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REVIEW

Receptor-like kinases and receptor-like proteins: keys to pathogen recognition and defense signaling in plant innate immunity

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Abstract **Plants have evolved multiple layers of defense against various pathogens in the environment. Receptor-like kinases/proteins (RLKs/RLPs) are on the front lines of the battle between plants and pathogens since they are present at the plasma membrane and perceive signature molecules from either the invading pathogen or damaged plant tissue. With a few notable exceptions, most RLKs/RLPs are positive regulators of plant innate immunity. In this review, we summarize recently discovered RLKs/RLPs that are involved in plant defense responses against various classes of pathogens. We also describe what is currently known about the mechanisms of RLK-mediated initiation of signaling via protein-protein interactions and phosphorylation.**

Keywords receptor-like kinases (RLKs), receptor-like proteins (RLPs), biotrophic fungi, necrotrophic fungi, bacterial pathogens

Introduction

Receptor-like kinases (RLKs) and receptor-like proteins (RLPs) in plants are involved in many biologic processes including development, innate immunity, cell differentiation and patterning, nodulation and self-incompatibility. As more and more plant genome sequences have become available, the number of genes annotated as RLKs or RLPs in plants has been growing. The *Arabidopsis* genome contains more than 600 RLKs and 57 RLPs, accounting for almost 2.5% of the *Arabidopsis* genome (Shiu and Bleecker, 2001; Wang et al.,, 2008). The rice genome contains 2210 RLKs and more than 443 of rice RLKs appear to share common ancestors with *Arabidopsis* RLKs (Shiu et al.,, 2004). Ninety genes were predicted to be RLPs in the rice genome and 73 of these are believed to be involved in pathogen defense (Fritz-Laylin et al.,, 2005). Additionally, over 650 RLKs were identified in the soybean genome by searching for RLK homologs in an EST database (Liu et al., 2009). While the functions of most RLKs and RLPs are unknown, increasing experimental data points to their importance in the plant.

A typical RLK contains an extracellular domain, a transmembrane domain (TM) and an intracellular kinase domain. Some RLKs lack an extracellular domain and are designated as receptor-like cytoplasmic kinases (RLCKs). RLPs are composed of an extracellular domain, a transmembrane domain and a short cytoplasmic region and lack an associated kinase domain (Wang et al., 2008). The extracellular domains of both RLKs and RLPs function primarily in recognition of either endogenous or exogenous molecular cues. For example, extracellular leucine-rich repeat domains (eLRR) in RLKs are well characterized and have been shown to be involved in recognition of general elicitors (FLAGELLIN SENSITIVE 2 [FLS2], Gómez-Gómez and Boller, 2000) and plant hormones (BRASSINOSTEROID INSENSITIVE 1 [BRI1], Li and Chory, 1997). Some RLK/RLP extracellular domains have also been shown to bind carbohydrate derivatives such as chitin (CHITIN ELICITOR RECEPTOR KINASE 1 [CERK1], Iizasa et al., 2010) and oligogalacturonides (WALL-ASSOCIATED KINASE 1 [WAK1], Decreux and Messiaen, 2005). The transmembrane domain (TM) is critical for localization of RLKs and RLPs to the plasma membrane and deletion of the TM domain results in

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cytoplasmic localization of an RLK (Bleckmann et al., 2010). Additionally, transmembrane domains are known to play critical roles in many protein-protein interactions (Reviewed by Senes et al., 2004). The intracellular kinase domain of RLKs is involved in phosphorylation of other proteins to relay signals and initiates downstream signaling pathways. Interestingly, a large number of RLKs are actually receptor-like cytoplasmic kinases (RLCKs). It has been reported that there are 379 putative RLCKs in the rice genome (Vij et al., 2008) and 200 RLCKs in *Arabidopsis* (Jurca et al., 2008). Since they lack an extracellular domain, RLCKs do not perceive a signal directly but interact with other receptors to form a complex that then proceeds to activate the downstream signal (Rowland et al., 2005; Veronese et al., 2006; Lu et al., 2010). In the last decade, many RLKs and RLPs have been characterized that function in plant-pathogen interactions and have critical roles in the initiation and transduction of signals in major plant defense pathways. In this review, we will summarize our current understanding of RLKs and RLPs that are involved in plant innate immunity and what is known regarding their mechanism of action in plant defense pathways. An overview of all RLKs and RLPs discussed in this review is summarized in Table 1.

RLKs and RLPs are involved in defense against fungal pathogens via PAMP and DAMP recognition

Plants recognize and respond to pathogen attack by sensing pathogen-associated molecular patterns (PAMPs), pathogen effectors and danger-associated molecular patterns (DAMPs) (Reviewed by Postel and Kemmerling, 2009). To date, many elicitors have been identified that originate from either the pathogen, such as the fungal elicitors chitin and xylanase and the bacterial elicitors flagellin, elongation factor Tu (EF-Tu) and lipopolysacchride, or from plants themselves, such as oligogalacturonide (OG) and the peptide signal Pep1 (Reviewed by Postel and Kemmerling 2009). However, only a few RLKs and RLPs have been identified that act as receptors for these known elicitors. These RLKs and RLPs perceive PAMPs from pathogens and go on to initiate PAMP-triggered immunity (PTI), the first layer of plant innate immunity.

