FACTORS (RGFs) that can rescue the extreme short-root phenotype of *tpst* when PSK and PSY1 are both supplied (Matsuzaki et al., 2010). *RGFs* are expressed in the quiescent center and columella stem cells. RGFs diffuse with a gradient into the root meristem to define the expression levels of PLETHORA (PLT) transcription factors and thereby to maintain the root stem cell niche. Loss of function of *RGFs* results in a short-root phenotype due to impaired root meristem (Aida et al., 2004; Matsuzaki et al., 2010). RGF peptides were also named CLE-LIKE (CLEL)/GOLVEN (GLV) because they contain a conserved CLEL/GLV domain responsible for root length, root growth direction, and lateral root initiation (Meng et al., 2012; Whitford et al., 2012).

Matsubayashi's group expressed all 95 RLKs that could serve as ligand receptors with a large extracellular domain in tobacco (*Nicotiana tabacum*) BY-2 cells. Three LRR-RLKs named RGF RECEPTORs (RGFRs) were identified by exhaustive binding assay using photoaffinity-labeled RGF1 against membrane fractions of the transgenic lines (Shinohara et al., 2016). A total of five RGFRs, also designated as RGF1 INSENSITIVE (RGI) proteins, were independently identified by two other groups based on yeast two-hybrid screening and ligand recognition motif analysis, respectively (Ou et al., 2016; Song et al., 2016). The stability of these RGFR/RGI receptors are finely tuned by the ubiquitin-specific proteases UBP12 and UBP13 (An et al., 2018). The gradients of PLT1/2 in the root meristem were drastically impaired in the *rgfr/rgi* mutants that showed extremely shortened roots and were insensitive to exogenously applied RGF peptides, consistent with their role as the receptors of RGFs (Ou et al., 2016; Shinohara et al., 2016).

Two conserved motifs (RxR and RxGG) in the extracellular domains of RGFRs/RGIs were revealed to be crucial for the recognition of RGF1 by its receptors. Biochemical assays showed that RGF1 can induce the interaction between the extracellular LRR domains of RGFRs/RGIs and BAK1/SERKs, suggesting that SERK family members function as coreceptors of RGFRs/RGIs. This notion was further supported by genetic analyses with *serk* mutants that displayed short roots with smaller meristems (Song et al., 2016; Fig. 1D). In line with this, RGFRs/RGIs were also identified by a yeast two-hybrid screening using BAK1 as a bait (Ou et al., 2016). It was proposed that the new surface formed by the interaction of RGFRs/RGIs and RGFs could be used as a platform to recruit a SERK member to mediate RGF signaling (Song et al., 2016). In addition, the wavy growth of wild-type roots upon RGF1 treatment disappeared in the *rgi1/2/3/4* quadruple mutants (Ou et al., 2016), indicating that the gravitropic response caused by RGF treatment may also be mediated by the RGFR/RGI receptors.

THE HAE-SERK COMPLEX SENSES THE HYDROXYLATED PEPTIDE IDA TO REGULATE CELL SEPARATION PROCESSES

INFLORESCENCE DEFICIENT IN ABSCISSION (IDA) and eight IDA-LIKE (IDL) homologs in Arabidopsis

are a different type of peptide (Butenko et al., 2003). The mature active IDA is generated from the C terminus of its preproprotein and posttranslationally hydroxylated on its Pro residues (Vie et al., 2015). *IDA* is specifically expressed in floral abscission zones. *ida* mutants show altered abscission characteristics, and their senesced floral organs remain attached to the plant (Butenko et al., 2003). Consistent with this phenotype, constitutive and ectopic expression of *IDA* resulted in earlier abscission of floral organs and ectopic abscission of other organs, such as branches and cauline leaves (Stenvik et al., 2006). *IDA* encodes a secreted precursor protein containing a conserved motif named extended PIP (EPIP) that is sufficient to rescue the defective abscission phenotype seen in the *ida* mutants, and synthetic EPIP peptide induces abscission in the wild type and *ida* mutants, suggesting that proteolytic processing is required to produce a mature and bioactive form of IDA (Stenvik et al., 2008). Three subtilisin-like proteinases involved in processing the IDA precursor into the mature and bioactive 14-amino acid peptide were identified by biochemical approaches (Schardon et al., 2016). The central Pro residue in the minimal 12-amino acid IDA peptide must be hydroxylated for its activity (Butenko et al., 2014; Santiago et al., 2016).

