Chapter 18
Pathogen Recognition and Immune Signaling

Tsutomu Kawasaki

Abstract Rice blast and bacterial blight, two important rice diseases, are caused by infection with a fungal pathogen *Magnaporthe oryzae* and a bacterial pathogen *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), respectively. Recent studies on the interaction between rice and these pathogens provided important knowledges of the molecular mechanisms of rice immune responses such as receptor-mediated pathogen recognition, host immune signaling, and pathogen effector-mediated susceptibility. So far, many disease resistance (*R*) genes have been genetically identified based upon disease resistance traits against *M. oryzae* and *Xoo*. Most rice blast *R* genes isolated to date encode pathogen recognition receptors. In contrast, the majority of bacterial blight *R* genes are involved in transcriptional regulation of host resistance or susceptibility factors. Genetic and biochemical studies of rice immune signaling have identified important immune factors including OsRac1, OsRLCK185, and WRKY45. Identification of rice factors that interact with OsRac1, OsRLCK185, and WRKY45 revealed the molecular mechanisms of a variety of immune responses, including the expression of defense-related genes, production of reactive oxygen species (ROS), activation of mitogen-activated protein kinase (MAPK), and lignification.

Keywords Disease resistance gene · Pattern recognition receptor · NB-LRR receptor · Pathogen effector · GTPase · RLCK · MAPK · Reactive oxygen species · Lignification · WRKY

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18.1 Introduction

Plants have evolved the ability to recognize and defend against infection of pathogens. Recognition of pathogens activates intracellular immune signaling mediated by protein kinases, G proteins, and transcription factors, which control a series of immune responses including the synthesis of antimicrobial compounds, cell wall reinforcement, and production of reactive oxygen species (ROS). To overcome host defenses, pathogens deliver a variety of effectors into host cells. The effectors target host factors to inhibit the induction of host immune responses or alter nutrition distribution suitable for pathogen proliferation. To counteract these effectors, plants have developed receptors to recognize the effectors. Plants also possess an immune system against secondary infection of pathogens, referred to as systemic acquired resistance (SAR), which confers long-lasting protection against a broad spectrum of pathogens. SAR is regulated by the salicylic acid (SA)-mediated pathway. In this chapter, recent progress on the topic of pathogen recognition and immune signaling in rice is reviewed.

18.2 Plant Immune Receptors

Plants have developed a sophisticated two-tier immune system to defend against infection and the growth of pathogens (Fig. 18.1). The first layer of plant immunity is initiated by the perception of pathogen-associated molecular patterns (PAMPs) including fungal chitin and bacterial flagellin and peptidoglycan, by plasma membrane (PM)-localized pattern recognition receptors (PRRs). PRRs are receptor-like kinases (RLKs) with an intracellular kinase domain or receptor-like proteins (RLPs) (Dangl et al. 2013). Both RLKs and RLPs possess a ligand-binding ectodomain and transmembrane domain. The PAMP-induced immunity, referred to as pattern-triggered immunity (PTI), involves transcriptional activation of large numbers of immune-related genes through the rapid activation of MAPKs and the generation of ROS (Dangl et al. 2013), which limits microbial colonization. To overcome host PTI, pathogens deliver effectors into plant cells. The second layer of immunity is induced by direct or indirect recognition of pathogen effectors by host intracellular immune receptors of the nucleotide-binding leucine-rich repeat (NB-LRR) protein family, termed NB-LRR receptors (NLRs). This immunity is termed effector-triggered immunity (ETI). ETI displays a remarkable disease resistance, often accompanied by hypersensitive cell death. Some NLR proteins have been identified as disease resistance (R) proteins encoded by *R* loci, which were defined genetically based on disease resistance traits (Dangl et al. 2013).