For example, both the RLP chitin oligosaccharide elicitor-binding protein (CEBiP) and RLK chitin elicitor receptor kinase 1 (CERK1) contain LysM domains that have been shown to bind chitin and trigger chitin-mediated defense signaling (Kaku et al., 2006; Miya et al., 2007; Wan et al., 2008; Shimizu et al., 2010). CEBiP was purified from suspension-cultured rice cells and shown to bind chitin fragments. Microarray analysis showed that a majority of chitin-responsive genes did not respond to chitin treatment in CEBiP-RNAi knockdown rice cells (Kaku et al., 2006). Transgenic rice plants were also constructed to suppress the CEBiP transcripts using RNA interference (RNAi). Data from these experiments showed that CEBiP RNAi lines had more cells penetrated by the rice blast fungus *Magnaporthe oryzae*. Overexpression of CEBiP in rice repressed *M. oryzae* infection to some extent and increased levels of reactive oxygen species (ROS) production (Kishimoto et al., 2010). The barley HvCEBiP protein is an ortholog of CEBiP that shares 60% amino acid identity with the rice protein. When barley *HvCEBiP* was silenced using virus-induced gene silencing (VIGS), the silenced plants developed more severe symptoms compared to control plants inoculated with the fungal pathogen *M. oryzae mossd1*, a mutant that fails to infect rice and barley (Tanaka et al., 2010). The rice ortholog of CERK1, OsCERK1, was identified from a group of 10 rice LysM RLKs and shown to interact with CEBiP (Shimizu et al., 2010) Similar to CEBiP, knockdowns of OsCERK1 in RNAi rice cell lines also blocked the induction or repression of most chitin responsive genes upon chitin treatment. ROS induced by chitin was also suppressed in OsCERK1-RNAi cell lines (Shimizu et al., 2010). In *Arabidopsis*, CERK1 was shown to be the major receptor that binds and perceives chitin elicitors (Wan et al., 2008; Miya et al., 2007; Iizasa et al., 2010). *Arabidopsis* CERK1 knockout mutants exhibited impaired immunity to the biotrophic fungus *Golovinomycetes cichoracearum* and the necrotrophic fungus *Alternaria brassicicola*. Although three other CEBiP-like proteins were also identified in *Arabidopsis*, their functions remain unknown (Wan et al., 2008).

Ethylene-induced xylanase (EIX) is a potent fungal elicitor that stimulates ethylene production, the alkalinization response and necrosis when applied to tobacco and tomato leaves (Enkerli et al., 1999). Two genes *LeEix1* and *LeEix2* were identified from tomato as LRR RLPs potentially involved in the response to this elicitor (Ron et al., 2000; Ron and Avni, 2004). EIX-induced cell death was suppressed in *LeEix1*-RNAi transgenic *Nicotianana tabacum cv Samsun* plants that are known to respond to EIX. Interactions between EIX and tobacco cells were not detected in silenced lines. The study showed that while both LeEIX1 and LeEIX2 proteins were able to bind EIX only LeEIX2 was capable of inducing the hypersensitive response (HR) (Ron and Avni, 2004). Recent work by Bar et al., (2010) showed that LeEIX1 and LeEIX2 interact with each other in tobacco cells upon EIX treatment. The function of LeEIX1 in tobacco appears to attenuate EIX-induced LeEIX2 endocytosis and subsequent EIX-induced defense responses (Bar et al., 2010).

Elicitins are conserved extracellular proteins that are secreted by the fungal pathogen *Phytophthora infestans*. Treatment of plants with elicitins triggers the hypersensitive response (HR) and necrotic lesions in tobacco (Ricci et al., 1989). *NbLRK1*, a lectin RLK found in *Nicotiana benthamiana*, was identified as an interactor of the protein INF1, an elicitin from *P. infestans* (Kanzaki et al., 2008). Yeast two-hybrid experiments using a series of truncated NbLRK1 proteins showed that INF1 interacted with the VIb subdomain of NbLRK1's intracellular kinase domain. In

Table 1 RLKs and RLPs involved in plant innate immunity

Name of RLK/RLP	Organism	Type of RLK/RLP	Resistant	Susceptible	References
BIK1	*Arabidopsis*	RLCK	*B. cinerea* *A. brassicicola*	Pst DC3000	Veronese et al., 2006
BIR1	*Arabidopsis*	LRR RLK		*H. parasitica* Noco2	Gao et al., 2009
SOBIR1	*Arabidopsis*	LRR RLK	Pst DC3000		Gao et al.,2009
OSBRR1	Rice	LRR RLK	*M. oryzae*		Peng et al., 2009
BSR1	*Arabidopsis*	RLCK	*C. higginsianum* Pst *DC3000*		Dubouzet et al., 2011
CERK1/LysM RLK1	*Arabidopsis*	LysM RLK	*G. cichoracearum* *A. brassicicola*		Wan et al., 2008; Miya et al., 2007;
OsCERK1	Rice	LysM RLK			Shimizu et al., 2010
CEBiP	Rice	LysM RLP	*M. oryzae*		Kaku et al., 2006; Kishimoto et al., 2010
HvCEBiP	Barley	LysM RLP	*M. oryzae*		Tanaka et al., 2010
LeEix1 and 2	Tobacco	LRR RLP			Ron and Avni, 2004
CBRLK1	*Arabidopsis*	S-locus RLK		Pst DC3000	Kim et al., 2009
EFR	*Arabidopsis*	LRR RLK	*A. tumefaciens*		Zipfel et al., 2006
ERECTA	*Arabidopsis*	LRR RLK	*P. cucumerina* *P. irregulare*		Llorente et al., 2005; Adie et al., 2007
FLS2	*Arabidopsis*	LRR RLK	Pst DC3000		Gómez-Gómez and Boller 2000; Zipfel et al., 2004
FER	*Arabidopsis*			*G. orontii* Pst DC3000	Kessler et al., 2010; Keinath et al., 2010
NbLRK1	*N. benthamiana*	Lectin-like RLK			Kanzaki et al., 2008
AtPepR1 and 2	*Arabidopsis*	LRR RLK			Yamaguchi et al., 2006; Krol et al.,2010
NgRLK1	*N. glutinosa*	B-lectin, S-locus glycoprotein			Kim et al., 2010
TaRLK-R1,2,and 3	Wheat		Wheat stripe rust		Zhou et al., 2007
AtRLP30	*Arabidopsis*	LRR RLP	*P. syringae pv phaseolicola 1448A*		Wang et al., 2008
RIPK	*Arabidopsis*	RLCK		Pst DC3000	Liu et al., 2011
NbSERK3/BAK1	N. benthamiana	LRR RLK	*Pta* 11528 *PtoDC3000* *Pto*DC3000 *hrcCP. infestans*		Heese et al., 2007; Chaparro-Garcia et al., 2011
SNC2	*Arabidopsis*	LRR RLP	Pst DC3000		Zhang et al., 2010b
SNC3	*Arabidopsis*	LRR RLP			Zhang et al., 2010b
TARK1	Tomato	LRR RLK	*Xanthomonas campestris* pathovar vesicatoria (Xcv)		Kim et al., 2009
TPK1b	Tomato	RLCK	*B. cinerea* Tobacco hornworm (*Manteca seta*)		AbuQamar et al.,2008
Ve1	Tomato	LRR RLP	*V. dahliae* *V. albo-atrum*		Fradin et al., 2009
Vfa4	Apple	LRR RLP		*V. inaequalis*	Malnoy et al., 2008
Vfa1 and Vfa2	Apple	LRR RLP	*V. inaequalis*		Malnoy et al., 2008; Belfanti et al., 2004
WAK1	*Arabidopsis*	EGF-like RLK	*B. cinerea*		Decreux and Messiaen 2005; Decreux et al., 2006
OsWAK1	Rice	EGF-like RLK	*M. oryzae*		Li et al., 2009b
XA21	Rice	LRR RLK	*Xanthomonas oryzae* pv. *oryzae*		Lee et al., 2009
Xa3/Xa26	Rice	RLK	*Xanthomonas oryzae* pv. *oryzae*		Sun et al., 2004
Xa21D	Rice	RLP	*Xanthomonas oryzae* pv. *oryzae*		Wang et al., 1998

