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• REVIEW •

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Plant pattern-recognition receptors controlling innate immunity

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INTRODUCTION

Unlike animals, plants lack an adaptive immune system, and entirely rely on innate immunity to resist numerous potential pathogens in their environment (Jones and Dangl, 2006; Boller and Felix, 2009). They have evolved diverse immune receptors to detect potential pathogenic microbes via recognition of pathogen-associated molecular patterns (PAMPs) and effectors encoded by pathogens. PAMPs can be detected by surface-localized pattern-recognition receptors (PRRs) that are receptor kinases (RKs) or receptor proteins (RPs), thereby activating pattern-triggered immunity (PTI). Plant PRRs are structurally and functionally analogous to animal Toll-like receptors (TLRs). In addition to microbial molecules, some PRRs can recognize damage-associated molecular patterns (DAMPs) that are plant derived molecules released during pathogen infection. Phytopathogens are capable of secreting effectors into plant apoplast or cytoplasm to enhance virulence. However, further evolution in plants has resulted in PRRs that recognize apoplastic effectors and intracellular immune receptors that recognize cytoplasmic effectors. Plant intracellular immune receptors contain nucleotide-binding, leucine-rich repeat domains and are homologous to animal NOD-like receptors (NLRs). Immunity initiated by NLRs is also referred to as effector-triggered immunity.

Plant receptor-like kinases (RLKs) and receptor-like proteins (RLPs) play diverse role in plant growth, development, reproduction, adaptation to abiotic stress, symbiosis, and disease resistance (Morris and Walker, 2003; Tör et al., 2009). To date, only a relatively small number of RLKs and RLPs, such as XA21, FLS2, and EFR, have been shown to directly perceive ligands. They are referred to as RKs and RPs in this review. Plant genomes encode a large number of RLKs and RLPs, many of which show lineage-specific expansion, suggesting a role in the adaptation to pathogens (Shiu and Bleecker, 2001; Shin-Han and Bleecker, 2003). Indeed, a growing number of RLKs and RLPs have been found to be PRRs. Recent advances have uncovered commonalities and differences concerning how PRRs recognize diverse ligands to activate downstream signaling. In this review, we discuss our current understanding of biological functions, mechanisms of PRR activation, and dynamic regulation of receptor complexes during immune signaling.

RLKS AND RLPS BELONG TO SUPER FAMILIES IN HIGHER PLANTS

RLKs and RLPs mediate perception of a variety of endogenous or exogenous signals (Tör et al., 2009). An RLK contains a single-pass transmembrane domain, an intracellular kinase domain, and an extracellular domain (ECD), which perceives extracellular molecules (Gómez-Gómez and Boller, 2000; Li and Chory, 1997; Zipfel et al., 2006). In contrast, RLPs only have a very short intracellular domain and lack kinase domain (Gust and Felix, 2014; Liebrand et al., 2014). The number of RLKs and RLPs in plants far exceeds their counterparts in

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animals (Shiu and Bleecker, 2001). There are ~ 410 RLKs and 170 RLPs in *Arabidopsis*, ~640 RLKs and 90 RLPs in rice (Fritz-Laylin et al., 2005; Shiu and Bleecker, 2001; Shiu et al., 2004) (Figure 1A and B), among which many members are functionally unknown. The expansion of RLK and RLP families in plants is likely linked to the sessile nature of plants, which cannot escape from assaults from their surrounding environment. And the presence of a large number of RLKs and RLPs might have played a fundamental role in the success of terrestrial plants.

RLKs and RLPs are divided into multiple subfamilies according to their ECDs which include leucine-rich repeat (LRR), lysin motif (LysM), Lectin, and epidermal growth factor-like (EGF) domains (Macho and Zipfel, 2014). The LRR subfamilies are the largest among RLKs and RLPs (Figure 1B). Phylogenetic analyses showed that the LRR-XII subfamily of *Arabidopsis* RLK, which contains multiple PRRs, undergoes an expansion possibly as a result of host-pathogen co-evolution (Shiu et al., 2004; Wu and Zhou, 2013). Although the number of RLPs is much smaller than RLKs, they also possess diverse ECDs, and their expansion is similarly linked to host adaptation to pathogens. Indeed, recent advances have identified several RLPs as new PRRs (Albert et al., 2015; Jehle et al., 2013; Zhang et al., 2013, 2014).

RKS AND RPS AS PRRS

Up to now, only a handful PRR-ligand pairs have been elucidated. And different subfamilies of PRRs exhibit the commonalities and differences in recognition of diverse ligands.