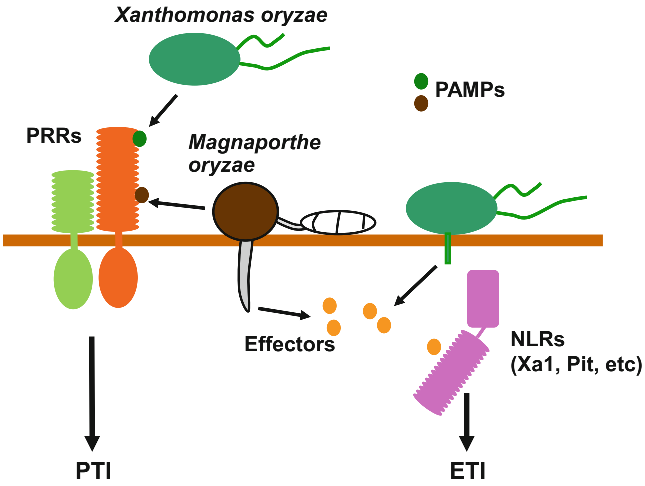

Fig. 18.1 PRR- and NLR-mediated pathogen recognition. PRRs recognize pathogen-associated molecular patterns including fungal chitin and bacterial flagellin. Pathogens deliver effectors into plant cells, which are perceived by NLRs

18.2.1 Rice R *Genes*

Rice blast and bacterial blight diseases are most serious diseases for rice production. So far, 25 *R* genes against rice blast have been identified (Liu et al. 2014). Among these, 24 of these rice blast *R* genes encode NLRs, which recognize corresponding pathogen effectors inside plant cells.

Based on genetic analyses of bacterial blight resistance, 41 *R* genes have been registered in the Oryzabase database (http://shigen.nig.ac.jp/rice/oryzabase/gene/list). Twenty-nine *R* genes are dominant and 12 are recessive. Among these, ten genes (*Xa1*, *xa5*, *Xa10*, *xa13*, *Xa21*, *Xa23*, *xa25*, *Xa26*/*Xa3*, *Xa27*, and *xa41*) have been isolated. *Xa1* encodes an NLR (Yoshimura et al. 1998). Xa21 and Xa26/Xa3 are LRR-RLKs (Zhang and Wang 2013). *xa13*, *xa25*, and *xa41* are caused by loss-of-function mutations of the *SWEET* genes, which belong to a newly identified family of sugar transporters (Zhang and Wang 2013). Expression of their corresponding functional genes *Xa13*, *Xa25*, and *Xa41* was enhanced by transcription activator-like (TAL) effectors of *Xoo* (Fig. 18.2; see Chap 19 for details), which may lead to supply sugars to the pathogens. A limited transportation of sugar, which was caused by the *xa13*, *xa25,* and/or *xa41* mutations, resulted in enhanced resistance to bacterial blight disease.

Xa10, Xa23, and Xa27 are novel proteins with unknown functions (Zhang et al. 2015). Xa10 shares approximately 50% amino acid sequence identity with Xa23. Expression of these three genes was also induced by TAL effectors. However, in contrast to the *SWEET* genes, expression of *Xa10*, *Xa23*, and *Xa27* induced resistance to *Xoo* (Fig. 18.2). Therefore, these genes have been referred to as