NbLRK1-silenced tobacco plants, INF1-induced H_2O_2 production was inhibited and the HR response was delayed. Another RLK, NgRLK1, was discovered in *Nicotiana glutinosa* and has been shown to interact directly with the fungal elicitin capsicein from *Phytophthora capsici* (Kim et al., 2010). Both *NbLRK1* and *NgRLK1* are potential candidate genes for elicitin-mediated immunity though no direct evidence for a role in innate immunity has been shown to date.

Oligogalacturonide (OG) is known to trigger extensive gene expression in plants and is classified as a DAMP generated from plant cell wall pectin (Denoux et al., 2008; Postel and Kemmerling, 2009). *Arabidopsis* wall-associated kinase 1 (WAK1) is a receptor-like kinase that interacts with pectin and OG *in vitro* (Decreux and Messiaen, 2005; Decreux et al., 2006). In a chimeric receptor study, the WAK1 extracellular domain was shown to interact with OGs and activate downstream defense responses (Brutus et al., 2010). *Arabidopsis* plants overexpressing WAK1 were more resistant to the necrotrophic fungi *Botrytis cinerea* (Brutus et al., 2010). *OsWAK1*, a homolog of WAK1 identified in rice, was induced significantly by *M. oryzae* infection and overexpression of OsWAK1 in rice plants conferred increased resistance to *M. Oryzae* (Li et al., 2009b).

Another plant DAMP, *Arabidopsis* peptide 1 (AtPep1), is a 23 amino acid peptide derived from a 92 aa precursor found in leaf tissue (Huffaker et al., 2006). Treatment of *Arabidopsis* plants with AtPep1 induces expression of the defense marker gene *PDF1.2* and production of H_2O_2. Overexpression of AtPep1 in *Arabidopsis* confers increased resistance to the oomycete *Pythium irregulare* (Huffaker et al., 2006). An ortholog of AtPep1, ZmPep1, was identified in corn and pretreatment of maize plants with this peptide enhanced plant resistance to the fungal pathogens *Cochliobolis heterostrophus* and *Colletotrichum graminicola* (Huffaker et al., 2011). The receptor for AtPep1 (AtPepR1) was isolated from *Arabidopsis* suspension-cultured cells and identified as an LRR RLK (Yamaguchi et al., 2006). Another protein, *AtPepR2,* was first identified as a homolog of *AtPepR1* in *Arabidopsis* but was subsequently found to interact directly with AtPep1 (Yamaguchi et al., 2010). Plants with mutations in both proteins (*pepr1*/ *pepr2*) were completely insensitive to AtPep1 treatment while single mutations in either *pepr1* or *pepr2* showed only partial insensitivity to AtPep1 treatment (Krol et al.,2010). However, there was no significant difference in the response of wild type and *pepr1*, *pepr2* and *pepr1*/*pepr2* mutants infected with the fungal pathogens *P. irregulare* and *A. brassicicola* without AtPep1 pretreatment (Yamaguchi et al., 2010). Though compelling this data cannot exclude the possibility that AtPepR1 and AtPepR2 function in AtPep1-mediated resistance against fungal pathogens in some capacity.

Orphan RLKs/RLPs

While ligands have been identified for a few RLKs/RLPs, the binding partners of most RLKs/RLPs in the plant genome remain unknown. Several orphan RLKs/RLPs have been shown to be important in plant innate immunity, though their mechanism of action was revealed only by further study. Llorente et al. surveyed 75 *Arabidopsis* accessions and found that *Landsberg erecta* (Ler-0) was highly susceptible to the necrotrophic fungi *Plectosphaerella cucumerina* (Llorente et al., 2005). Quantitative trait loci (QTL) analysis showed that the LRR RLK *ERECTA* was a candidate gene for Ler-0s resistance to *P. cucumerina*. Loss-of-function mutants in *ERECTA* showed that both the receptor and kinase domains were required for resistance to *P. cucumerina* (Llorente et al., 2005) and to the oomycete pathogen *Pythium irregulare* (Adie et al., 2007). Further experimentation showed that ERECTA-mediated resistance was associated with cell wall content alteration suggesting that ERECTA may also function as a sensor for cell wall integrity in plants (Sánchez-Rodríguez et al., 2009).

In *Arabidopsis*, *BOTRYTIS-INDUCED KINASE 1* (*BIK1*) is highly induced by inoculation with the necrotrophic fungi *Botrytis cinerea.* T-DNA insertional mutants of *bik1* displayed more severe disease symptoms than wild type plants inoculated with *B. cinerea* and *A. brassicicola.* Interestingly, *bik1* is more resistant to the bacterial pathogen *P. syringae* DC3000, suggesting that *BIK1* regulates basal resistance to pathogens instead of race-specific resistance (Veronese et al., 2006). The tomato homolog of *BIK1*, The TOMATO PROTEIN KINASE 1b(*TPK1b*) was shown to be induced by various stimuli including infection with *Botrytis cinerea* and *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst* DC3000), wounding and treatment with the herbicide paraquat. *TPK1b* RNAi plants showed increased susceptibility to *Botrytis* and supported more fungal growth than wild type plants. However, data showed that *TPK1b* was not required for resistance to the bacterial pathogen *Pst* DC3000. Overexpression of *TPK1b* in *Arabidopsis* suppressed the susceptible phenotype of the *bik1* mutant suggesting that TPK1b and BIK1 may have similar functions in plant innate immunity (AbuQamar et al., 2008).