LRR-containing RLKs are the largest subfamilies in *Ara-*

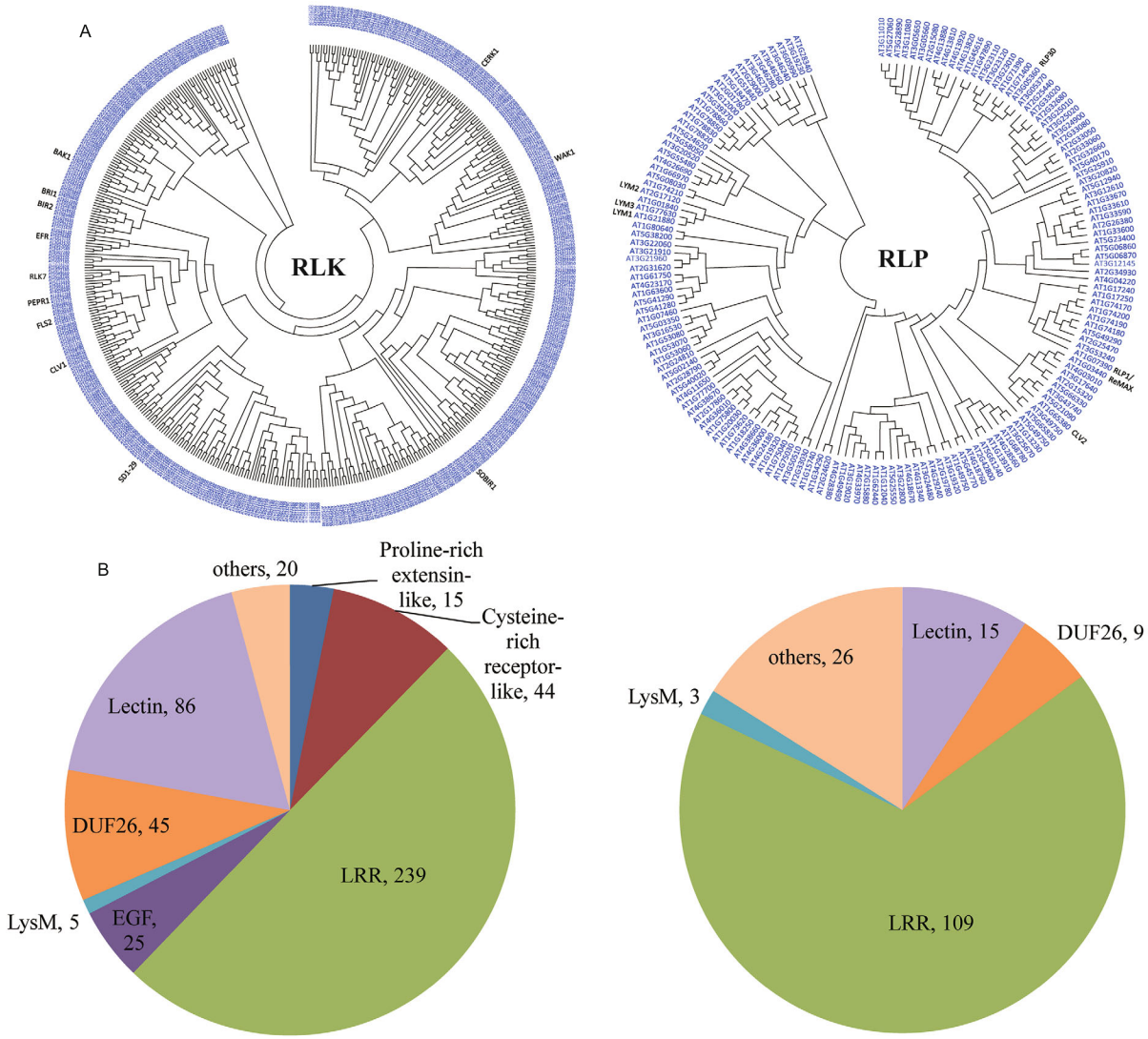

Figure 1 An expanded RLK/RLP gene families in plant kingdom. A, Phylogenetic tree of RLK/RLP in *Arabidopsis*. All known *Arabidopsis* RLK and RLP sequences were retrieved from the genome database, and full length sequences were aligned to generate the neighbor-joining tree by ClustalX 2.0. B, The number of genes with indicated extracellular domain in *Arabidopsis*.