HAESA (HAE) and its paralog HAESA-LIKE2 (HSL2), two LRR-RLKs, are also strongly expressed in the floral organ abscission zones (Jinn et al., 2000; Cho et al., 2008). Similar to the *ida* mutants, the *hae hsl2* double mutants exhibit strong abscission defects and the floral organs fail to abscise (Cho et al., 2008; Stenvik et al., 2008). Overexpression of *IDA* cannot restore the abscission defects of the *hae hsl2* double mutants, demonstrating that the function of IDA relies on HAE/HSL2, and IDA and HAE/HSL2 act in the same signaling pathway (Cho et al., 2008; Stenvik et al., 2008). The repressed expression of *HAE* by AGAMOUS-LIKE15 (AGL15) can be released through the abscission process when AGL15 is phosphorylated by a MKK4/5-MAPK3/6 cascade, which thus regulates the IDA-mediated floral organ abscission in a positive feedback manner (Cho et al., 2008; Patharkar and Walker, 2015). Higher-order *serk* mutants display defective floral organ abscission similar to that of the *hae hsl2* and *ida* mutants, indicating that SERKs redundantly regulate floral organ shedding. IDA can induce heterodimerization via the extracellular domains of HAE/HSL2 and SERKs, and the IDA signal can be transduced by transphosphorylations between HAE/HSL2 and SERKs (Meng et al., 2016). Structural results demonstrated that SERKs function as coreceptors of HAE/HSL2. In the presence of SERK1, HAE perceives hydroxylated IDA with a much higher binding affinity (Santiago et al., 2016; Fig. 1E). Similar IDA/IDL1-HAE/HSL2 ligand-receptor pairs are also required to control other cell separation processes, including lateral root emergence and root cap sloughing (Aalen et al., 2013; Kumpf et al., 2013; Shi et al., 2018; Zhu et al., 2019). However, no coreceptors of HAE/HSL2 have been reported yet in regulating lateral root emergence and root cap sloughing. The IDA/IDL peptide signaling is evolutionarily conserved, and some key components of this pathway have been identified in all orders of flowering plants, including some important crops (Shi et al., 2019). Genetic breeding targeting these genes may generate crop varieties to decrease severe yield and quality losses caused by untimely organ abscission.

ERF/EMS1 (EXS)-SERK PAIRS MEDIATE CYS-RICH PEPTIDES TO REGULATE STOMATA PATTERN AND TAPETUM SPECIFICATION

The EPIDERMAL PATTERNING FACTOR (EPF) and EPF-LIKE (EPFL) peptide family in Arabidopsis comprises 11 small secreted Cys-rich peptides, including EPF1, EPF2, and nine EPFLs. Mature EPF peptides contain six or eight conserved Cys residues that form intramolecular disulfide bonds important for their functions (Silverstein et al., 2007; Hara et al., 2009; Ohki et al., 2011; Torii, 2012). *EPF1* confers the one-cell-spacing stomatal pattern (stomata are not adjacent to each other). Overexpression of *EPF1* resulted in decreased stomatal density while the *epf1* mutant exhibited clustered stomata and moderately increased stomatal density (Hara et al., 2007). Different from EPF1, EPF2 inhibits protoderm cells from entering into the stomatal lineage, and excessive numbers of stomata and numerous small epidermal cells are produced in the *epf2* mutant while most stomata still obey the one-cell-spacing rule (Hara et al., 2009; Hunt and Gray, 2009). By contrast, STOMAGEN, also named EPFL9, a mesophyll-derived inner-tissue EPF/EPFL family peptide, positively regulates stomatal development in the epidermis. Overexpression of *STOMAGEN* leads to numerous clustered stomata, whereas loss of function of *STOMAGEN* results in reduced stomatal density (Hunt et al., 2010; Kondo et al., 2010; Sugano et al., 2010). Three other EPFL peptides, EPFL6/CHALLAH, EPFL5/CHALLAH-LIKE1 (CLL1), and EPFL4/CLL2, are involved in region-specific regulation of stomatal production (Abrash and Bergmann, 2010; Abrash et al., 2011).

The ERECTA subfamily (ERf) LRR-RLKs, including ERECTA (ER), ERECTA-LIKE1 (ERL1), and ERL2, play overlapping but diverse roles as negative regulators to promote pavement cell differentiation and inhibit stomatal lineage formation. The triple *er* mutants generate high-density stomatal clusters (Shpak et al., 2005; Shpak, 2013). Overexpression of *EPF1/2* and *STOMAGEN* in the *er* triple mutants cannot decrease stomatal density (Hara et al., 2007, 2009; Lee et al., 2015). On the other hand, the *epf2 er* double mutant exhibited stomatal density similar to the *er* single mutant (Hunt and Gray, 2009). The *er erl1 erl2 epf1 epf2* and *stomagen er erl1 erl2* mutants exhibit stomatal density similar to the *er* triple mutants (Hara et al., 2009; Lee et al., 2015). These results demonstrated that ERf members are necessary for EPF/EPFL peptides to regulate stomatal development.