Another orphan RLK, the rice blast resistance-related gene 1 (*OsBRR1*), is highly induced by infection with the rice blast fungi *M. oryzae*. Knockdowns of *OsBRR1* in RNAi transgenic plants displayed increased susceptibility to a weakly virulent isolate of *M. oryzae*. *OsBRR1* expression is not induced significantly by abscisic acid (ABA), salicylic acid (SA), or jasmonic acid (JA) suggesting that it is not involved in the defense pathways mediated by these hormones (Peng et al., 2009). In wheat, *TaRLK-R1*, *2* and *3* were identified and cloned as three receptor-like kinases that were induced by stripe rust infection. Virus-induced gene silencing of *TaRLK-R1*, *2* and *3* transcripts resulted in more senescence-like symptoms and the appearance of more rust sori on infected leaves (Zhou et al., 2007).

Two homologs of *Arabidopsis* BAK1/SERK3 (BRI1 ASSOCIATED RECEPTOR KINASE 1) were found in *N.*

Benthamiana and knockdowns of both genes using VIGS lines resulted in enhanced susceptibility to *P. infestans* but not to *P. mirabilis*, an avirulent species. In tobacco plants NbSERK3A/B was shown to be required for INF1-triggered innate immunity since silencing *NbSERK3A/B* lead to a significant reduction in cell death in INF1-treated tobacco (Chaparro-Garcia et al., 2011). The oomycete pathogen *Hyaloperonospora parasitica* (*Hp*) Waco9 was able to infect *NbSERK3*-silenced *N. benthamiana* but not wild type plants (Heese et al., 2007) suggesting a general role for SERK3/BAK1 in plant innate immunity.

The BROAD-SPECTRUM RESISTANCE 1 (BSR1) protein was identified as a rice receptor-like cytoplasmic kinase (RLCK) in a screen for *Pst* DC3000 resistant rice-FOX *Arabidopsis* lines that overexpress full-length rice cDNAs (Dubouzet et al., 2011). Overexpression lines of *BSR1* in *Arabidopsis* were also resistant to the hemitrophic fungal pathogen *Colletotrichum higginsianum*. Transgenic rice lines overexpressing *BSR1* were more resistant to the rice fungal pathogen *Magnaporthe grisea*.

The *Ve1* gene has also been shown to be an RLP that plays an important role in resistance against *Verticillium* wilt diseases (Fradin et al., 2009). Fradin et al. (2009) compared coding sequences of *Ve1* among several resistant and susceptible tomato cultivars. A single nucleotide deletion that resulted in a truncated Ve1 protein was found only in susceptible but not in resistant cultivars of tomato. Silencing of *Ve1* via VIGS compromised the resistance of tomato plants to *Verticillium dahliae*. Meanwhile overexpression of *Ve1* in susceptible tomato cultivars enhanced plant resistance to *V. dahliae* and *Verticillium albo-atrum*.

The Apple *Vf* locus contains four orphan LRR RLPs (*Vfa1*, *Vfa2, Vfa3* and *Vfa4*) that confer resistance to the fungal pathogen *Venturia inaequalis* (Xu and Korban, 2002). Introduction of *Vfa1* and *Vfa2* into two apple cultivars (Galaxy and McIntosh) enhanced resistance to *Venturia inaequalis* compared to non-transformed plants (Malnoy et al., 2008; Belfanti et al., 2004). Interestingly, *Vfa4* is a negative regulator of apple innate immunity as *Vfa4* transformants are more susceptible to *V. inaequalis*.

Negative Regulators of Plant Innate Immunity

Although many RLKs/RLPs are involved in positive regulation of defense against pathogens, several have been identified that act as negative regulators of plant innate immunity. For example, FERONIA (FER), an RLK controlling pollen tube reception, plays a critical role in negatively regulating *Arabidopsis* defense against the powdery mildew *Golovinomyces orontii* (Kessler et al., 2010). Due to the similarity between powdery mildew hyphal tip growth and plant pollen tube reception, it is hypothesized that powdery mildew may produce ligands similar to that of plant pollen tube cells, which may cause FER-mediated susceptibility (Govers and Angenent, 2010).

Another negative regulator in *Arabidopsis* innate immunity is the *BAK1-interacting receptor-like kinase* (*BIR1*) (Gao et al., 2009). T-DNA insertional mutations in *BIR1* cause over-accumulation of H_2O_2 and SA. The *bir1-1* mutant is highly resistant to the oomycete *Hyaloperonospora parasitica* Noco2. Another protein, *SOBIR1*, (suppressor of *BIR1*), also encodes an LRR RLK and suppressed the cell death and resistance phenotype observed in the *BIR1* mutant. The authors showed that *SOBIR1* alone is not required for basal resistance to *Pst* DC3000; however, overexpression of *SOBIR1* in *Arabidopsis* can induce cell death and enhance resistance to bacterial pathogens (Gao et al., 2009).