bidopsis genome with more than 230 members. Several well-known PRRs are RKs belonging to these subfamilies. The *Arabidopsis* RK FLS2 is the receptor of a conserved 22 amino acid epitope (flg22) of bacterial flagellin, defining the first plant PRR-PAMP pair to be identified (Bauer et al., 2001; Gómez-Gómez and Boller, 2000). Surprisingly, the mammalian immune receptor TLR5 also recognizes bacterial flagellin through binding to a different epitope (Hayashi et al., 2001; Yoon et al., 2012). Although both TLR5 and FLS2 contain LRR ectodomains, they have evolved independently and recognize different parts of flagellin (Boller and Felix, 2009; Nürnberger et al., 2004). Another well-studied PRR is the *Arabidopsis* LRR-RK EFR that senses the N-acetylated peptide with 18 amino acids of the N-terminus of elongation factor Tu (EF-Tu), which is the most abundant protein in the bacterial cell (Kunze et al., 2004; Zipfel et al., 2006). In addition, the rice LRR-RK XA21 perceives the tyrosine-sulfated protein RaxX from *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) species to trigger effective resistance to *Xoo* (Pruitt et al., 2015; Wei et al., 2016). The *Arabidopsis* LRR-RKs PEPR1 and PEPR2 perceive conserved Pep sequence shared by a small family of *Arabidopsis* ProPep proteins that are released during pathogen infection (Huffaker and Ryan, 2007; Krol et al., 2010; Yamaguchi et al., 2010). Pep perception not only amplifies the PTI signaling (Liu et al., 2013b; Tintor et al., 2013), but also contributes to systemic acquired resistance (Ross et al., 2014). Recent findings indicate that Pep perception also allows plants to sense the perturbation of immune system by pathogens (Yamada et al., 2016). Similar to Pep, another plant endogenous peptide PIP1 was induced by a variety of pathogens and PAMPs. The LRR-RK RLK7 can bind PIP1 and is required for PIP1-induced immune signaling, suggesting that RLK7 is a potential PRR for PIP1 (Hou et al., 2014). RLK7 may cooperate with PEPR to amplify the immune response triggered by PAMPs. Interestingly, FLS2, EFR, PEPR, RLK7, and XA21 all belong to subfamily LRR-XII of RLKs (Shiu et al., 2004), but they bind different ligands, suggesting that this subfamily RLKs might recognize diverse proteinaceous ligands for immune activation.

Similar to LRR-RLKs, a large number of LRR-RLPs (~100) were found existing in *Arabidopsis* genome. Several LRR-RLPs have been identified as likely PRRs. The *Arabidopsis* RLP1/ReMAX detects a *Xanthomonas* protein, although molecular identity of which is unknown (Jehle et al., 2013). RLP30 recognizes an unknown proteinaceous elicitor from the necrotrophic fungal pathogen *Sclerotinia sclerotiorum* (Zhang et al., 2013). The *Arabidopsis* RLP42, is required for the recognition of fungal endopolygalacturonases (Zhang et al., 2014). The *Arabidopsis* RLP23 recognizes necrosis and ethylene-inducing peptide 1-like proteins, a large class of proteins secreted by bacterial, fungal and oomycete pathogens, to activate immunity in a manner dependent on RLKs SOBIR1 and BAK1 (Albert et al., 2015). Besides PAMPs, many filamentous phytopathogens apoplastic effectors are also perceived by RLPs (de Jonge et al. 2011). The tomato Cf proteins are LRR-RLPs that confer resistance to *C. fulvum* carrying cognate apoplastic effectors (Joosten and de Wit, 1999). For instance, the tomato RLP Cf-2 recognizes the *C. fulvum* apoplastic effector Avr2 to induce hypersensitive response, although the ligand responsible for this recognition has yet to be identified (Dixon et al., 1996; Kruger et al., 2002; Luderer et al., 2002; Rooney et al., 2005). In addition, the tomato RLPs Cf-4, Cf-9 and Cf-4E can perceive *C. fulvum* effectors Avr4, Avr9, and Avr4E, respectively (Wulff et al., 2009). These findings suggest that RKs and RPs with LRR ECDs specialized in the recognition of proteinaceous ligands.

While *Arabidopsis* encodes only five LysM-containing RLKs and three RLPs, more evidence showed that they play important roles in triggering plant defenses by sensing specific fungal chitin and bacterial peptidoglycan (PGN), which are microbial *N*-acetylglucosamine (GlcNAc)-containing glycans and can act as PAMPs (Silipo et al., 2010). In rice, the LysM-RP CEBiP is the high affinity chitin receptor (Kaku et al., 2006). Chitin-triggered immunity also requires CERK1, a LysM-RLK (Shimizu et al., 2010). *Arabidopsis* does not appear to carry a functional counterpart of CEBiP. Instead, the *Arabidopsis* LysM-RK CERK1 has been shown to bind chitin and is required for chitin-induced immunity (Liu et al., 2012b; Miya et al., 2007; Petutschnig et al., 2010; Wan et al., 2008). A recent report suggests that another *Arabidopsis* LysM-RK, LYK5, is a high affinity chitin receptor (Cao et al., 2014). Likewise, PGN can elicit defense responses in plants (Gust et al., 2007; Erbs et al., 2008). In *Arabidopsis*, the LysM-RPs LYM1 and LYM3 specifically bind PGN to trigger resistance to bacterial pathogens (Willmann et al., 2011; Shinya et al., 2012). CERK1, although does not bind PGNs, is also required for PGN-induced immunity (Shinya et al., 2012; Willmann et al., 2011). Moreover, the rice LysM-RLPs LYP4 and LYP6 act together with CERK1 for PGN-induced immunity (Liu et al., 2012a; Gust, 2015). The LysM-mediated perception of PGN in plants contrast PGN perception in mammals, which involve structurally diverse immune receptors including the founding members of NLR proteins NOD1 and NOD2, TLR2, and PGN recognition proteins (PGRPs, PGLYRPs) (Chamaillard et al., 2003; Dziarski and Gupta, 2010; Girardin et al., 2003; Kurata, 2010; Takeuchi et al., 1999). In adition, RLKs or RLPs carrying LysM domain are also involved in recognition of Nod factors (NFs) and Myc factors (MFs), which are rhizobium/arbuscular mycorrhiza-derived chitin-related lipochitooligosaccharides with short carbon backbones (3-5 *N*-GlcNAc residues) (Gust et al., 2012). For example, *Lotus japonicus* LysM-RKs NF receptor 1 (NFR1)

