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Multi-tasking of somatic embryogenesis receptor-like protein kinases

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Receptor-like protein kinases (RLKs) are transmembrane proteins crucial for cell-to-cell and cell-to-environment communications. The extracellular domain of a RLK is responsible for perception of a specific extracellular ligand to trigger a unique intercellular signaling cascade, often via phosphorylation of cellular proteins. The signal is then transduced to the nucleus of a cell where it alters gene expression. There are more than 610 RLKs in *Arabidopsis thaliana*, only a handful of them have been functionally characterized. This review focuses on recent advances in our understanding of a small group of RLKs named somatic embryogenesis receptor-like protein kinases (SERKs). SERKs act as coreceptors in multiple signaling pathways via their physical interactions with distinct ligand-binding RLKs.

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Introduction

Multicellular organisms utilize transmembrane receptor-like protein kinases (RLKs) for cell-to-cell and cell-to-environment communications during normal growth and development. A typical plant RLK contains an extracellular domain perceiving chemical signals from surrounding environment, a single-pass transmembrane domain anchoring the protein to the plasma membrane, and a cytoplasmic kinase domain transducing extracellular signals to intracellular processes via protein phosphorylation. Plant RLKs were initially classified as serine/threonine protein kinases [1], but recent studies indicate that some RLKs may have serine/threonine and tyrosine dual kinase activities [2]. Arabidopsis genome encodes at least 610 RLKs and receptor-like cytoplasmic kinases (RLCKs), which lack extracellular domains. RLKs and RLCKs belong to a large monophyletic superfamily, representing nearly 2.5% of proteins encoded in the Arabidopsis genome [3,4]. Based on their sequence and structure similarities, RLKs were classified into more than 10 subfamilies, among which the leucine-rich repeat (LRR) RLKs, LRR-RLKs, belong to the largest subfamily containing at least 223 members [5•].

A variety of approaches have been used to unfold the biological functions of about 30 LRR-RLKs [5•], but the roles of majority of LRR-RLKs are yet to be elucidated. LRR-RLKs have been found to be crucial in regulating numerous physiological processes such as microsporogenesis and male fertility [6–8], embryo pattern formation [9], vascular tissue differentiation [10], organ shape and inflorescence architecture [11], maintenance of meristematic cells [12], stomatal patterning and differentiation [13], brassinosteroid (BR) signaling [14–16], floral organ abscission [17], cell death control [18••,19,20], and innate immunity [21,22].

A surprising discovery from recent studies is that some LRR-RLKs have dual or multiple roles. For example, Arabidopsis SERKs were found to regulate distinct signaling pathways mediating development and innate immunity [23]. *SERK* was first isolated in *Daucus carota* (carrot) as a marker gene to monitor the transition from somatic to embryogenic cells in carrot cell culture [24]. In Arabidopsis, there are five homologs of DcSERK, named SERK1 to SERK5 [25]. SERK3 and SERK4 were also named as brassinosteroid insensitive 1 (BRI1) associated receptor kinase 1 (BAK1) and BAK1-like 1 (BKK1) due to their functions in the BR signaling pathway [15,16,20]. Interestingly, members of SERKs showed both significantly overlapped and divergent functions [23]. Identification of multiple roles of SERKs raised interesting questions about specificity of members of SERK subfamily and crosstalk among SERK-mediated signaling pathways. This review focuses on recent advances in our understanding of the functions of SERKs in various signaling pathways.

Several SERKs interact with BRI1 to regulate BR signaling pathway

The function of BAK1/SERK3 in regulating BR signaling was independently identified via an activation tagging genetic screen for extragenic suppressors of a weak Arabidopsis *BRI1* mutant named *bri1–5* [15,26], and by a yeast two-hybrid screen for BRI1 interacting proteins [16]. Recent studies demonstrated that the bona-fide