Receptor-like kinases/proteins are involved in defense against bacterial pathogens

Positive regulators in defense against bacteria

Many RLKs/RLPs are involved not only in resistance to fungal pathogens but also in resistance to bacterial pathogens. For example, *Arabidopsis* CERK1/LysM RLK1 was reported to be targeted and ubiquitinated for degradation by AvrPtoB, a type III effector of the bacterial pathogen *P. syringae*. In the absence of AvrPtoB, AtCERK1/LysM RLK1 plays a critical role in restricting bacterial growth in *Arabidopsis* (Gimenez-Ibanez et al., 2009), suggesting that AtCERK1/LysM RLK1 may bind an unknown PAMP in bacteria. The ERECTA RLK was also shown to play a role in defense against *Ralstonia solanacearum*, the causal agent of bacterial wilt (Godiard et al., 2003). An RLP, SNC2 (SUPPRESSOR OF *NPR1-1*, C*ONSTITUTIVE 2*), was found to be autoactivated by a mutation in the second Gly in the conserved GXXXG motif of its transmembrane domain, resulting constitutive activation of defense responses. However, null mutations in SNC2 lead to impairment of basal resistance in *Arabidopsis* resulting in more bacterial growth on the plant (Zhang et al., 2010b). The rice receptor-like cytoplasmic kinase BSR1 (BROAD-SPECTRUM RESISTANCE 1) confers resistance to Pst DC3000 in *Arabidopsis* and to *X. oryzae pv. oryzae* (*Xoo*) in rice (Dubouzet et al., 2011). Additionally, silencing of *NbSERK3* in *N. Benthamiana* enhances susceptibility to the bacterial pathogens *p. syringae pv. tabaci* 11528 (*Pta* 11528), *P. syringae pv. tomato* DC3000 (*Pto* DC3000) and the nonpathogenic strain *Pto* DC3000 *hrcC* (Heese et al., 2007).

Besides RLKs/RLPs listed above, many RLKs/RLPs have only been investigated for their role in bacterial resistance. The Flagellin-sensitive 2 (FLS2) and EF-Tu (EFR) receptors are LRR RLKs that bind the bacterial PAMPs flg22 (A conserved N-terminal peptide of flagellin) and EF-Tu respectively (Gómez-Gómez and Boller 2000; Zipfel et al., 2006). Null mutations in *FLS2* or *EFR* render mutant plants insensitive to their ligands (flg22 or elf18 respectively) resulting in susceptibility to bacterial pathogens (Zipfel et al., 2004; Zipfel et al., 2006). Expression of EFR in *N. benthamiana* and tomato, which are insensitive to elf18,

causes ROS production and expression of defense-responsive genes upon elf18 treatment (Lacombe et al., 2010). Transgenic *N. benthamiana* and tomato plants expressing EFR showed increased resistance to bacterial pathogens when compared to wild type plants.

Mutations in the RLKs *AtPepR1* (*damage-associated molecular pattern peptide 1*) and *AtPepR2* (*damage-associated molecular pattern peptide 2*) are also known to impact resistance to bacterial pathogens. Both *pepr1* and *pepr2* mutants displayed no difference in their resistance response compared to wild type plants after inoculation with *Pst* DC3000 without AtPep1 pretreatment (Yamaguchi et al., 2010). However upon pretreatment of wild type, *pepr1* or *pepr2* plants with AtPep1 there were marked reductions in the disease symptoms caused by infection with *Pst* DC3000. AtPep1 pretreated *pepr1/pepr2* double mutants had a similar level of susceptibility to *Pst* DC3000 to the untreated double mutant plants suggesting that both *AtPepR1* and *AtPepR2* are required for initiating AtPep1-mediated defense responses against bacterial pathogens (Yamaguchi et al., 2010).

The rice RLK *XA21* confers resistance to a broad spectrum of *Xoo* (*Xanthomonas oryzae* pv. *oryzae*) races through the recognition of a sulfated peptide Ax21 (activator of XA21-mediated immunity) (Lee et al., 2009). Transgenic plants carrying Xa21 are highly resistant to 29 of 32 *Xoo* isolates from eight countries (Wang et al., 1996). Xa21D, a natural variant of Xa21, encodes a receptor-like protein that carries an LRR domain but lacks the transmembrane and kinase domains. Plants carrying Xa21D also recognize pathogens carrying Ax21 and display partial resistance to *Xoo* (Wang et al., 1998). Another RLK/RLP in rice, Xa3/Xa26/Xa22(t), also confers resistance to *Xoo*. Transgenic plants carrying Xa26 displayed high levels of resistance to *Xoo.* Although Xa21 and Xa26 both confer resistance to *Xoo*, there are differences between the mechanisms the two genes use to mediate immunity (Sun et al., 2004). Xa21-mediated resistance increases progressively from the susceptible early seedling stage to full resistance at adult stage. In contrast, Xa26-mediated resistance can be detected from the juvenile stage through the adult stage in rice.

In tomato, the cytosolic domain of tomato atypical receptor-like kinase 1 (TARK1) interacts with XopN, a type III effector of the bacterial pathogen *Xanthomonas campestris pathovar vesicatoria* (Xcv). During infection, XopN compromises tomato defense pathways by suppressing callose deposition and expression of PAMP-triggered immunity (PTI) marker genes such as *PTI5*, *WRKY28*, *LRR22*, and *GRAS2*. Null mutations of XopN in Xcv resulted in reduced pathogenicity in tomato. TARK1 RNAi tomato plants supported more *Xcv ΔNopN* growth than did wild type tomato plants, indicating that TARK1 is a positive regulator of tomato basal innate immunity. Interestingly, TARK1 has been shown to be an inactive kinase and it may function in innate immunity by interacting with other primary receptors (Kim et al., 2009).

Negative regulators in plant-bacterial interactions

Several RLKs were found to negatively regulate plant defense responses to bacterial pathogens. The RIN4-interacting receptor-like kinase (RIPK) was identified from the RIN4 protein complex in *Arabidopsis* expressing the bacterial effector *avrRpm1. RIPK* encodes a receptor-like cytoplasmic receptor that negatively regulates plant innate immunity (Liu et al., 2011). T-DNA knockout mutants of *RIPK* were more resistant to Pst DC3000 after spray inoculation. There was however no difference between *ripk* KO mutants and wild type plants when inoculating Pst DC3000 on plants via syringe infiltration (Liu et al., 2011). These results indicate that RIPK is capable of suppressing *Arabidopsis* defense at an early stage of infection.

An S locus RLK, CBRLK1 (Calmodulin Binding Receptor-like Protein Kinase), also acts as a negative regulator of *Arabidopsis* defense against bacterial pathogens. *Cbrlk1-1* mutants are resistant to Pst DC3000 and the mechanism of resistance is most likely due to enhanced PR gene expression (Kim et al., 2009). Despite its role in powdery mildew infection, FER also negatively regulates *Arabidopsis* innate immunity to the bacterial pathogen PstDC3000 as FER protein levels are induced within 5 min of flg22 treatment (Keinath et al., 2010). Flg22-induced ROS levels were significantly higher and stomata remained constantly closed in *fer* mutants, which may account for its resistance to *P. syringae* infection.