and NFR5, *Medicago truncatula* NF perception (NFP) and LYK3, and *Pisum sativum* Sym37 and Sym10 are required for recognizing NFs of *Rhizobium* (Amor et al., 2003; Limpens et al., 2003; Madsen et al., 2003; Radutoiu et al., 2003; Smit et al., 2007; Zhukov et al., 2008). Moreover, *Parasponia andersonii* NFP and *Medicago truncatula* NFP are also required for the perception of MFs during symbiosis with arbuscular mycorhiza (Op den Camp et al., 2011; Maillet et al., 2011). These findings demonstrate that plant LysM receptors are specialized in the recognition of GlcNAc-containing microbial signals to mediate plant immune activation or symbiosis.

Arabidopsis encodes approximately 100 proteins with Lectin ECDs, several of which have also been shown to play an important role in plant immunity. LORE, an RK containing a plant specific B-type Lectin domain, senses lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria (Vaid et al., 2012; Ranf et al., 2015). LPS are composed of O-antigen biological repeats, core oligosaccharide, and lipid A (Knirel et al., 2006). LORE binds LPS mainly through lipid A, which is similar to the recognition of LPS lipid A moiety by mammalian immune receptor TLR4 that activates proinflammatory responses (Park et al., 2009; Tan and Kagan, 2014). However, TLR4 carries an LRR ECD instead of a Lectin ECD. It is unexpected that the lipid A moiety is recognized by receptors of completely different structure in plants and mammals. One possibility is that these receptors detect distinct acylation patterns existing in plant and animal bacterial pathogens (Ranf et al., 2015). Another Lectin family PRR LecRK-I.9 has been shown to perceive extracellular ATP (eATP) to regulate cellular responses (Choi et al., 2014). As ATP is probably released by plant cell into extracellular matrix during wounding and infection of pathogen, ATP can be considered as another DAMP. In addition, the Lectin-RLK LecRK-VI.2 was found to act as a key modulator in plant PTI responses, although the underlying mechanism remains unknown (Singh et al., 2012). Recently, three G-type Lectin family RLKs LecRK1, LecRK2 and LecRK3 were shown to be required for brown planthopper resistance in rice (Liu et al., 2015). Broad-spectrum bacteria and insect resistance of LecRK-VI.2 in *Arabidopsis* and LecRK1-3 in rice indicate that Lectin-RLKs prime PTI response to both pathogen and insect attacks by either directly or indirectly perceiving conserved microbe- or insect-derived elicitors or DAMP.

Arabidopsis contains 25 RLKs with EGF-like motif ectodmain, among which wall-associated kinases (WAKs) play key roles in plant immunity shown by previous findings (Brutus et al., 2010; Delteil et al., 2016; Kohorn et al., 2009). Plant cell wall component oligogalacturonides, a well-known class of DAMPs released during pathogen attacks, are sensed by WAK1 in *Arabidopsis* (Brutus et al., 2010; Decreux and Messiaen, 2005; Decreux et al., 2006). Another *Arabidopsis* EGF-like motif-containing RK, WAK2 can bind pectin and activates the mitogen-activated protein kinases (MPK) (Kohorn et al., 2009). Moreover, WAK14, WAK91 and WAK92 are required for quantitative resistance to the rice blast disease (Delteil et al., 2016). These findings indicate that perception of plant cell wall components is uniquely important for plant disease resistance.