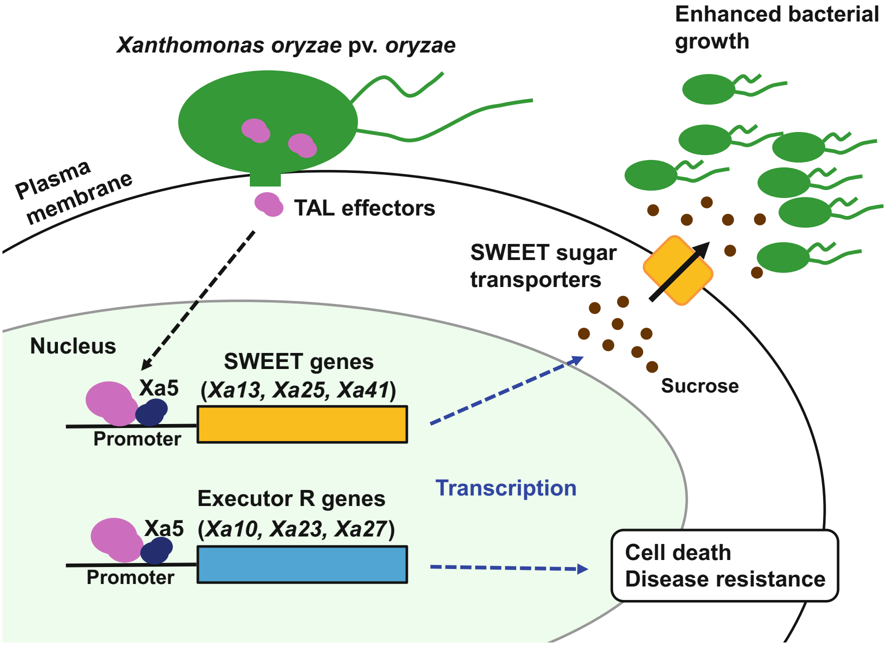

Fig. 18.2 *Xoo* TAL effector-mediated expression of *SWEET* and executor *R* genes in rice. TAL effectors are secreted into rice cells and move to nucleus using their nuclear localization signals. TAL effectors bind to cis-elements in the promoters of *SWEET* and executor R genes and activate their transcription. TAL effector-mediated transcription requires Xa5. Expression of *SWEETs* encoding sugar transporters facilitates diffusion of sucrose across plasma membranes, which results in increased sugar availability of *Xoo*. In contrast, expression of executor *R* genes such as *Xa10*, *Xa23*, and *Xa27* induces cell death and resistance to *Xoo*

"executor *R* genes." The *Xa5* dominant allele encodes the transcription factor IIA gamma subunit 5 (TFIIAγ5). A direct interaction between Xa5 and TAL effectors is required for the expression of *Xa23* and susceptibility genes including the *SWEET* genes (Yuan et al. 2016). Because the *xa5* mutant protein loses the ability to interact with TAL effectors, the TAL effectors are not able to induce the expression of susceptibility genes in *xa5* mutant plants.

18.2.2 Rice PRRs

Rice contains more than 1100 RLKs/RLPs (Shiu et al. 2004), which are predicted to be involved in immunity and development. Xa21, an RLK with an extracellular LRR, was initially identified as an R-protein for bacterial blight resistance (Song et al. 1995), because it induces robust defense responses including HR-like cell death. However, the ligand for Xa21 was recently reported to be a sulfated *Xoo*

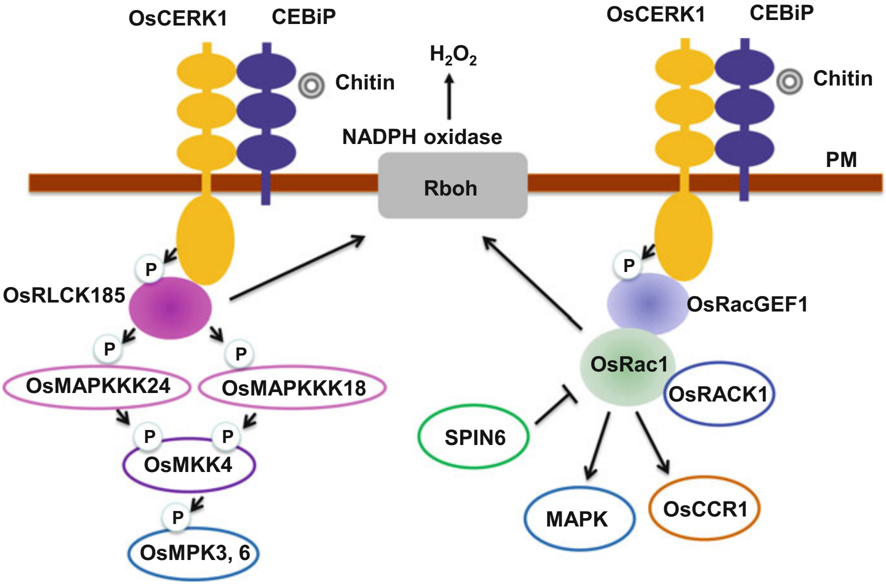

Fig. 18.3 Chitin-activated immune signaling in rice. Upon perception of chitin, OsCERK1 phosphorylates OsRLCK185 and OsRacGEF1, which trigger activation of the MAPK cascade and OsRac1. OsRac1 directly regulates the activities of OsCCR1 and ROS-generating NADPH oxidase (Rboh)