How do RLKs activate plant immunity?

The most well characterized RLK activation model is the FLS2/BAK1/BIK1 complex (Fig. 1A). In this system, BIK1 is associated with FLS2 under normal conditions in plants. When the elicitor flg22 is perceived by its receptor FLS2, the FLS2 receptor changes its conformation allowing it to interact directly with some members of the SERK family such as BAK1, SERK1, SERK2 and BKK1 (BAK1-LIKE 1; Roux et al., 2011). Among these four SERKs, BAK1 and BKK1 are important for flg22 induced immunity. The formation of the FLS2/BAK1 heterodimer has been shown to occur in less than 2 s (Schulze et al., 2010). After heterodimer formation between the extracellular LRR domains, the cytoplasmic kinase domains of FLS2 and BAK1 are brought into close enough proximity to transphosphorylate one another (Fig. 1A; Chinchilla et al., 2007; Schulze et al., 2010). This interaction and transphosphorylation are essential for induction of immune responses as *bak1* mutants are impaired in both early and late responses to flg22. Phosphorylation of FLS2 has also been shown to increase receptor sensitivity to flg22 (Chinchilla et al., 2007). Following FLS2/BAK1 phosphorylation, FLS2-associated BIK1 (and possible BAK1-associated BIK1) is phosphorylated rapidly (Fig. 1A; Lu et al., 2010) This phosphorylation appears to be dependent on the kinase activity of both FLS2 and BAK1

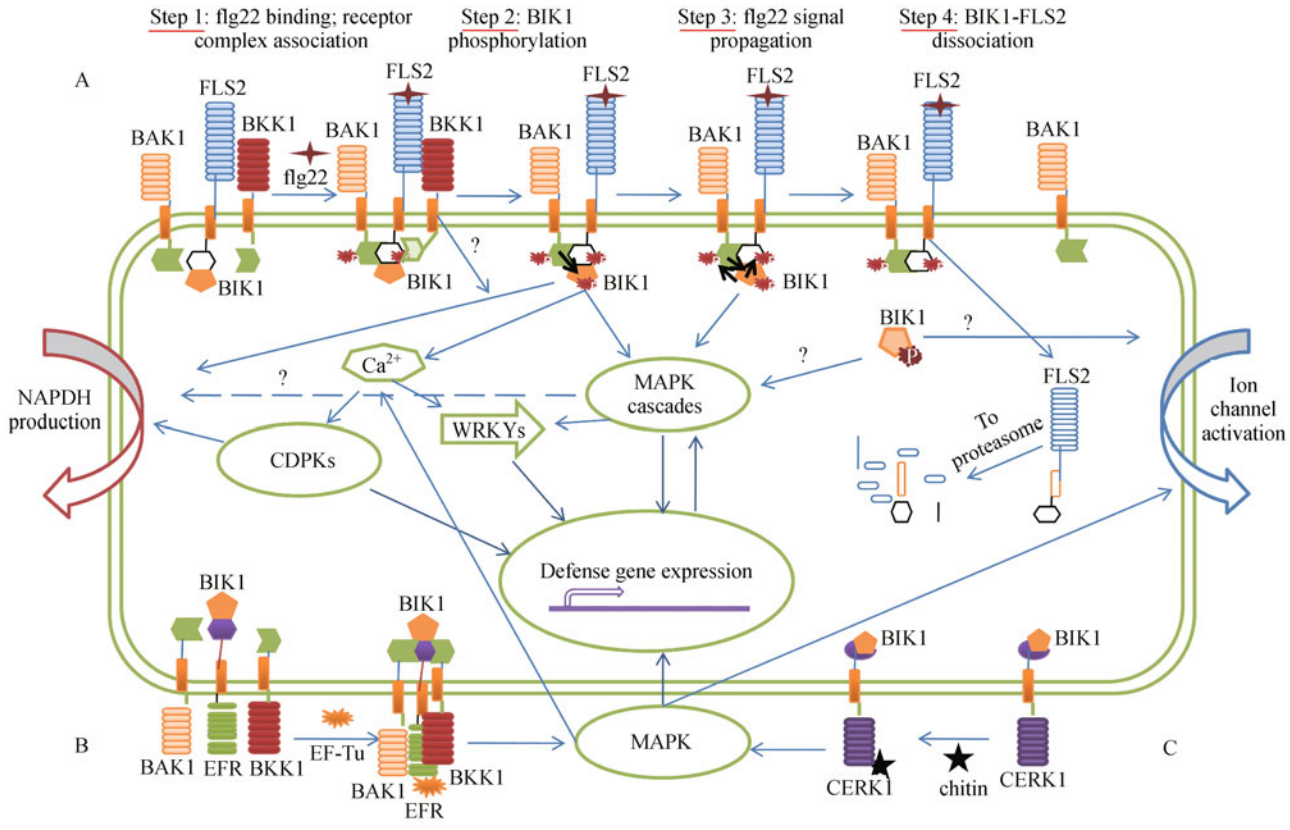

Figure 1 Models of activation of the *Arabidopsis* FLS2, EFR and CERK1 RLKs. (A) In the absence of flg22, BIK1 associates with FLS2. Step 1: Upon flg22 treatment, FLS2 interacts with BAK1 and BKK1 directly. Simultaneously both FLS2 and BAK1 are phosphorylated. Step 2: BIK1 is then phosphorylated rapidly and may then activate downstream disease resistance genes, thereby positively regulating PAMP signaling. Step 3: Phosphorylated BIK1 can also transphosphorylate FLS2 and BAK1. The fully activated FLS2/BAK1 complex may further phosphorylate BIK1 at alternate sites. These transphosphorylation and phosphorylation events may lead to the activation of ion channels and the NADPH oxidase complex. Step 4: After phosphorylation, BIK1 dissociates from FLS2. After activating the flagellin signaling pathway, FLS2 is internalized into the cytoplasm within 20–40 min. It is then ubiquitinated and degraded. (B) Like FLS2, the EFR can also interact with both BAK1 and BIK1, in fact FLS2 and EFR share a common signaling pathway. (C) The chitin receptor CERK1 is also capable of interacting with BIK1 but not with BAK1. All three PAMP receptors activate MAPK cascades.