BR receptor BRI1 and coreceptor BAK1 follow a reciprocal and sequential phosphorylation model [27••]. The BRI1 kinase domain can be activated via autophosphorylation upon the binding of BR to the extracellular domain of BRI1. The active BRI1 then recruits BAK1 to its protein complex likely forming a heterotetramer [28]. Specific residues within the BAK1 activation loop are therefore transphosphorylated by BRI1, resulting in activation of BAK1. BAK1 transphosphorylates the Ser/Thr residues in the juxtamembrane and C-terminal domains of BRI1, enhancing the kinase activity of BRI1. Genetic data obtained from *bak1 bkk1* double mutant plants suggested that BRI1 retains a basal activity even without SERK proteins [27••]. Since SERK1 and additional BAK1 paralogs are also likely involved in BR signaling, the significance of SERKs in BR signaling still needs to be reevaluated in mutant plants lacking *BAK1* and all its functionally redundant genes.

SERKs bind to BIR1 to control plant cell death

The fact that the *bak1* single mutant only shows subtle *bri1*-like phenotype suggested that there must be other *BAK1*-like genes playing functionally redundant roles with *BAK1*. Among five Arabidopsis SERKs, SERK4 and SERK5 are the two closest paralogs of BAK1/SERK3. The *SERK4* and *SERK5* genes are found as a tandem repeat on chromosome 2. It is therefore impractical to generate *serk4 serk5* double or *bak1 serk4 serk5* triple mutants in order to analyze the significance of these presumed functionally redundant proteins in regulating plant growth and development. In the Arabidopsis accession Columbia (Col-0), but not in accession WS2, however, *SERK5* bears a natural point mutation which alters Arg401 to Leu within its conserved 'RD' motif. This substitution may have abolished the kinase activity of SERK5, as overexpression of *SERK4* but not *SERK5* (from Col-0) can partially suppress the defective phenotypes of *bri1–5*, similar to that of *BAK1* [20]. When Leu401 is mutagenized to Arg in Col-0 SERK5, SERK5 can regain partial function in the BR signaling pathway [20]. The *bak1 bkk1* double mutant is practically a *bak1 bkk1 serk5* triple mutant in Col-0 background.

Surprisingly, the double mutant did not show the expected typical *bri1*-like defects. Instead, it exhibited a seedling lethality phenotype due to constitutive defense responses and spontaneous cell death [20]. The seedling lethality is salicylic acid (SA) and light dependent [20,29]. These results suggest that BAK1 and BKK1 not only modulate cell elongation via their function in BR signaling, but they also play critical roles in a light-dependent cell death control process. Since BAK1 regulates BR signaling through its interaction with the ligand-binding receptor BRI1, it is possible that BAK1 controls cell death via its interaction with another unknown ligand-binding RLK [29].

In an attempt to identify genes important for innate immunity response, Gao *et al.* [18••] used a systematic reverse genetic approach to determine the functions of genes whose expression levels are elevated upon treatment with the bacterial pathogen *Pseudomonas syringae pv. Maculicola* ES4326. A null mutant of a novel *RLK* gene showed constitutive defense response, cell death, and seedling lethality phenotypes similar to that of *bak1 bkk1* double mutant. Using a co-immunoprecipitation approach followed by a proteomic analysis, it was found that this RLK interacts with BAK1 *in vivo*. The RLK was therefore named as BAK1-interacting receptor-like kinase 1 (BIR1) [18••]. BIR1 is a member of the LRR-RLK X subfamily. Using bimolecular fluorescence complementation (BiFC) approach, it was found that BIR1 interacts with BAK1 paralogs including SERK1, SERK2, and BKK1/SERK4. The seedling lethality phenotype of *bir1* mutant is also SA dependent, as blocking SA biosynthesis can partially rescue the *bir1* phenotype [18••].