Further protein interaction analyses indicated that ERf RLKs are the primary receptors of EPF1/2 and STOMAGEN (Lee et al., 2012, 2015). EPF2-ER and

EPF1-ERL1 pairs initiate asymmetric entry divisions for stomatal lineage fate and enforce spacing divisions, respectively (Lee et al., 2012). EPF2 activates ER-mediated signaling to inhibit stomatal initiation, whereas STOMAGEN competes with EPF2 to bind to ER for blocking the signaling pathway, leading to optimal stomatal patterning (Lee et al., 2015). TOO MANY MOUTHS (TMM), an LRR-RLP, is also required to form a receptor complex with ERf for EPF binding in controlling stomatal development with distinct functions in different organs (Nadeau and Sack, 2002; Shpak et al., 2005; Hara et al., 2007, 2009; Hunt and Gray, 2009; Kondo et al., 2010; Sugano et al., 2010; Lee et al., 2012, 2015). However, structural results suggested that a coreceptor is still necessary for ERfs to transduce EPF signals, since EPFs cannot induce ERfs to dimerize no matter whether TMM is present or not (Lin et al., 2017).

The *serk1 serk2 bak1* knockout mutants produce clustered stomata, similar to the *er* triple mutants. SERKs play unequal redundant roles in regulating stomatal patterning, as revealed by analyzing a series of higher-order *serk* mutants in the *bak1-5* background, a semidominant allele of *BAK1* without defects in brassinosteroid signaling and cell-death control. Application of EPF1/2 can enhance the interactions between ERf and SERKs, and in vitro kinase assays indicated that ER and BAK1 can transphosphorylate each other. In addition, the *serk1 serk2 bak1* mutants were insensitive to exogenous treatment or induced expression of bioactive EPF1/2 peptides regarding the clustered stomata. Taken together, these results demonstrated that SERKs function as coreceptors for ERf-mediated EPF signaling in regulating stomatal patterning through transphosphorylation between SERKs and ERf RLKs (Fig. 1F; Meng et al., 2015). However, no structural data are currently available to further reveal the molecular mechanisms by which SERKs function together with TMM and ERf in regulating stomatal patterning.

TAPETUM DETERMINANT1 (TPD1) is another type of secreted Cys-rich peptide with four Cys residues after posttranslational processing that plays a crucial role in specifying the tapetal cells during anther development (Yang et al., 2003; Huang et al., 2016). *TPD1* is expressed early in the archesporial cells and the descendant cells, and later predominantly in the sporogenous cells and microsporocytes. The *tpd1* anthers produce excess microsporocytes and lack the tapetal cell layer, whereas overexpression of *TPD1* delays the degeneration of the tapetal cells, indicating that TPD1 plays an important role in communicating between the tapetum and microsporocytes (Yang et al., 2003, 2005). Blocking the TPD1-mediated communication between the tapetum and microsporocytes by directing TPD1 into vacuoles resulted in defective anther development, and no pollen grains can be produced (Huang et al., 2016).

TPD1 is synthesized in the sporogenous cells/microsporocytes and secreted to the primary tapetum/tapetal cells, where it is perceived by EMS1/EXS, an LRR-RLK, to coordinate tapetal cell specification (Canales et al., 2002; Zhao et al., 2002). *EMS1/EXS* is predominantly expressed in the tapetal cells, exhibiting a partially complementary expression pattern compared with that of *TPD1* (Yang et al., 2003). Similar to the *tpd1* mutant, the *ems1/exs* mutant anthers cannot properly specify the tapetum (Canales et al., 2002; Zhao et al., 2002). Genetic analysis indicated that the *tpd1*, *ems1/exs*, and *tpd1 ems1/exs* mutants all show the same tapetal defects and that functional EMS1/EXS is required for TPD1 signaling, supporting that TPD1 and EMS1/EXS function in the same genetic pathway (Yang et al., 2003; Jia et al., 2008). Protein interaction assays demonstrated that TPD1 interacts with the extracellular LRR domain of EMS1/EXS, and TPD1 can induce the phosphorylation of EMS1/EXS in planta (Jia et al., 2008). Moreover, EMS1/EXS is required for proper TPD1 localization to the plasma membrane.