since in *fls2* and *bak1* mutant plants, flg22 failed to induce the phosphorylation of BIK1 (Lu et al., 2010; Zhang et al., 2010a). The fact that expression of $BIK1^{S33A}$, $BIK1^{T94A}$, $BIK1^{K105A}$, $BIK1^{D202A}$, $BIK1^{S236A}$, $BIK1^{T237A}$, and $BIK1^{T242A}$ in *bik1* either partially restored or completely abrogated flg22-induced resistance/basal resistance (Laluk et al., 2011) suggests that BIK1 phosphorylation is an essential component in the activation of flg22-induced signaling pathways and the eventual expression of downstream resistance genes acting as a positive regulator of PAMP responses.

After phosphorylation, BIK1 is capable of transphosphorylating both FLS2 and BAK1 (Lu et al., 2010). Additionally, the fully activated FLS2/BAK1 complex may in turn further phosphorylate BIK1. In this way flg22 induced signaling is amplified. As the kinase inhibitor K252a completely blocks flg22-triggered ROS production (Nühse et al., 2007) and electrical signaling (Jeworutzki et al., 2010), phosphorylation of BIK1, FLS2 and BAK1 may also be important in the activation of the NADPH oxidase complex and of ion channels (Fig. 1A). Post-phosphorylation, BIK1 dissociates from FLS2 (Zhang et al., 2010a). This dissociation is dependent on *both* BIK1 phosphorylation and BAK1 activity, as in *bak1* mutants or in protoplasts expressing AvrPto, the BIK1/FLS2 complex failed to dissociate (Zhang et al., 2010a). Although both BAK1 and BIK1 are known to interact with FLS2, there has been some controversy regarding the ability of BAK1 and BIK1 to directly interact with one another (Lu et al., 2010; Zhang et al., 2010a). This is an interesting and important question that remains to be resolved.

After activation of fls22-induced signaling, the FLS2 receptor is internalized into the cell's cytoplasm within 20–40 min where it is subsequently ubiquitinated and sent to the proteasome for degradation (Fig. 1A; Robatzek et al., 2006). In fact, recent work indicated that anterograde trafficking of FLS2 is important for flg22-triggered immunity in the *rtnlb1* or *rtnlb2* mutants. FLS2 transport to the plasma membrane is impaired while flg22-induced pathogen resistance is reduced

in both *rtnlb1* and *rtnlb2* (Lee et al., 2011). Numerous studies have shown that MAPK cascades involving MKK4/5, MPK3/6, MEKK1, MKK1/2, and MPK4 are all involved in PAMP-triggered immunity downstream of FLS2 (Asai et al., 2002; Ichimura et al., 2006; Gao et al., 2008). Once activated, these MAPK cascades lead to induction of WRKY transcription factors that go on to induce defense gene expression (Asai et al., 2002). Although no experimental data has shown a direct interaction between FLS2, BIK1 and other proteins, it is conceivable that dissociated BIK1 and internalized FLS2 could contribute to the MAPK cascades and/or the activity of WRKY transcription factors. Recently, Qi et al. found that FLS2 is physically associated with three resistance proteins: RPM1, RPS2 and RPS5 (Qi et al., 2011). Although there is no functional analysis regarding the interactions, there appears to be some crosstalk between PTI and ETI (effector triggered immunity) signaling networks.

Like FLS2, the EFR RLK also interacts with BAK1 SERK1, SERK2, BKK1 and BIK1 (Fig. 1B; Chinchilla et al., 2007; Zhang et al., 2010a; Roux et al., 2011). In fact both FLS2 and EFR share a common signaling pathway and treatment of plants with either flg22 or EF-Tu results in increased transcription of both *FLS2* and *EFR* (Zipfel et al., 2006). Additionally, they also appear to activate the same set of ion channels in the plasma membrane (Jeworutzki et al., 2010).

Unlike FLS2 and EFR, CERK1 cannot interact with the BAK1 RLK but CERK1 does interact with BIK1 (Fig. 1C; Zhang et al., 2010a). CERK1 contains three extracellular LysM domains and a cytoplasmic kinase domain. The CERK1 protein has been shown to directly bind chitin and its extracellular LysM domains are necessary for its binding ability in *Arabidopsis* (Petutschnig et al., 2010). Treatment of plants with chitin rapidly induces phosphorylation of multiple sites in the kinase domain of CERK1 in vivo (Petutschnig et al., 2010). Functional analyses showed that CERK1 kinase activity is necessary for CERK1 phosphorylation, early chitin-induced defense responses and induction of downstream signals such as ROS generation and activation of MAP kinases (Petutschnig et al., 2010). These data point to the possibility that CERK1 may be capable of autophosphorylation and phosphorylation of other unknown substrates that are important in CERK1-mediated chitin signaling (Fig. 1C).

In rice, the most characterized RLK is XA21. As XA21D is still able to confer partial resistance to *X. oryzae pv. oryzae*, it is believed that XA21's extracellular LRR domains are responsible for the race-specific resistance(Wang et al., 1998). XA21 is capable of interacting with a lot of other proteins including the XA21 binding (XB) proteins XB3, XB10, XB15, and XB24. The XB3 protein is an E3 ubiquitin ligase that interacts with the intracellular kinase domain of XA21. Recent work has shown that functional XB3 is necessary for accumulation of XA21 and for Xa21-mediated resistance (Wang et al., 2006). XB10 another XA21 binding protein is a WRKY transcription factor that has been shown to negatively regulate basal defenses and XA21-mediated resistance (Peng et al., 2008). XB15 acts as a negative regulator of XA21-mediated immunity and dephosphorylates autophosphorylated XA21 in a temporal- and dosage-dependent manner (Park et al., 2008). Finally, XB24 is an ATPase that promotes the autophosphorylation of XA21 leading to the negative regulation of Xa21-mediated immunity (Chen et al., 2010). Since XA21's autophosphorylation and kinase activity are crucial for *X. oryzae pv. oryzae* immunity (Xu et al., 2006), it is reasonable to hypothesize that XA21 may activate its associated signaling pathway via autophosphorylation and dephosphorylation of itself and by phosphorylating other substrates that have yet to be identified. No other RLKs or RLPs have been shown to interact directly with XA21 in a manner similar to the FLS2/BAK1 complex. However rice OsBAK1, the closest relative of *Arabidopsis* BAK1 (Li et al., 2009a) and the receptor-like protein XA21D both confer partial resistance to *X. oryzae pv. oryzae* (Wang et al., 1998). It is possible that either OsBAK1 or another unknown protein are able to act as co-regulators and could function in amplification of the Ax21 signal assisting in signal transmission from the extracellular space to the cytoplasm (Fig. 2).