The phenotypic similarity between *bir1* and *bak1 bkk1* mutants and the physical interaction of BAK1 and BIR1 suggest that *bir1* and *bak1 bkk1* may block the same signaling pathway, which resulted in cell death. If this is the case, it suggests that BIR1 is a ligand-binding RLK, similar to BRI1 in the BRI1/BAK1-mediated BR signaling pathway, which can sense the 'surviving' signal yet to be determined. This notion is supported by the fact that BIR1 belongs to the same LRR-RLK X subfamily as known ligand-binding LRR-RLKs such as BRI1 and EMS1/EXS [6,14,30]. The extracellular domain of BRI1 perceives BRs, whereas the extracellular domain of EMS1/EXS interacts with a small secreted peptide TPD1 [31,32•]. The MAP kinase cascade regulated by MEKK1, MKK1/MKK2, and MPK4 may also be involved in the BIR1-midiated signaling pathway. The *mekk1* mutant shows a cell death phenotype similar to *bir1* [33]; and the defective phenotypes of both mutants can be suppressed by higher temperature. Whether the *bak1 bkk1* double mutant phenotype can also be suppressed by higher temperature has not yet been reported. Future identification of the 'surviving' signal as well as elucidation of the rest of the signaling pathway should provide significant insight into mechanisms of RLK-mediated cell death control in plants.

SERKs are crucial in regulating anther development

Because the carrot *SERK* is transcriptionally induced during the transition to somatic embryogenesis, Arabidopsis SERK1 was thought to be involved in embryogenesis. Overexpression of *SERK1* can efficiently increase the initiation of somatic embryogenesis [25], although no role in embryogenesis has been determined through loss-of-function genetic analyses. In order to analyze the biological functions of SERK1 and its closest paralog SERK2, two independent groups generated *serk1* and *serk2* single and *serk1 serk2* double mutants. Neither *serk1*

nor *serk2* showed any obvious morphological phenotypes, but the double mutant is sterile due to lack of mature pollen grains [7,8]. Detailed analysis found that the double mutant does not contain the characteristic tapetal cell layer which is essential for anther development. The double mutant produces more sporogenous cells that fail to develop into mature pollen grains after meiosis. These phenotypic defects are consistent with the expression patterns of *SERK1* and *SERK2*. Although both genes have a broad expression patterns in locules at an early anther developmental stage (stage 5), their expression is restricted to the tapetal cell layer at a later developmental stage (stage 9) [7,8].

The phenotypes of *serk1 serk2* double mutant are similar to *ems1/exs* and *tpd1* mutants. *EMS1/EXS* encodes an LRR-RLK of LRR-RLK X subfamily, whereas *TPD1* encodes a secreted small protein, which can directly bind to the extracellular domain of EMS1/EXS [32•]. The phenotypic similarity of the mutants raised an intriguing question: do these three different genes control the same signaling pathway? If this is the case, we would expect a ligand (TPD1)-dependent interaction between EMS1/EXS and SERK1 or SERK2. This is indeed a tempting hypothesis to be tested in the future.

SERKs associate with a number of pattern recognition receptors to modulate multiple plant innate immunity responses

There are at least two layers of plant defense responses against pathogens. One involves the pattern recognition receptors (PRRs) which perceive the pathogen associated molecular patterns (PAMPs). Perception of PAMPs by PRRs can trigger a basic but weak defense response. The second layer of innate immunity is the classic gene-for-gene defense. Once a pathogen breaks down the first layer of defense, it may release species-specific effectors into the cytoplasm of a plant cell via a type III secretion system (TTSS). If a plant has a dominant resistant gene, R gene, its product may interact directly or indirectly with the pathogen effectors, which can trigger a more intensive defense response named hypersensitive response. Such an immunity response is also called effector-triggered immunity (ETI) [34].

