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Novel Insights into Rice Innate Immunity Against Bacterial and Fungal Pathogens

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Keywords

PTI, ETI, effectors, *Magnaporthe oryzae*, *Xanthomonas oryzae* pv. *oryzae*, *Oryza sativa*

Abstract

Rice feeds more than half of the world's population. Rice blast, caused by the fungal pathogen *Magnaporthe oryzae*, and bacterial blight, caused by the bacterial pathogen *Xanthomonas oryzae* pv. *oryzae*, are major constraints to rice production worldwide. Genome sequencing and extensive molecular analysis has led to the identification of many new pathogen-associated molecular patterns (PAMPs) and avirulence and virulence effectors in both pathogens, as well as effector targets and receptors in the rice host. Characterization of these effectors, host targets, and resistance genes has provided new insight into innate immunity in plants. Some of the new findings, such as the binding activity of *X. oryzae* transcriptional activator–like (TAL) effectors to specific rice genomic sequences, are being used for the development of effective disease control methods and genome modification tools. This review summarizes the recent progress toward understanding the recognition and signaling events that govern rice innate immunity.

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INTRODUCTION

Important Rice Diseases

Rice (*Oryza sativa*) is a staple food crop for more than 50% of the world's population, with the majority of rice consumption occurring in developing countries. A large number of pathogenic microorganisms cause important diseases in rice, leading to significant yield losses worldwide and threatening global food security (**Table 1**). Rice blast (caused by the fungal pathogen *Magnaporthe oryzae*) and bacterial blight (caused by the bacterial pathogen *Xanthomonas oryzae* pv. *oryzae*) are the most devastating rice diseases (119) and are among the 10 most important fungal and bacterial diseases in plants (32, 95). Owing to their scientific and economic importance, both pathosystems have been the focus of concentrated study over the past two decades, and they are now advanced molecular models for plant fungal and bacterial diseases. Although this article focuses on rice blast and bacterial blight diseases, other diseases, including rice sheath blight (caused by the fungal pathogen *Rhizoctonia solani*), false smut (caused by the fungal pathogen *Ustilaginoidea virens*), bacterial leaf streak (caused by *X. oryzae* pv. *oryzicola*), and bacterial panicle blight (*Burkholderia glumae*), are emerging globally as important rice diseases (53, 72, 180) (**Figure 1**). Where appropriate, insights into rice innate immunity learned from these pathogens are included.

Molecular Analysis of Rice Diseases

As early as the 1960s, genetic studies of disease resistance and characterization of rice pathogens were initiated in Japan and at the International Rice Research Institute (IRRI) in the Philippines.

Table 1 Important fungal and bacterial diseases in rice

	Rice yield loss	Pathogen	Reference genome strain/assemble size	References
Fungal disease				
Rice blast	Up to 100%	*Magnaporthe oryzae*	70–15/~42 Mb	(33)
Rice sheath blight	Up to 50%	*Rhizoctonia solani*	AG1 IA/~40 Mb	(180)
False smut	Up to 44%	*Ustilaginoidia virens* (Cooke) Takah	Not available	**http://www.apsnet.org/publications/imageresources/Pages/FI00163.aspx**
Sheath rot	Up to 85%	*Sarocladium oryzae* (Sawada) W. Gams & D. Hawksworth	Not available	**http://www.knowledgebank.irri.org/rice.htm**
Brown spot	Up to 45%, caused Great Bengal Famine in 1942	*Cochliobolus miyabeanus*	WK1C/~33 Mb	(30)
Bakanae	Yield reductions and mycotoxin contamination	*Fusarium fujikuroi*	IMI58289/~44 Mb	(155)
Bacterial disease				
Bacterial blight	10%–50%	*Xanthomonas oryzae* pv. *oryzae*	KACC10331 (KXO85)/~5 Mb	(74)
Bacterial leaf streak	8%–32%	*X. oryzae* pv. *oryzicola*	BLS256/~10 Mb	(9)
Bacterial panicle blight	Up to 85%	*Burkholderia glumae*	BGR1/~7 Mb	(88)