It was proposed that perception of the reproductive cell-secreted TPD1 by its somatic cell-localized receptor EMS1/EXS activates a signaling pathway that promotes the division of the secondary parietal cells and then specifies the fate of the tapetal cells that consequently suppress microsporocyte proliferation (Jia et al., 2008; Huang et al., 2016). MULTIPLE SPOROCYTE1, TPD1-LIKE1A/MICROSPORELESS2, and MULTIPLE ARCHESPORIAL CELLS1, the homologs of EMS1/EXS or TPD1 in rice and maize, function in a similar manner to regulate early anther cell specification (Zhao et al., 2008; Hong et al., 2012; Wang et al., 2012; Yang et al., 2016). Two SERKs, SERK1 and SERK2, function redundantly as the coreceptor of EMS1/EXS to control anther cell specification in Arabidopsis. Similar to the *tpd1* and *ems1/exs* mutants, the *serk1 serk2* mutant anthers cannot specify the tapetum (Albrecht et al., 2005; Colcombet et al., 2005). The *ems1 serk1 serk2* mutant anthers exhibited tapetal and microsporocyte defects similar to *tpd1*, *ems1/exs*, and *serk1 serk2*. Ectopic expression of *TPD1* in *serk1 serk2* anther epidermis still exhibited similar defects to the *serk1 serk2* mutant, whereas six somatic cell layers could be formed when *TPD1* was ectopically expressed in wild-type anthers. Moreover, SERK1 physically interacts with and transphosphorylates EMS1/EXS to enhance EMS1/EXS kinase activity that is critical for EMS1/EXS to regulate anther cell specification. These results demonstrated that SERK1/2 function in the same genetic pathway as TPD1-EMS1/EXS and that the functions of SERK1/2 are required for TPD1-EMS1/EXS signaling (Fig. 1G; Li et al., 2017).

A conserved role of *GhSERK1* in regulating anther development was also revealed in cotton (Shi et al., 2014). Very recently, it was revealed that BES1 and its homologs, a group of transcription factors, are employed as a common downstream signaling component by the BR-BRI1-SERK and TPD1-EMS1/EXS-SERK signaling pathways to regulate cell elongation and anther cell differentiation, respectively (Chen et al., 2019; Zheng et al., 2019).

HSL1/TDR (PXY)-SERK PAIRS PERCEIVE CLE PEPTIDES TO REGULATE STOMATAL DEVELOPMENT AND CAMBIUM CELL PROLIFERATION

CLAVATA3 (CLV3)/EMBRYO SURROUNDING REGION-related (CLE) family precursors contain a conserved CLE domain near their C termini that are proteolytically processed to produce mature CLE peptides with 12 to 13 amino acid residues. CLE peptides regulate a variety of biological processes in plant development and responses to stresses (Yamaguchi et al., 2016; Goad et al., 2017). For instance, upon dehydration stress, root-derived CLE25 moves to the leaves to modulate stomatal closure, enhancing drought resistance (Takahashi et al., 2018). As valves in the epidermis, stomata control gas exchange and water loss between plants and the ambient atmosphere. As aforementioned, the EPF-ERf peptide-receptor pairs strictly regulate critical steps of stomatal development, including spacing and density.

Recently, it was revealed that the CLE9 and CLE10 peptides, identical mature peptides produced by *CLE9* and *CLE10*, also regulate stomatal development (Qian et al., 2018). *CLE9/10* genes are expressed in stomatal lineage cells, and exogenous application of synthetic CLE9/10 peptide decreased the number of stomatal lineage cells. The *cle9* single mutants showed increased number and density of stomatal lineage cells, similar to a *cle9 cle10* double mutant, indicating that *CLE9* plays a major role in repressing the meristemoid mother cell identity during stomatal development (Qian et al., 2018). Application of CLE9/10 peptide can still decrease the number of stomatal lineage cells in the *er* triple mutant, whereas EPF2 depends on the function of ERf (Hara et al., 2009), indicating that CLE9/10 functions independently of the EPF-ERf signaling pathway and that its corresponding receptor is required to control stomatal development (Qian et al., 2018).

By testing the sensitivity of mutants from group XI LRR-RLKs to CLE9/10 treatment in stomatal development, HSL1 was identified as the receptor of CLE9/10. Compared with wild-type plants, the *hsl1* mutants produced more stomatal lineage cells, which were not decreased upon CLE9/10 treatment. Biochemical assays indicated that the extracellular LRR domain of HSL1 can directly and specifically bind to CLE9/10. However, HSL1 homodimerization cannot be induced upon CLE9/10 binding, suggesting that a coreceptor is needed for HSL1-mediated signaling during stomatal development. In fact, interactions between SERKs and HSL1 can be specifically induced by CLE9/10. On the other hand, SERK1 can significantly increase the binding affinity between HSL1 and CLE9/10 (Qian et al., 2018). These results indicated that SERKs are recruited as coreceptors of HSL1 for sensing CLE9/10 to regulate stomatal development. Future structural analysis will facilitate our understanding of this important biological process (Fig. 1H).