Kemmerling *et al.* showed that *bak1* single mutant exhibited a spreading necrosis phenotype due to uncontrolled cell death triggered by the pathogen infection [19]. This result clearly suggested that BAK1 may act as PRRs or coreceptors of PRRs to control innate immunity responses. The best characterized PRRs are FLS2 and EFR [21,22]. Both RLKs are members of the LRR-RLK XII subfamily. FLS2 and EFR sense the conserved 22-amino acid epitope of bacterial flagellin, named flg22, and the N-terminal portion of elongation factor Tu (EF-Tu) called elf18/elf26, respectively. Recent reports demonstrated that FLS2 can heteromerize with BAK1 [35,36]. The interaction is ligand dependent, reminiscent of the interaction between BAK1 and BRI1 [37]. Without the stimulation of flg22, FLS2 and BAK1 are not associated with each other [35,36]. Upon the stimulation by flg22 for only seconds, these two LRR-RLKs can form a protein complex almost instantaneously and transphosphorylate each other, which subsequently initiate a defense signaling cascade including MAPK activation [38•]. BAK1 is a positive regulator of PAMP signaling pathways shared by different plant species. In Arabidopsis, two *BAK1* T-DNA insertion mutants, *bak1–3* and *bak1–4*, showed drastically reduced defense responses such as seedling growth inhibition, oxidative burst, and MAPK activation upon treatments with flg22 and elf18. The responsiveness of *bak1–3* is slightly more than that of *bak1–4* because *bak1–3* is a leaky mutant expressing trace amounts of wild-type *BAK1*, whereas *bak1–4* is a true null allele (our unpublished data).

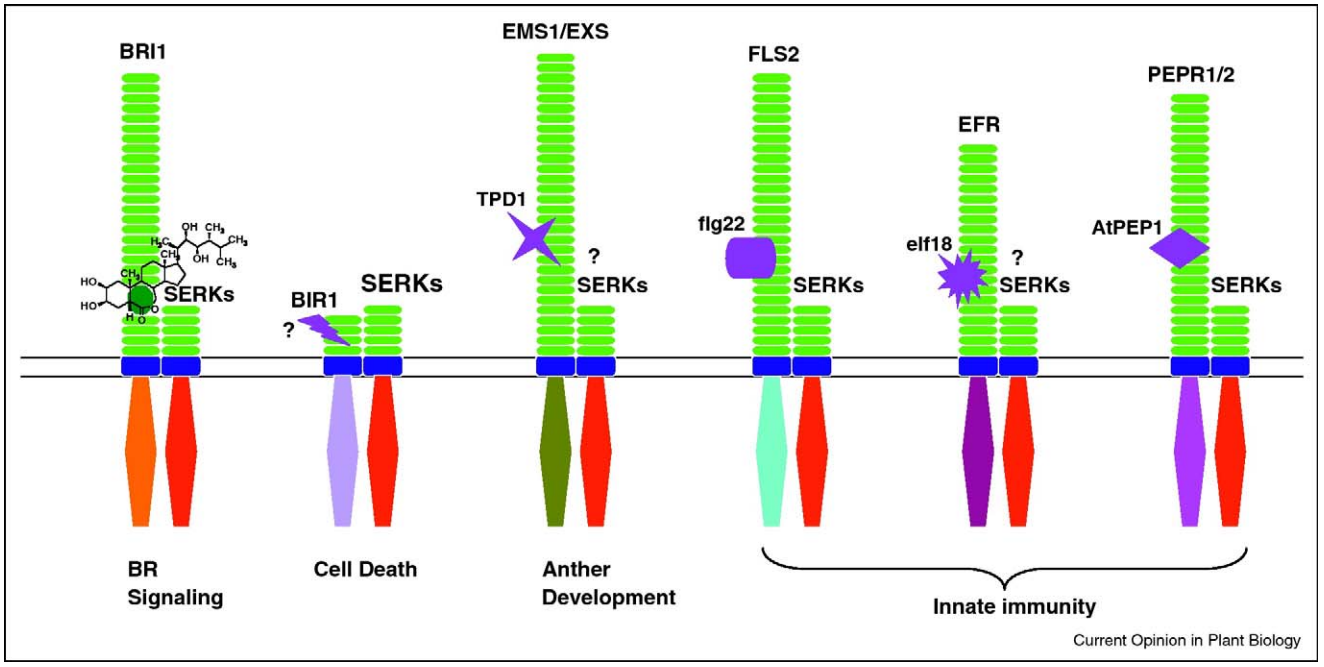
More recently, using a yeast two-hybrid approach, BAK1 was identified as a coreceptor of two additional LRR-RLKs, PEPR1 and its closest homolog PEPR2, implicating BAK1 in a general activation role in diversified plant immunity responses [39•]. PEPR1 and PEPR2 are members of LRR-RLK XI subfamily which consists of at least 26 genes [40]. The ligand for PEPR1, AtPEP1, is a wound-induced and plant-derived endogenous peptide, which differs from pathogen-derived elicitors such as flg22 and elf18/elf26. Recognition of AtPEP1 by PEPR1 triggers plant immunity response and enhances plant resistance against *Pytium irregulare* infection [41,42]. The detailed molecular mechanisms of BAK1 in regulating PEPR1 and PEPR2-mediated responses need to be elucidated in the future. These results suggest that BAK1 may interact with numerous ligand-binding PRRs in controlling a wide range of microbes [36].