protein RaxX, which is conserved in many pathogenic *Xanthomonas* species (Pruitt et al. 2015), suggesting that Xa21 is a PRR. Xa21 requires co-receptor OsBAK1 for recognition of the ligand (Chen et al. 2014), which is consistent with the fact that *Arabidopsis* PRRs, FLS2, and EFR for bacterial flagellin and elongation factor-Tu, respectively, associate with BAK1 in a ligand-dependent manner (Liebrand et al. 2014). In addition, the ubiquitin E3 ligase XB3, the protein phosphatase XB15, and ATPase XB24 interact with Xa21 (Chen et al. 2010c), which are required for proper control of Xa21-mediated immune signaling.

Among PRR-mediated immune responses in rice, fungal chitin-induced immune signaling has been well investigated as a model system for rice PTI (Fig. 18.3). Rice chitin receptor OsCEBiP is a PM-localized RLP with an extracellular lysin motif (LysM) domain (Kaku et al. 2006). The LysM domain directly binds to chitin and subsequently interacts with a LysM-RLK-type co-receptor OsCERK1 (Shimizu et al. 2010). OsCERK1 phosphorylates the receptor-like cytoplasmic kinase (RLCK) family protein OsRLCK185 and the guanine-nucleotide exchange factor OsRacGEF1 (Fig. 18.3) (Yamaguchi et al. 2013; Akamatsu et al. 2013), which activates intracellular immune signaling. A U-box ubiquitin E3 ligase OsPUB44 was also reported to play an important role in chitin signaling (Ishikawa et al. 2014). In addition to chitin recognition, OsCERK1 also participates in the perception of bacterial peptidoglycan (PGN) by interaction with two LysM-RLP-type PGN receptors LYP4 and LYP6 (Kouzai et al. 2014). In fact, OsCERK1 regulates defense responses against both fungal pathogen *M. oryzae* and bacterial pathogen *Xoo* (Kouzai et al. 2014).

18.2.3 Rice NLRs

Most rice blast R-proteins are intracellular NLRs. Rice blast resistance is often mediated by paired NLRs that are tandemly clustered in the genome. For example, the NLR pair *RGA4* and *RGA5* are encoded by the *Pi-CO39*/*Pia R* locus (Cesari et al. 2014). In the pair, RGA4 functions as the inducer for disease resistance and cell death, which is suppressed by RGA5 in the absence of the pathogen. RGA5 recognizes the *M. oryzae* effectors AVR-CO39 and AVR-Pia through direct binding of the effectors to the RATX1 (Related to ATX1) domain of RGA5. The recognition of the effectors by RGA5 leads to derepression of RGA4, which results in the activation of immune responses. The RATX1/HMA domain was also found in rice blast R-protein Pi-k, and it interacted directly with the *M. oryzae* effector AvrPi-k (Kanzaki et al. 2012). Of note, Pi21 containing the RATX1/HMA domain functions as a susceptibility factor for rice blast. In fact, a loss-of-function mutation of *Pi21* reduces disease symptoms of the fungus (Fukuoka et al. 2009). These results suggested that rice blast fungus somehow uses host RATX1/HMA proteins for its virulence, and plants integrate the RATX1/HMA domains into NLR proteins as decoy domains to detect blast infection.

As mentioned above, *Xa1* encodes the only NLR among *R* genes against bacterial blight. Recently, Xa1 was reported to recognize *Xoo* TAL effectors (Ji et al. 2016), which induce ETI. However, the molecular mechanism of how Xa1 recognizes the corresponding TAL effectors remains to be analyzed.