The TRACHEARY ELEMENT DIFFERENTIATION INHIBITORY FACTOR (TDIF) dodecapeptide, a homolog of the Arabidopsis CLE41/44 peptide, which specifically suppresses the tracheary element differentiation, was originally identified in a *Zinnia elegans* xylogenic culture. When TDIF was added, the transition of procambial cells to tracheary elements was suppressed (Ito et al., 2006). Overexpression of *CLE44* or exogenous application of TDIF resulted in discontinuous xylem vessels and stele enlargement caused by increased procambial cells that were suppressed to differentiate into xylem vessel cells in Arabidopsis (Hirakawa et al., 2008). Consistent with this, loss of function of *CLE41/44* results in decreased numbers of procambial cells and some xylem vessel cells adjacent to the phloem cells (Hirakawa et al., 2010; Yamaguchi et al., 2017). Both *CLE41* and *CLE44* are expressed in the phloem and the pericycle. However, the CLE41/44 peptide was specifically detected in the apoplast surrounding the phloem precursors in root tips and in the procambial cells of hypocotyls, indicating that the CLE41/44 peptide is produced by the phloem cells and function in a non-cell-autonomous manner in the procambium.

CLE41/44 is perceived by TDIF RECEPTOR (TDR), an LRR-RLK also named PHLOEM INTERCALATED WITH XYLEM (PXY), to promote the maintenance of vascular stem cells and suppress their differentiation into xylem cells (Fisher and Turner, 2007; Hirakawa et al., 2008; Etchells and Turner, 2010; Zhang et al., 2016c). *TDR/PXY* expression is restricted in procambial cells. *TDR/PXY* mutations result in more flattened vascular bundles with phloem adjacent to or interspersed with the xylem because of defective orientation of cell division during vascular development. Procambial cell proliferation in *tdr* hypocotyls cannot be enhanced by TDIF treatment (Fisher and Turner, 2007; Hirakawa et al., 2008, 2010; Etchells and Turner, 2010).

It was reported that *SERK1* is expressed in vascular tissues and that TDIF induces the interaction between the extracellular LRR domains of TDR/PXY and SERKs (Kwaaitaal and de Vries, 2007; Zhang et al., 2016b, 2016c). The *serk1 serk2 bak1* triple mutant cannot maintain the procambial cells, and the xylem is adjacent to the phloem. Moreover, the *serk1 serk2 bak1* triple mutant showed impaired responses to TDIF treatment, similar to that in *pxy* (Fisher and Turner, 2007; Zhang et al., 2016c). Crystal structure results further supported that SERKs function as the coreceptors of TDR/PXY to regulate cell-to-cell communication during vascular stem cell maintenance and xylem differentiation (Fig. 1I; Zhang et al., 2016b).

CLV-CIK PAIRS MEDIATE CLV3 SIGNAL TO REGULATE THE SAM

Plants generate aerial organs, such as stems, branches, leaves, and flowers, during postembryonic development to establish appropriate architectures for survival in their life spans. The whole process is dependent on the SAM, which contains pluripotent stem

cells that keep generating daughter cells to renew themselves and to replenish cells for new tissues or organs (Vernoux and Benfey, 2005; Williams and Fletcher, 2005; Aichinger et al., 2012; Wu et al., 2018; Kitagawa and Jackson, 2019). CLV3, the founding member of the CLE peptide family, is a secreted arabinosylated glycopeptide containing 13-amino acid residues and plays a crucial role in maintaining SAM homeostasis (Ohyama et al., 2009). Mutations of *CLV3* resulted in an enlarged SAM and a fasciated stem (Fletcher et al., 1999; Rodriguez-Leal et al., 2019). A feedback regulation mediated by CLV3 and WUSCHEL (WUS), a critical transcription factor, delicately balances self-renewal and differentiation of the stem cells in the SAM (Brand et al., 2000; Schoof et al., 2000; Rojo et al., 2002; Lenhard and Laux, 2003; Yadav et al., 2011; Perales et al., 2016). Recent studies indicated that HAIRY MERISTEM (HAM) transcription regulators are required interacting cofactors of WUS, and the HAM concentration gradient spatially specifies the *CLV3* expression domain (Zhou et al., 2015, 2018).

Loss of function of CLV1, a typical LRR-RLK, leads to an enlarged SAM and extra floral organs, similar to *clv3* (Clark et al., 1993, 1997). CLV3 can directly bind to the extracellular LRR domain of CLV1 to repress the expression of *WUS* in the organizing center (Fletcher et al., 1999; Schoof et al., 2000; Ogawa et al., 2008). On the other hand, CLV3 promotes the membrane-localized CLV1 to move into lytic vacuoles for degradation, which is a possible mechanism to buffer CLV3 signaling in the maintenance of stem cells (Nimchuk et al., 2011). RECEPTOR-LIKE PROTEIN KINASE2 (RPK2), another typical LRR-RLK, and CLV2/CORYNE (CRN), a complex of an LRR-RLP and an RLCK without kinase activity, are also involved in sensing CLV3 (Kayes and Clark, 1998; Jeong et al., 1999; Müller et al., 2008; Kinoshita et al., 2010). Different from CLV1, however, CLV3 cannot directly bind to the LRR domain of RPK2 or CLV2 (Shinohara and Matsubayashi, 2015). Genetic evidence suggested that the CLV3 signal is possibly transduced by three parallel pathways mediated by CLV1, CLV2/CRN, and RPK2, respectively (Müller et al., 2008; Kinoshita et al., 2010).