BAK1 is a common coreceptor for a number of PAMPs. Interestingly, pathogens evolved unique strategies to target such general defense component to weaken the PRR-associated plant immunity in order to successfully invade plant cells. A recent report provides an excellent example for such unique tactics pathogens use for their successful attacking purposes [43••]. During the infection process, two sequence-distinct *Pseudomonas syringae* effectors AvrPto and AvrPtoB are injected into plant cells and interact with BAK1. The interaction between AvrPto/AvrPtoB and BAK1 interferes with the associations of BAK1 with different PRRs and with BRI1 [43••].

Conclusions

There is clear evidence that SERKs are able to regulate many developmental and innate immunity signaling pathways (Figure 1). In cases that have been studied in details, SERKs act as coreceptors rather than ligand-binding receptors. The first obvious question would be how the specificity of each of the SERK-mediated signaling pathways is controlled. From the story of BRI1 and

Figure 1



SERKs interact with multiple ligand-binding LRR-RLKs and control multiple developmental and defense-related signaling pathways. The interaction of BRI1 and BAK1 was found to be BR dependent [15,16,37]. The interaction of BIR1 and SERKs was confirmed by a number of different approaches [18••]. This pathway was thought to prevent plant cell death. The assumed ligand (a 'surviving' signal) is yet to be identified in the future. Available evidence indicated that TPD1, EMS1/EXS and SERK1, 2 may control a common signaling pathway [6–8,30,32•]. An interaction between SERKs and EMS1/EXS has not yet been reported. Association between FLS2 and BAK1 has been demonstrated in previous studies [35,36]. Although genetic evidence did show that SERKs may participate in EFR-mediated signaling pathway, the physical interaction between EFR and SERKs was not reported. Using yeast two-hybrid analysis, PEPR1 and PEPR2 were found to interact with BAK1 [39•], and may also interact with other members of SERK subfamily. Question marks in the figure indicate hypothetical processes that have not been experimentally proved yet.

BSKs [44], it can be concluded that the determination of a signaling pathway may rely more on the ligand-binding receptors rather than the shared coreceptors. The second apparent question would be why in some cases members of SERKs exhibit divergent biological functions. Indirect evidence from previous studies suggested that members of SERKs may possess different biochemical properties [23]. In addition, expression patterns of SERK members are not always overlapped in some tissues [45]. A recent report on genome-wide cloning and sequence analysis of LRR-RLK cDNAs illustrated that more than 30 RLKs have alternatively spliced forms [5•]. It is very likely that the alternatively spliced forms represent another regulatory mechanism to determine specificity of RLK-associated signaling pathways. So far all known SERK/ligand-binding receptor pair showed ligand-dependent association. It is yet to be tested whether reciprocal and sequential phosphorylation of SERKs with their partner RLKs represents a common mechanism in all SERK-related signaling pathways.

Proteomic approaches have been widely used to identify signaling components involved in RLK related signaling pathways [46]. In the future, identification of other SERK interacting RLKs may help to reveal additional roles of SERKs. LRR-RLK II subfamily contains 14 members, but studies have been mainly focused on 5 SERKs. It is likely that other members of LRR-RLK II or members of other RLK families may also serve as coreceptors in many unknown signaling pathways modulating plant growth, development, and immunity responses.

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