18.2.4 RLCK-Mediated Immune Signaling

Rice contains 379 receptor-like cytoplasmic kinase (RLCK) proteins (Vij et al. 2008), which are classified into 13 subfamilies (RLCK I–XIII). Recent reports indicated that RLCK VII family proteins interact with the intracellular kinase domains of RLKs and are involved in ligand-dependent intracellular signaling (Couto and Zipfel 2016). OsRLCK185 was identified as a target of the *Xoo* XopY (Xoo1488) effector, which suppresses rice immunity (Yamaguchi et al. 2013). OsRLCK185 is phosphorylated by OsCERK1 at the PM in a ligand-dependent manner, which was inhibited by XopY. OsRLCK185 regulates early signaling immune responses such as MAPK activation and ROS production. In addition, OsRLCK57, OsRLCK107, OsRLCK118, and OsRLCK176 were reported to play roles in chitin-induced immunity (Ao et al. 2014; Li et al. 2017). Recently, we found that OsRLCK185 interacts with and phosphorylates OsMAPKKK18, 1 of

75 rice MAPKKKs, which triggers chitin-induced activation of MAPKs, OsMPK3, and OsMPK6, in rice (Yamada et al. 2017). In rice, chitin-induced activation of these MAPKs is known to be regulated through a MAPKK, OsMKK4 (Kishi-Kaboshi et al. 2010). In fact, OsMAPKKK18 phosphorylates OsMKK4 (Yamada et al. 2017). In addition, OsMAPKKK24 was also reported to be regulated by OsRLCK185 (Wang et al. 2017). Thus, it is likely that OsRLCK185 plays major roles in chitin-induced MAPK activation. Recently, we found that the chitin-induced MAPK signaling pathways are conserved in rice and *Arabidopsis* (Yamada et al. 2016, 2017).

In addition to the activation of MAPK cascades, OsRLCK185 regulates chitin-induced ROS production. In *Arabidopsis*, the FLS2-associated RLCK VII BIK1 activates a PM-localized NADPH oxidase, AtRbohD, by phosphorylation of its N-terminal region, which triggers flagellin-induced ROS production (Kadota et al. 2014). Therefore, it is possible that OsRLCK185 may regulate rice Rboh activity in similar way to BIK1.

BSR1 (OsRLCK278), a member of the RLCK VII family, was identified by the fact that overexpression of BSR1 enhanced disease resistance in *Arabidopsis*. Transgenic rice plants overexpressing BSR1 displayed resistance to four different pathogens, a fungal pathogen *M. oryzae*, two bacterial pathogens *Xoo* and *Burkholderia glumae*, and a rice stripe virus (Maeda et al. 2016). However, the molecular mechanism of how BSR1 regulates rice immunity is unknown. Thus, increasing evidence indicates that the RLCK family proteins are important regulators of PRR-mediated immunity.

18.2.5 Activation of OsRac1 by PRRs and NLRs

Plant Rac/Rop small GTPases are conserved in plants and constitute a unique subfamily of the Rho family of small GTPases. These GTPases are regulated by shuttling between a GDP-bound inactive form and a GTP-bound active form. The shuttling is regulated by two regulatory proteins, GDP/GTP exchange factors (GEFs) and GTPase-activating proteins (GAPs). There are seven Rac/Rop proteins in rice (Chen et al. 2010b). Among them, OsRac1 has been well investigated to function as a key regulator in PRR- and NLR-mediated immunity in rice (Kawasaki et al. 1999; Ono et al. 2001; Akamatsu et al. 2013; Kawano et al. 2010). OsRac1 is activated by at least two types of GEFs, OsRacGEF1 and OsSWAP70 (Akamatsu et al. 2013; Yamaguchi et al. 2012). OsRacGEF1 belongs to a plant-specific ROP nucleotide exchanger (PRONE)-type GEF family, whereas OsSWAP70 is a rice homolog of human SWAP70 containing a disuse B-cell lymphoma (Dbl) homology domain as a GEF-catalytic domain.

OsRacGEF1 forms a complex with OsCERK1 (Akamatsu et al. 2015). In response to chitin perception, OsRacGEF1 is phosphorylated by OsCERK1, which is required for the GEF activity toward OsRac1 (Akamatsu et al. 2013). As mentioned above, because OsCERK1 also phosphorylates OsRLCK185 to activate immune responses (Yamaguchi et al. 2013), there are at least two pathways downstream of OsCERK1, mediated by OsRacGEF1 or OsRLCK185. Whether these two pathways are cooperatively or independently regulated in chitin signaling remains to be identified.