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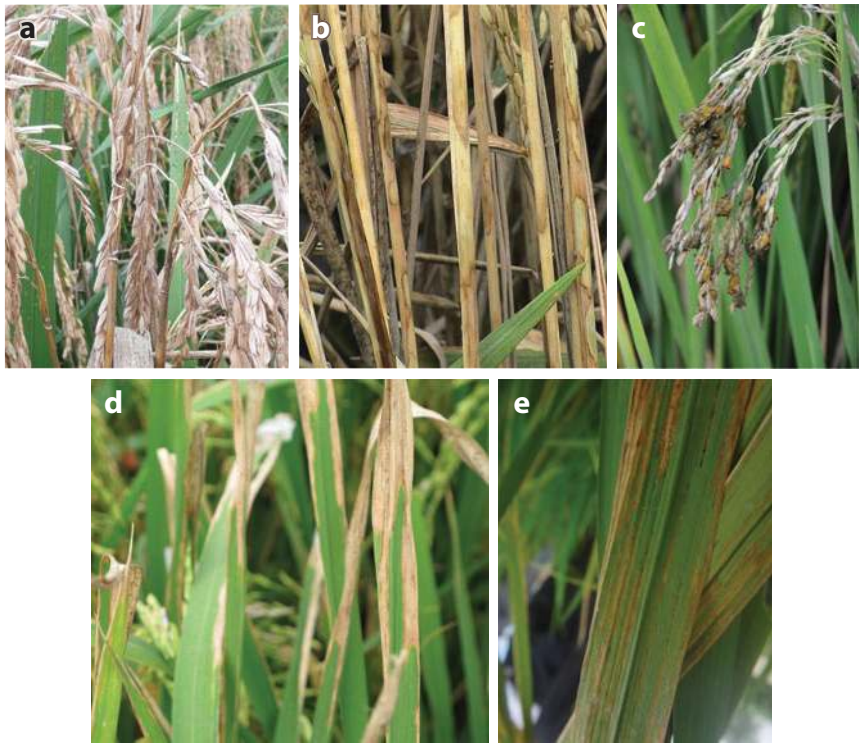

Figure 1

Important fungal and bacterial diseases of rice. (*a*) A rice blast outbreak in a field in Hunan Province, China. Rice blast is caused by *Magnaporthe oryzae*, a fungus that affects all parts of rice but causes the greatest losses when the neck and panicle are affected. The fungus often infects nodes on the rice stem, causing a rotting of the neck (neck blast), failure of grain filling or maturation, and/or drooping of the panicle. Image provided by G.L. Wang. (*b*) Rice sheath blight, caused by *Rhizoctonia solani*, usually appears in later growth stages (late tillering or early internode elongation). Lesions initiate on sheaths of lower leaves and develop into green-gray, water-soaked spots. Later, the lesions dry and turn grayish-white to tan; sclerotia are produced around the lesions. Image courtesy of S. Zuo, Yangzhou University, China. (*c*) Rice false smut, caused by *Ustilaginoidea virens*, can reduce yield and contaminate the grain because of production of the mycotoxin ustiloxin. Fungal spore balls on the panicles are greenish-black when mature. (*d*) Bacterial blight of rice caused by *Xanthomonas oryzae* pv. *oryzae*. The rice bacterial blight pathogen invades through wounds or hydathode water pores to gain access to the plant's xylem vessels, where it multiplies to plug the vessels. (*e*) Bacterial leaf streak of rice caused by *Xanthomonas oryzae* pv. *oryzicola* is emerging as an important disease in Africa, Asia, and Australia. The pathogen invades through wounds or stomates, and moves and lives between the mesophyll parenchyma cells of the rice leaves. Images in panels *c*, *d*, and *e* courtesy of Y. Liu, Institute of Plant Protection, Jiangsu Academy of Agricultural Sciences, China.

Molecular mapping of disease resistance (R) genes was enabled by the publication of the first molecular linkage map of rice in 1988 (97). At the same time, genetic studies of pathogen virulence and race specificity (31, 55, 141) and molecular characterization of rice pathogen populations were being conducted in many laboratories (68, 73, 146). More than any other advances in the past decade, the availability of genome sequences for rice and its major pathogens propelled our understanding of molecular events occurring in rice-pathogen interactions. High-quality genome sequences for representative cultivars of the two major types of rice (*japonica* and *indica*) were reported in 2002 (48, 170), and resequenced or draft genome sequences for many other rice

varieties are appearing in the literature at a rapid pace (41, 98). Sequences for seven rice pathogen species, including multiple strains of some species, were reported over the past decade (**Table 1**). In this review, we discuss the new insights into rice immunity and microbial pathogenesis made possible by these sequence resources and advanced genomic technologies. We also compare and contrast rice defense mechanisms against fungal and bacterial pathogens.