OLIGOMERIZATION AS A COMMON MECHANISM FOR PRR ACTIVATION

Ligand-induced oligomerization between RKs and RLKs or RPs and RLKs are a common mechanism for the activation of PRRs. In *Arabidopsis*, FLS2 and EFR can form heterodimer with co-receptor SERK3/BAK1, an RLK belonging to a small family of RLKs called SERKs with 5 members, after flg22 and elf18 treatment, respectively (Chinchilla et al., 2007; Heese et al., 2007; Schulze et al., 2010; Sun et al., 2013a). The involvement of BAK1 as a co-receptor appears to be common for LRR RKs. Indeed, a recent report showed that Pep1 also induces PEPR1 heterodimerization with BAK1 (Tang et al., 2015). Moreover, phytosulfokine (PSK), a disulfated pentapeptide, promotes PSKR-SERK1/SERK2/BAK1 heterodimerization between PSKR and BAK1 or BAK1 paralogs SERK1 or SERK2 in the regulation of plant development (Wang et al., 2015). BAK1 not only is required for LRR-RKs function, but also for LRR-RP function. Recent evidence indicated that the LRR-RLK suppressor of BIR1 (SOBIR1) as an adaptor interacts with multiple LRR RPs in *Arabidopsis* (RLP1, RLP23, RLP30 and RLP42) and tomato (Cf, Ve1, and Eix). It is now clear that BAK is also recruited to RP/SOBIR1 complex to regulate immune signaling output following ligand stimulation (Gust and Felix, 2014).

In contrast to LRR-RKs and RPs, LysM-RK and RPs do not seem to require BAK1 for function with one exception (Henty-Ridilla et al., 2013). In rice, chitin induced heterodimerization between CEBiP and CERK1 is necessary for chitin-induced immune activation. Similarly, PGN induces heterodimerization between LYM1/LYM3 and CERK1 in *Arabidopsis* or LYP4/LYP6 and CERK1 in rice (Gust, 2015). Together, the aforementioned findings indicate that ligand induced oligomerization between RLK-RK or RLK-RP is a universal mechanism for immune activation by plant PRRs.

Protein structure analyses have provided atomic level understanding of ligand-induced activation of RKs. The structures of the ECDs of *Arabidopsis* FLS2, BRI1, and carrot PSKR LRR-RKs complexed with their cognate co-receptors and ligands have been solved recently (Santiago et al., 2013; Sun et al., 2013a, b; Wang et al., 2015). The structural studies explain previous genetic data and provide mechanistic insight concerning how the receptors recognize their cognate ligands. The ECDs of FLS2, BRI1 and PSKR all adopt a right-hand superhelical structure, which seems to be common to plant

LRR-RKs (Zhang and Thomma, 2013; Han et al., 2014). Equal proportion of receptor/ligand/co-receptor in the complex of FLS2-flg22-BAK1, BRI1-BL-BAK1, and PSKR-PSK-SERK2 was revealed by crystal structures (Santiago et al., 2013; Sun et al., 2013a, b; Wang et al., 2015). However, the ligands do not induce homo-oligomerization of their receptors (Santiago et al., 2013; Sun et al., 2013a, b; Wang et al., 2015), which is different from animal TLRs (Song and Lee, 2012). Apart from the commonalities, there are obvious differences in activation mechanisms among the three receptor complexes. Flg22 and BL do not induce conformation change of FLS2 and BRI1, and both ligands are directly involved in the formation of heterodimerization by contacting with N-terminus of BAK1 LRR (Santiago et al., 2013; Sun et al., 2013a, b). A protuberance of non-LRR structure called island domain (ID) interrupts ECDs of BRI1 and PSKR (Santiago et al., 2013; Sun et al., 2013b; Wang et al., 2015) (Figure 2). The ID is responsible for ligand binding, which is much larger in BRI1 compared to that in PSKR (Wang et al., 2015). A change of conformation occurs in PSK bound $PSKR^{ID}$, which is more similar to BRI^{ID} compared with a free $PSKR^{ID}$ (Wang et al., 2015). Contrary to flg22 and BL, PSK does not directly interact with SERK2, the N-terminus of which only interacts with PSK bound $PSKR^{ID}$ (Wang et al., 2015). As a similar short ID also exists in other RLPs and RLKs, it will be interesting to find whether they adopt the same mechanism to activate receptor complex. The FLS2 LRR domain does not contain an ID. Instead, 14 LRRs of FLS2 directly associate with Flg22 (Sun et al., 2013a). The C-terminal flg22 residue Gly18 acts as "molecular glue" to mediate interaction between FLS2LRR and BAK1LRR (Sun et al., 2013a).

Although the crystal structures of ECDs perfectly reveal mechanisms by which cognate ligands induce receptor complexes formation, they do not readily explain trans-phosphorylation of the intracellular kinase domain as ectodomain structures do not reveal molecular event in kinase domain. Recent investigation of kinase domain revealed that dimerization supports slight conformational change of the intracellular domain (Yan et al., 2012; Bojar et al., 2014), which may favor the trans-phosphorylation and activation of kinase domain. In all, dimerization of ECDs induced by ligands paves the way for juxtaposition of intracellular kinase domain, which is a general activation strategy of plant RLK/RLPs.