As mentioned above, most rice blast *R* genes encode NLRs. However, how these NLRs transduce intracellular immune signaling is largely unknown. Pit is a PM-localized NLR that induces hypersensitive cell death by recognition of the *M. oryzae* AvrPit effector. The Pit-mediated immune response requires OsRac1, because the resistance was compromised by silencing of OsRac1 (Kawano et al. 2010). Ectopic expression of Pit induces activation of OsRac1 in cells (Kawano et al. 2010). The PM localization of Pit is regulated by palmitoylation of the N-terminal region of Pit (Kawano et al. 2014), which is required for the interaction with and the activation of OsRac1.

18.2.6 OsRac1- and Gα-Mediated Immune Responses

Extensive research on OsRac1-mediated immunity revealed that OsRac1 interacts with a variety of proteins such as NADPH oxidase OsRbohB, Hsp90, Hsp70, Hop/Sti1, RAR1, the scaffold protein OsRACK1, the lignin biosynthetic enzyme Cinnamoyl-CoA reductase 1 (OsCCR1), and the basic helix-loop-helix transcription factor RAI1 (Wong et al. 2007; Oda et al. 2010; Chen et al. 2010a; Nakashima et al. 2008; Kawasaki et al. 2006; Kim et al. 2012). Hop/Sti1 was originally identified as interacting with OsRac1 (Chen et al. 2010a). Hop/Sti1 forms a cochaperone with Hsp90, which regulates efficient transport of OsCERK1 from the ER to the PM where Hop/Sti1 and Hsp90 form a complex with OsRac1.

ROS induced by pathogen recognition do not only directly kill the pathogens but also function as a second messenger to induce immune responses. OsRac1 directly interacts with the N-terminal region of the PM-localized NADPH oxidase OsRbohB in a GTP-form dependent manner and activates its oxidase (Wong et al. 2007; Oda et al. 2010). In fact, expression of a constitutively active mutant of OsRac1 enhanced ROS production *in planta*. Recently, the interaction between OsRac1 and OsRbohB was reported to occur in PM microdomains that consist mainly sphingolipids and sterols (Nagano et al. 2016). As mentioned above, OsRLCK185 also plays a role in chitin-induced ROS production. Whether OsRac1 cooperates with OsRLCK185 in ROS production remains to be analyzed.

Lignification is important for plant cell wall reinforcement against pathogen attack. Lignin is polymerized through peroxidase activity using H_2O_2 in the cell wall. OsCCR1, the first committed enzyme of the lignin branch biosynthetic pathway, was identified as interacting with OsRac1 (Kawasaki et al. 2006). Expression of OsCCR1 was induced during immune responses, and the interaction of

OsCCR1 with OsRac1 led to the enzymatic activation of OsCCR1. Thus, it is likely that OsRac1 stimulates the production of monolignols during immune responses by activation of OsCCR1. As mentioned above, OsRac1 also regulates ROS production through interaction with the N-terminal regulatory domain of OsRbohB. Thus, OsRac1 seems to have a dual function in lignin biosynthesis to control synthesis and polymerization of monolignols through regulation of OsCCR1 and NADPH oxidase, respectively (Kawasaki et al. 2006).

Heterotrimeric G proteins consist of α, β, and γ subunits, which are involved in a variety of cellular responses including immunity and development (Urano and Jones 2014). The loss-of-function mutation of Gα subunit (*dwarf1*) reduces PTI and disease resistance to rice blast (Suharsono et al. 2002). OsRac1 functions downstream of Gα in immune signaling. Silencing of *OsRac1* and the *dwarf1* mutation reduce the protein levels and activity of OsMPK6, suggesting a connection among OsRac1, Gα, and the MAPK cascade. In addition, the scaffold protein OsRACK1 was identified as an interactor with OsRac1 and shown to regulate rice immunity in cooperation with OsRac1 (Nakashima et al. 2008). Recently, *Arabidopsis* RACK1 was reported to be a MAPK scaffold protein that connects heterotrimeric G protein with the MAPK cascade (Cheng et al. 2015). Therefore, it is possible that OsRACK1 functions as a scaffold protein for the rice immune network connecting OsRac1, Gα, MAPK, and NADPH oxidase.