When *CLV1* function is compromised, *BARELY ANY MERISTEMS* (*BAMs*), the close homologs of *CLV1*, are ectopically expressed in the rib meristem, which partially compensates for the loss of *CLV1* (Deyoung and Clark, 2008; Nimchuk et al., 2015). Consistent with this, photoaffinity labeling showed that CLV3 can directly bind to BAM1 and BAM2 (Shinohara and Matsubayashi, 2015). The CLV-WUS negative signaling pathway is conserved in higher plants and has also been extensively studied in crops, such as tomato, rice, and maize. The components in this pathway are potential targets for genetic manipulation to improve yield traits (Somssich et al., 2016; Fletcher, 2018; Kitagawa and Jackson, 2019).

Although SERKs function as critical coreceptors in various signaling pathways, no evidence supports that they are involved in the CLV-WUS signaling pathway to control stem cell homeostasis in the SAM. Recently, another group of coreceptors named CIKs were identified to function together with CLV1, CLV2/CRN, and RPK2 in mediating the CLV3 signal to maintain the SAM (Hu et al., 2018). The *cik* quadruple mutants exhibited severe SAM defects similar to *clv3* and *clv1 clv2 rpk2* triple mutants. Genetic analyses demonstrated that *cik* mutants were epistatic to the receptor mutants. Moreover, CIKs can interact with and be phosphorylated by CLV1 and RPK2. The *cik* quadruple mutant was insensitive to exogenous application of CLV3, and the phosphorylation level of CIKs cannot be elevated by CLV3 treatment in *clv1 bam1 bam2*. Taken together, these results suggest that CIKs function as shared coreceptors to integrate three parallel CLV signaling pathways mediated by CLV1, CLV2/CRN, and RPK2 (Fig. 2; Hu et al., 2018).

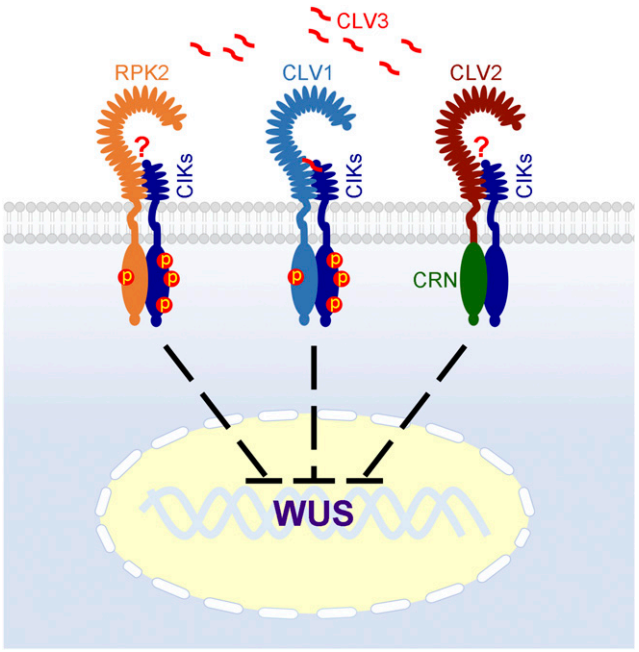

Figure 2. CIKs integrate RLK-mediated pathways to maintain stem cell homeostasis in the SAM. CIKs redundantly interact with CLV1, CLV2/CRN, and RPK2 to transduce the CLV3 signal into the nucleus while suppressing the expression of *WUS*. CIKs can at least be phosphorylated by CLV1 and RPK2 for signaling, according to the results from phosphorylation assays (Cui et al., 2018; Hu et al., 2018). Question marks indicate that no physical interaction between CLV3 and RPK2 or CLV2 has been confirmed.