RLCKS LINK PRRS WITH DOWNSTREAM SIGNALING

A major challenge to the field of plant immunity is to understand how the activation of PRRs leads to diverse defense responses. Following the activation of PRR complexes, many cellular responses are triggered, including reactive oxygen species (ROS) production, Ca^{2+} burst, a rapid activation of MPKs and the up-regulation of defense gene expression (Boller and Felix, 2009; Dodds and Rathjen, 2010; Macho and Zipfel, 2014; Monaghan and Zipfel, 2012; Wu and Zhou, 2013). These early signaling events are responsible for orchestration of diverse defenses that ultimately restrict pathogen progression. In recent years, several receptor-like cytoplasmic kinases (RLCKs) have emerged as central components of PRR complexes that link PRR activation to various early signaling events.

Botrytis-induced kinase 1 (BIK1) and PBS1-like 1 (PBL1), two highly homologous members of RLCK-VII family, act as positive regulator in multiple PRR complexes (Lu et al., 2010;

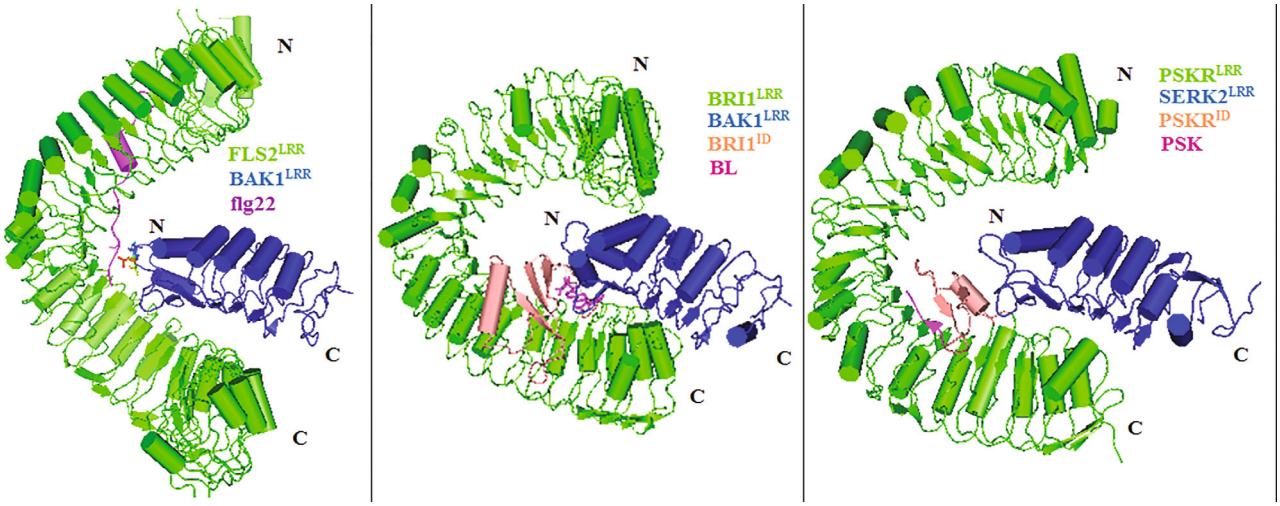

Figure 2 Atomic structures of FLS2LRR-flg22-BAK1LRR, BRI1LRR-BL-BAK1LRR, and PSKRLRR-PSK-SERK2LRR. The ECDs of FLS2, BRI1, and PSKR form the right-hand superhelical structure. Flg22 interacts with 14 LRRs of the concave of FLS2. C-terminal residue Gly18 of flg22 directly mediates N-terminus of BAK1LRR interaction. BL and PSK bind the island domain (ID) of BRI1 and PSKR respectively. PSK induces conformational change of PSKR ID to recruit SERK2 to form stable PSKR-SERK2 complex.

Zhang et al., 2010). BIK1 and PBL1 can directly associate with unstimulated FLS2, EFR, CERK1 and PEPR1 (Zhang et al., 2010; Liu et al., 2013b). Accordingly, the *bik1 pbl1* double mutant exhibits reduced immune responses triggered by multiple PAMPs, such as ROS production, defense gene expression, callose deposition, and transient influx of calcium ion from the apoplast, and is severely compromised in nonadapted bacterial pathogen and pathogenic fungus *Botrytis cinerea* (Li et al., 2014b; Lu et al., 2010; Veronese et al., 2006; Zhang et al., 2010). Furthermore, both *Xanthomonas* effector AvrAC and *Pseudomonas* effector AvrPphB can specifically target *Arabidopsis* BIK1 and related PBLs, resulting in reduced kinase activity and inhibition of plant immunity (Feng et al., 2012; Zhang et al., 2010). The fact that unrelated effectors from completely different pathogens target BIK1/PBLs further highlights the importance of BIK1/PBLs in plant immunity.