ETI is often accompanied by hypersensitive cell death. To understand the molecular mechanism of cell death, rice mutants with lesion-mimic phenotypes in leaves have been utilized (Takahashi et al. 1999). *spotted leaf 11* (*spl11*) is a lesion-mimic mutant, which is caused by a loss-of-function mutation of rice U-box-type E3 ubiquitin ligase (Zeng et al. 2004). SPL11 regulates resistance to *M. oryzae* and *Xoo*. Recently, SPIN6, a Rho GTPase-activating protein (RhoGAP), was identified as a substrate of SPL11 (Liu et al. 2015). In fact, SPL11 ubiquitinates SPIN6 in vitro and degrades SPIN6 in vivo via the 26S proteasome-dependent pathway (Liu et al. 2015). A knockout mutation of *SPIN6* enhanced resistance to *M. grisea*, indicating that SPIN6 is a negative regulator of immunity. Because SPIN6 possesses GAP activity toward OsRac1, it is likely that degradation of SPIN6 by SPL11 upregulates OsRac1-mediated immune responses.

Sekiguchi lesion (*sl*)/*spotted leaf 1* (*spl1*) exhibits unique orange-colored lesions that are induced by infection with *M. oryzae*. The *sl*/*spl1* plants accumulate high levels of tryptamine dependent upon lesion formation (Ueno et al. 2003). The *SL*/*SPL1* gene encodes CYP71P1, cytochrome P450 monooxygenase. SL/SPL1 possesses tryptamine 5-hydroxylase enzyme activity that catalyzes the conversion of tryptamine to serotonin (Fujiwara et al. 2010). Expression of *SL*/*SPL1* gene was induced by treatment with PAMPs and infection with *M. oryzae*, indicating the involvement of serotonin in plant immunity. In fact, exogenous application of serotonin induced the expression of defense genes in OsRac1- and Gα-dependent manner.

18.3 WRKY45-Mediated Immunity

SAR is mediated by the SA signaling pathway. In rice, the SA pathway branches into two different pathways regulated by a WRKY-type transcription factor WRKY45 or a transcriptional cofactor OsNPR1 (Shimono et al. 2007). WRKY45 plays important roles as a transcriptional activator of immune-related genes in resistance to *M. oryzae* and *Xoo* induced by a defense activator benzothiadiazole (BTH) (Shimono et al. 2007). In fact, overexpression of *WRKY45* strongly enhanced resistance to both pathogens (Shimono et al. 2012). Therefore, WRKY45 was utilized as a suitable tool for the development of disease-resistant rice (Goto et al. 2016). Recent investigations also demonstrated that WRKY45 participates in resistance to the root hemiparasite witchweed *Striga hermonthica* (Mutuku et al. 2015).

Panicle blast 1 (*Pb1*) encodes a NB-LRR protein lacking the P loop and the other motifs conserved in typical NLRs, suggesting that Pb1 may not function as a pathogen recognition receptor. Pb1 was identified as an *R* gene that confers non-race-specific, durable, and quantitative resistance to rice panicle blast. Pb1 positively regulated the WRKY45 accumulation by direct interaction with WRKY45 (Inoue et al. 2013), which is considered to be a key step in Pb1-mediated blast resistance.

18.4 Conclusion

Rice blast and bacterial blight cause the most damaging diseases in rice worldwide. The most efficient strategy to prevent these diseases is to develop rice varieties with durable and broad-spectrum resistance. Understanding the molecular mechanism of rice immune responses provided powerful tools such as WRKY45, OsRac1, and the RLCK family for development of disease resistance plants. However, the molecular mechanisms of how plants recognize pathogens and induce immune responses are not fully understood. Isolation of new *R* genes and the identification of new immune factors are required in order to fully understand rice immunity.

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