BAM/RPK2-CIK PAIRS REGULATE ANTHER CELL SPECIFICATION

The Arabidopsis anther wall of each locule at stage 5 consists of four somatic cell layers, the epidermis, endothecium, middle layer, and tapetum from outside to inside, which surround the microspore mother cells (Sanders et al., 1999). Besides TPD1-EMS1/EXS (Jia et al., 2008; Huang et al., 2016; Li et al., 2017), no other peptide-RLK pairs have been characterized as

Table 1. *Receptors, coreceptors, and peptides involved in plant development mentioned in this review*

Ligand Name	Ligand Type	Receptor	Subfamily	Coreceptor	Function
Brassinosteroids	Phytohormone	BRI1	LRR X	SERK1, SERK2, BAK1, BKK1	Cell elongation and plant growth
PSK	Sulfated peptide	PSKR1, PSKR2	LRR X	SERK1, SERK2, BAK1	Cell division and cell expansion
PSY1	Sulfated peptide	PSY1R	LRR X	SERK1, SERK2, BAK1	Cell division and cell expansion
RGFs/CLELs/GLVs	Sulfated peptide	RGFR/RGI1 to RGI5	LRR XI	SERK1, SERK2, BAK1, BKK1	Root meristem size
IDA	Hydroxylated peptide	HAE, HSL2	LRR XI	SERK1, SERK2, BAK1, BKK1	Cell separation
EPF1, EPF2, EPFLs	Cys-rich peptide	ER, ERL1, ERL2	LRR XIII	SERK1, SERK2, BAK1	Stomatal development
TPD1	Cys-rich peptide	EMS1/EXS	LRR X	SERK1, SERK2	Tapetum specification
CLE9/10	CLE peptide	HSL1	LRR XI	SERK1, SERK2, BAK1	Stomatal development
TDIF/CLE41/44	CLE peptide	TDR/PXY	LRR XI	SERK1, SERK2, BAK1	Cambium cell proliferation
CLV3	CLE peptide	CLV1, BAM1, BAM2	LRR XI	CIK1, CIK2, CIK3, CIK4	SAM homeostasis
		RPK2	LRR X		
Unknown	Unknown	BAM1, BAM2	LRR XI	CIK1, CIK2, CIK3, CIK4	Anther development
Unknown	Unknown	RPK2	LRR X	CIK1, CIK2, CIK3, CIK4	Tapetum specification

specifying anther wall cells in Arabidopsis. Nevertheless, several other RLKs with long extracellular LRR domains have been identified as regulating anther cell specification. For instance, ERf members play important roles in promoting anther lobe formation and anther cell differentiation. The *er* triple mutants produced either antherless stamens or anthers with only defective abaxial lobes with disorganized somatic cell layers, especially abnormal tapetum and middle layer cells (Shpak et al., 2004; Hord et al., 2008). BAM1 and BAM2 play important roles in early anther development by specifying the identity of L2-derived somatic cells. The archesporial cells in the *bam1 bam2* anthers exhibited defective asymmetric cell division and produced extra microspore mother cells but lacked the endothecium, middle layer, and tapetum (Hord et al., 2006). RPK2 promotes tapetal cell fate. The inner secondary parietal cells in *rpk2* mutant anthers failed to differentiate into the middle layer cells and finally formed abnormally hypertrophic tapetal cells (Mizuno et al., 2007). It was recently reported that *RPK2* also regulates the periclinal division of the archesporial cells and the primary parietal cells: disruption of *RPK2* resulted in defective anthers lacking either two or three parietal cell layers (Cui et al., 2018). However, the ligands perceived by these RLKs during anther development have yet to be identified.

CIK RLKs play vital roles in redundantly regulating not only meristem homeostasis but also anther cell specification. The most severe defective anthers of *cik* mutants produced extra microspore mother cells surrounded only by the epidermis and lacked all other parietal cell layers because of abnormal anticlinal division of the archesporial cells, which is similar to that of *bam1 bam2* and *rpk2* mutants. The other defective *cik* anthers lacked either one or two parietal cell layers like *rpk2* because of the failure of division of the inner secondary parietal cells or the primary parietal cells. CIKs can physically interact with and be phosphorylated by BAM1/2 and RPK2 and can function as coreceptors of BAM1/2 and RPK2 to regulate parietal cell differentiation during early anther development. The RPK2-CIK and EMS1-SERK complexes may coordinate to regulate cell division of the inner secondary parietal cells and specification of the middle layer and the tapetum (Cui et al., 2018).