In rice, RLCK185 and RLCK176, two members of BIK1 family, directly interacts with CERK1 to mediate chitin- and PGN-induced plant immunity (Ao et al., 2014; Yamaguchi et al., 2013). Similarly, PBL27, an *Arabidopsis* ortholog of RLCK185, also interacts with CERK1 and contributes to chitin-induced immunity but not flg22-induced immunity (Shinya et al., 2014). In addition, BR-signaling kinase 1 (BSK1), associates with FLS2 and is required for flg22-induced ROS burst (Shi et al., 2013). Recently, another RLCK-VII family member PCRK1 was reported to play important roles during flg22-, elf18- and pep1-triggered immunity, although it is unknown whether it interacts with PRRs (Sreekanta et al., 2015). So far, the above mentioned findings suggest that while some RLCKs associate with multiple PRRs, others may interact with one or a few specific PRRs. It will be interesting to investigate whether different RLCKs regulate distinct or overlapping downstream components during immune signaling.

Transient Ca^{2+} influx is one critical early cellular response after FLS2, EFR and PEPR activation (Lecourieux et al., 2006; Qi et al., 2010). The calcium as a second messenger, almost participates in all the defense responses (Lecourieux et al., 2006). Recent work showed that BIK1 and PBL1 are required for the flg22-induced calcium influx, which is required for the activation of RbohD to regulate ROS production (Li et al., 2014b; Ranf et al., 2014). How PRR complexes activate transient Ca^{2+} influx is unknown. The fact that BIK1 and PBL1 are required for the flg22-idnuced calcium influx suggest that phosphorylation of an unknown calcium channel may lead to the opening of the Ca^{2+} channel.

ROS burst is another cellular response mediated by multiple PRRs. Recently, respiratory burst oxidase homolog D (RbohD), a membrane-localized enzyme responsible for transient ROS production (Torres et al., 2002), was identified as the first substrate of BIK1 (Kadota et al., 2014; Li et al., 2014b). RbohD directly associates with FLS2 and other PRR complexes before activation. Upon stimulation by PAMPs, RbohD is phosphorylated directly by the activated BIK1, and then dissociates from the PRR complex, allowing it to be activated by other signals, such as calcium (Kadota et al., 2014; Li et al., 2014b; Ma, 2014).

Recently, it was shown that heterotrimeric G proteins composed of Gα protein XLG2, Gβ protein AGB1, and Gγ proteins AGG1 and AGG2 are required for ROS production and disease resistance mediated by FLS2, EFR, and CERK1 (Liu et al., 2013a; Maruta et al., 2015). Most recent report showed that the G proteins directly interact with FLS2-BIK1 receptor complex. Upon activation of the FLS2-BIK1 complex by flg22, BIK1 directly phosphorylates the N terminus of XLG2 to enhance ROS production (Liang et al., 2016). However, the phosphorylated XLG2 did not affect XLG2-BIK1 interaction or BIK1 stability in the post-activation state. Considering that XLG2 associates with RbohD constitutively and that RbohD activity is regulated by binding to Ca^{2+} and phosphatidic acid (PA), and phosphorylation by BIK1 and CPK5 (Dubiella et al., 2013; Kadota et al., 2014; Li et al., 2014b; Liang et al., 2016; Zhang et al., 2009), it will be interesting to determine whether the phosphorylated XLG2 modulates these processes.

After PRR complexes are activated, MPK activation occurs within 1–2 min and then reaches a peak at 10–15 min, which plays crucial roles in multiple defense responses including cell death, defense gene expression and stomatal closure (Meng and Zhang, 2013). Although it has not been genetically established, multiple lines evidence support a role of BIK1/PBLs in MPK activation. For example, although the *bik1 pbl1* mutant exhibited normal flg22-induced activation of MPKs (Feng et al., 2012), the *Xanthomonas campestris* effector protein AvrAC, which specifically inhibits multiple PBLs by uridylylation, severely inhibited flg22-induced MPK activation (Feng et al., 2012). This suggests that additional PBLs are required for MPK activation, although it does not rule out the possibility that new components other than RLCKs are involved. In the future, it will be important to determine whether uncharacterized RLCKs play a specific role in MPK activation or multiple RLCKs act redundantly to control MPK activation.

DYNAMIC REGULATION OF PRR COMPLEXES

Rapid and robust activation of plant immune signaling is crucial for plants to mount effective defenses against invading pathogens. However, excessive immune signaling can be detrimental to plants. Thus the composition, activity, and abundance of PRR complexes must be subject to tight regulation both before and after immune activation.