Conclusions and future directions

The ability to perceive pathogen attack is critical for the initiation of plant defense responses. RLKs and RLPs are essential as a first line of defense in the perception of conserved molecular signatures from either microbes or plants and the activation of downstream defense signaling pathways. Many RLKs and RLPs act as positive regulators in plant innate immunity and inactivation of these receptors results in an increase in pathogen susceptibility. However RLKs and RLPs have also been identified that negatively regulate plant defense. While numerous RLKs and RLPs are known to occur in the plant genome, the majority of these have not been studied for their potential function in plant-microbe interactions. Future studies focusing on the identification and functional characterization of novel RLKs and RLPs involved in the plant immune response and their associated signaling partners will be crucial to increase our understanding of these complex pathways. In addition, the search for ligands of orphan RLKs and RLPs is of great interest and should provide valuable information on these pathways. The recent discovery of BAK1 as a co-adaptor for multiple RLKs has added a new angle to the current paradigm on PAMP and DAMP-triggered immunity and the search for new BAK1 interactors or other proteins that function similarly to BAK1 has begun (Chinchilla et al., 2009). Identification of additional interactors of characterized RLKs or RLPs involved in plant disease resistance will also be important in teasing apart these signaling pathways. In addition, it has been reported that bacterial effectors can target RLKs for degradation or may disrupt RLK complex

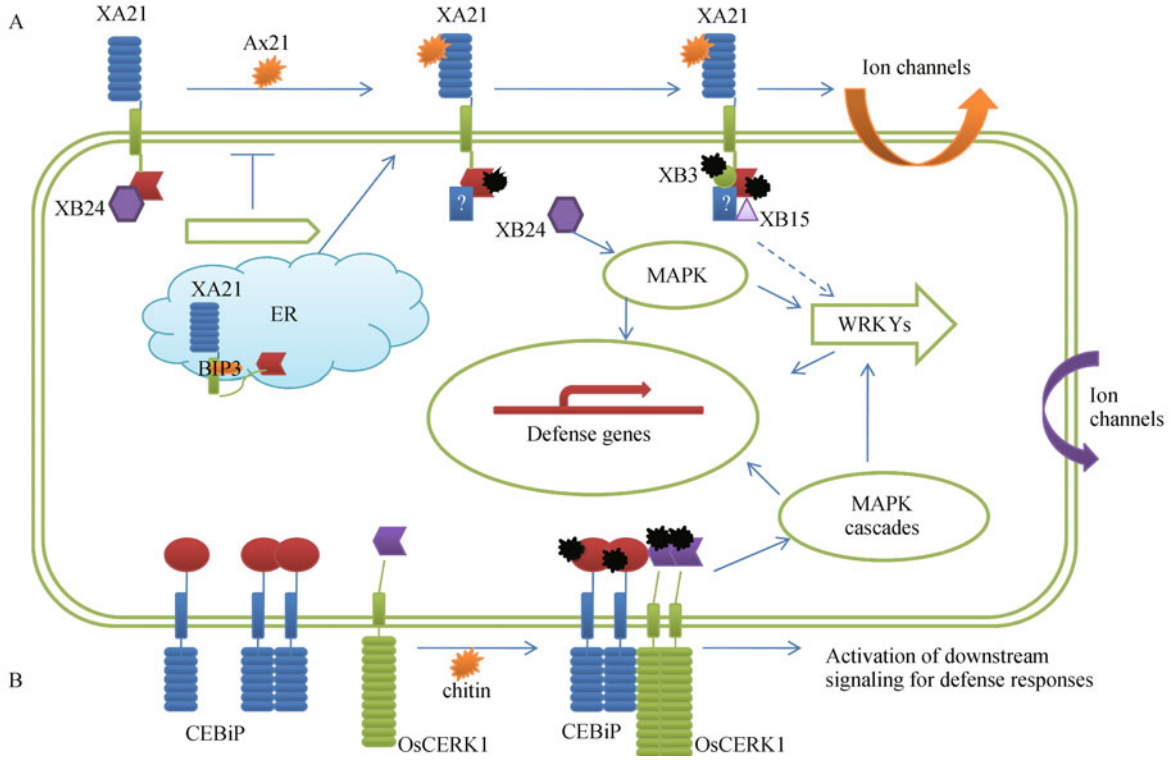

Figure 2 XA21 and CEBiP/OsCERK1 complex activation. (A) XA21 is localized to both the endoplasmic reticulum (ER) and the plasma membrane (PM). The interaction between Xa21 and BiP3 in the ER may function in its proper folding. Interactions between XA21 and its binding proteins such as XB3, XB10, XB15, XB24 and their phosphorylation may activate defense pathways. In this signaling pathway OsWRKY62 acts as a negative regulator of XA21 mediated defenses. (B) The chitin signaling pathway in rice requires two RLKs: CEBiP and OsCERK1. In unstimulated plant cells, CEBiP and OsCERK1 exist separately from one another and CEBiP forms homooligomers. Once activated by chitin, a receptor complex that includes both CEBiP and OsCERK1 forms immediately and may result in the activation of downstream signaling pathways leading to ROS production and activation of MAPK cascades.

formation (Shan et al., 2008; Gimenez-Ibanez et al., 2009). Further identification of effectors that associate with RLKs will also provide insight into RLK function in plant-pathogen interactions.

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