CONCLUSION AND PERSPECTIVE

Significant progress has been made in revealing various biological functions of RLKs and the underlying mechanisms in past years, leading to numerous fundamental breakthroughs in plant biology. This knowledge has dramatically promoted our understanding of this key type of plasma membrane-localized signaling molecule. It has been widely accepted that ligand-binding RLKs require coreceptors to form receptor complexes for transducing external signals during plant growth and development. Numerous lines of genetic and biochemical evidence demonstrated that SERK receptor kinases function as pivotal coreceptors in regulating many developmental processes and responses to biotic and abiotic stresses, although structural results are still accumulating. Recent results showed that CIK receptor kinases function as coreceptors of CLV1, BAM1/2, and RPK2 to control SAM stem cell homeostasis and anther wall cell specification (Cui et al., 2018; Hu et al., 2018). CIK members, CIK1/NSP-INTERACTING KINASE3, CIK2/CLE-RESISTANT RECEPTOR KINASE, and CIK3/SENESCENCE-ASSOCIATED RECEPTOR-LIKE KINASE, were reported to regulate antivirus response, root protophloem differentiation, and leaf senescence, respectively, although the cognate receptors have not yet been identified (Fontes et al., 2004; Xu et al., 2011; Anne et al., 2018). These results suggest that CIKs function as another group of RLK coreceptors in regulating plant growth, development, and responses to stresses, although more of the pairing receptors of CIKs need to be identified and further studied. See Table 1 for an overview of mentioned ligands, receptors, and coreceptors.

Efforts have been made to elucidate the signaling components after the perception of ligands by the receptor-coreceptor complexes. The BRI1-SERK complex-mediated brassinosteroid signaling recruits RLCKs,

OUTSTANDING QUESTIONS

- What are the principles that decide the recruitment of SERKs or CIKs as the coreceptors in a given signaling pathway?
- How is the specificity determined in various SERK- and CIK-mediated signaling pathways?
- What are other SERK- or CIK-regulated signaling pathways?
- What other ligands/receptors are involved in SERK- or CIK-mediated signaling pathways?
- What other downstream signaling components are in SERK- and CIK-mediated signaling pathways?
- Are there other SERK/CIK-like RLK coreceptors that regulate plant growth and development?

protein phosphatases, and GSK3/Shaggy-like kinases to activate the BES1 family transcription factors that directly regulate the expression of brassinosteroid-responsive genes and consequently modulate many aspects of plant growth and development (Planas-Riverola et al., 2019; Ackerman-Lavert and Savaldi-Goldstein, 2020). Recent reports indicated that both the BRI1-SERK and EMS1-SERK signaling pathways ultimately recruit the same BES1 family transcription factors to control cell elongation and anther development (Chen et al., 2019; Zheng et al., 2019). It is unknown, however, whether the EMS1-SERK pathway utilizes downstream signaling components similar to the BRI1-SERK pathway. Accumulating evidence indicates that RLCKs play essential roles in RLK-mediated signaling pathways, especially in plant immune responses (Liang and Zhou, 2018). Although RLCKs have been identified in the BRI1-SERK and HAE/HSL2-SERK pathways (Tang et al., 2008; Burr et al., 2011; Sreeramulu et al., 2013; Zhang et al., 2016a), it is still challenging to discover those possible RLCKs in other RLK-SERK pathways. The MAPK cascade is another signaling module found in many RLK-mediated signaling pathways, such as ERf-SERK-regulated stomatal patterning and HAE/HSL2-SERK-regulated cell separation processes (Wang et al., 2007; Cho et al., 2008; Aalen et al., 2013; Kumpf et al., 2013; Meng et al., 2015; Patharkar and Walker, 2015; Zhu et al., 2019). Whether other RLK-SERK pairs also employ a MAPK cascade is still elusive. As recently identified, however, the CIK-regulated signaling pathways are poorly understood with regard to their downstream signaling components.

In spite of the achievements that have been made in the RLK field, many interesting questions remain to be answered (see Outstanding Questions). SERKs and CIKs all belong to the LRR II-RLK family and have very similar structures (Cui et al., 2018). The current results support that the kinase domains of ligand-binding receptors determine their signaling specificity (Hohmann et al., 2018b). It is therefore fascinating to elucidate how a specific ligand-binding receptor selects a SERK or a CIK as its coreceptor. The specific phosphocode of SERKs or CIKs responding to diverse signals may be one of the solutions to determine the specificity (Perraki et al., 2018). Whether SERKs and CIKs employ similar mechanisms to transduce different signals is another open question. It is already known that the interaction between CIKs and CLV1 or RPK2 cannot be enhanced upon the application of CLV3, whereas the interaction between BAK1 and BRI1 can be dramatically elevated upon brassinosteroid application (Wang et al., 2005; Hu et al., 2018), suggesting that CIKs and SERKs may transduce signals differently, at least in some signaling pathways. Furthermore, the corresponding ligands and/or receptors of some SERK- or CIK-regulated biological processes have not been uncovered, such as the ligands involved in BAM-CIK and RPK2-CIK complex-controlled anther cell specification and the ligand and receptor in SERK-controlled stem cell division during embryogenesis. In addition, further studies are needed to uncover other unknown signaling pathways regulated by SERKs and CIKs and the unknown downstream components in SERK- and CIK-regulated signaling pathways.

Received October 29, 2019; accepted March 4, 2020; published March 6, 2020.

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