An important regulatory aspect is to control PRR com-

plexes formation prior to ligand perception. For example, recent findings showed that LRR-RLK BIR2, a pseudokinase, prevents the PRRs-BAK1 complex formation at resting state (Halter et al, 2014a). BIR2 associates with BAK1 constitutively to prevent the interactions of BAK1 with adjacent PRRs before PAMPs perception. After ligands perception, BIR2 is released from BAK1 and results in PRRs and BAK1 interaction and immune activation rapidly (Blaum et al., 2014; Halter et al., 2014a, b). In addition, another LRR-RLK BIR1 also interacts with BAK1 to negatively regulate plant defense responses (Gao et al., 2009). In contrast to BIR2, BIR1 is an active kinase and the kinase activity is partially required for its function, although they belong to the same subfamily and both *bir1* and *bir2* mutant have a cell death phenotype (Gao et al., 2009; Halter et al., 2014a, b). This suggests that BIR1 and BAK1 complex regulates plant immunity likely via a different molecular mechanism, such as perception of an unknown signal.

PRR complex stability is another important regulatory mechanism. Recent advances showed that BIK1 stability is known to be regulated by 26S proteasome pathway and that CPK28 facilitates BIK1 degradation to negatively regulate immunity in the pre-activation state (Monaghan et al., 2014). More recent studies showed that, in addition to regulating ROS production in the post-activation state, the heterotrimeric G proteins are directly coupled to FLS2-BIK1 receptor complex to stabilize the BIK1 protein, also in the pre-activation state (Liang et al., 2016). This allows plants to initiate robust immune responses once stimulated by flg22 (Liang et al., 2016). The findings indicate that CPK28 and G proteins control BIK1 turn-over oppositely by 26S proteasome pathway, ensuring optimum level of BIK1 for immune activation. Since CPK28 and the G proteins both regulate BIK1 in the pre-activation state, it is possible that they regulate BIK1 ubiquitination by the same, unknown E3 ligases.

In addition to pre-activation, PRR complex stability also is regulated after stimulation by PAMPs. For example, FLS2 is subject to degradation by the 26S proteasome pathway after flg22 perception to attenuate immune signaling (Lu et al., 2011). FLS2 is ubiquitinated by two U-Box E3 ligases PUB12 and PUB13 for degradation. PUB12 and PUB13 constitutively interact with BAK1 and are recruited to the FLS2 after flg22 perception, resulting in an flg22-induced ubiquitination and degradation of FLS2 but not BAK1 (Lu et al., 2011), which is crucial for preventing prolonged immune activation. These findings shed light on one important mechanism of how E3 ligases attenuate immune signaling after the PRR activation.

Ligand-induced endocytosis is another regulatory mechanism controlling PRR immune activation. After flg22 elicitation, FLS2 is subject to endocytosis and degradation within 1 h, which may prevent continuous immune activation (Smith et al., 2014). There is no evidence that FLS2 ubiquitination by PUB12/13 contributes to FLS2 endocytosis (Li et al., 2014a). The stimulated cells are replenished with newly synthesized FLS2 to restore flg22-sensing capability within 2 h (Smith et al., 2014). FLS2 endocytosis may also serve to promote flg22-signaling competency. For example, FLS2 co-localizes with the endosomal sorting complex required for transport (ESCRT)-I subunits at endosomes after flg22 perception, resulting in FLS2 endosomal sorting (Spallek et al., 2013). The ESCRT-I components VSP37-1 and VSP28-2 are required for not only FLS2 endocytosis, but also flg22-induced stomatal immunity (Spallek et al., 2013). Moreover, stomatal cytokinesis defective 1 (SCD1), which functions in clathrin-mediated endocytosis (McMichael et al., 2013), was also found as an FLS2 interaction partner required for flg22-induced ROS burst (Korasick et al., 2010). These findings raise interesting possibility that the activated PRR complex is mobilized to intracellular compartments to activate various downstream responses.

CONCLUDING REMARKS

Increasing evidences support that the RLK and RLP super families play a crucial role in the perception of diverse microbial and endogenous patterns, forming a powerful surveillance system at the cell surface against invading microbes and insects. We are far from that knowing the complete repertoire of PRRs in a plant species and ligands they perceive. A daunting task will be to assign biological and biochemical functions to the vast majority of RLKs and RLPs that are functionally unknown, particularly those involved in plant immunity.

RLK-RK or RLK-RP oligomerization induced by cognate ligand is a common mechanism for the activation of PRRs. The PRRs, as core components, can recruit RLCKs, substrates of RLCKs, and other regulators to form dynamic plant PRR immune complexes, allowing robust but controlled intracellular signaling in the face of pathogen attacks without unwanted effect on growth and development under normal conditions. An important question is how different components are organized in the PRR complex, whether they reside in the same complex or different complexes. Major gaps remain in our knowledge concerning regulation of early immune signaling events, such as the control of calcium burst and MPK activation. Future challenge is to identify new components linking PRR complexes and activation of various key signaling events.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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