Molecular Mechanisms of Plant Innate Immunity

During the evolutionary arms race with pathogenic microorganisms, plants evolved a repertoire of *R* genes to protect them from diseases. Genetic and molecular studies of plant diseases in model systems, particularly in *Arabidopsis thaliana* pathogen systems, have revealed numerous insights into host resistance mechanisms (4, 101). Like *Arabidopsis*, rice has evolved a two-layered innate immune system that includes pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) (91). PTI, the first line of defense, is governed by pattern recognition receptors (PRRs) that recognize highly conserved PAMPs to trigger a relatively weak immune response that restricts colonization by invading organisms. In contrast, ETI, the second line of defense, is a rapid and robust response, usually associated with a hypersensitive reaction (HR). ETI is initiated by archetypal R proteins that directly or indirectly recognize highly variable pathogen molecules called avirulence (Avr) effectors.

PAMP-TRIGGERED IMMUNITY RECOGNITION AND SIGNALING IN RICE

PAMP Recognition: Plant Receptor-Like Kinase and Receptor-Like Protein Gene Families

In animals, PRRs mainly comprise two different gene families: Toll-like receptors (TLRs) and nucleotide-binding (NB) domain, leucine-rich repeat (LRR)-containing receptors (NB-LRRs, also known as NLRs) (13). In contrast, plant PRRs are represented by transmembrane receptor-like kinases (RLKs) and receptor-like proteins (RLPs). RLKs typically contain extracellular LRR and intracellular kinase domains, whereas RLPs lack the kinase domain (182). Together, the RLK and RLP families comprise a large repertoire of defense responsive receptors that recognize a wide variety of activating ligands (lipid, protein, nucleic acids, carbohydrate, etc.) from various exogenous sources. The rice genome contains more than 1,131 RLK and 90 RLP genes that might be involved in cellular signaling and developmental events (43, 128). Conserved PAMPs sensed by rice PRRs include flagellin, peptidoglycan, lipopolysaccharide, and chitin from bacteria and fungi (**Table 2**) (21, 35, 63, 76, 89).

Flagellin-OsFLS2-Mediated Immunity

The best-characterized PRR protein, the receptor kinase flagellin sensing 2 (FLS2) of *Arabidopsis*, specifically binds a 22 amino acid bacterial flagellin peptide, flg22, to activate a defense signaling complex (26, 183). flg22 also triggers an immune response in rice through OsFLS2, the rice ortholog of *Arabidopsis*. OsFLS2 directly recognizes flg22 in rice and restores *fls2* mutant defects in *Arabidopsis* (127, 142). OsFLS2 also recognizes flg22 derivatives not recognized by FLS2 (142), suggesting that recognition specificity differs between plant species.

The activity and interactions of OsFLS2 strongly suggest a role in PTI. OsFLS2's cytoplasmic domain interacts with OsRac1GEF, a guanine nucleotide exchange factor that controls the PTI

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Table 2 Rice pattern recognition receptors (PRRs) that are involved in recognizing PAMPs/MAMPs

PRR gene	Protein structure	PAMPs/MAMPs	Reference
CEBiP	LysM RLP	Chitin	(63)
LYP4	LysM RLP	PGN and chitin	(89)
LYP6	LysM RLP	PGN and chitin	(89)
OsFLS2	LRR RLK	Flagellin	(127, 142)
XA21	LRR RLK	Not Determined	(135)

Abbreviations: MAMP, microbe-associated molecular pattern; PAMP, pathogen-associated molecular pattern; PGN, peptidoglycan; RLK, receptor-like kinase; RLP, receptor-like protein.

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regulator OsRac1 (2). OsRac1GEF also interacts with a PRR (OsCERK1) that recognizes chitin (2), suggesting overlap in the rice signaling pathways induced by flagellin and chitin. Unexpectedly, overexpression of *OsFLS2* in transgenic rice did not enhance resistance to the bacterial pathogen *Acidovorax avenae* (142), raising questions about the role of the OsFLS2 signaling pathway in defense against various rice pathogens. Because silencing lines have never been reported and the mutant is not available in rice mutant collections, it is plausible that OsFLS2 is also important for plant growth and development. Unavailability of these materials prevents accurate evaluation of the role of OsFLS2 in rice immunity.

Chitin–LysM Domain Protein-Mediated Immunity

Chitin (β-1,4-linked N-acetylglucosamine) is an important component of fungal cell walls and is recognized as a PAMP by plant PRRs (1). Several rice chitin PRRs directly or indirectly recognize chitin fragments and trigger defense responses (63, 120, 173). Chitin oligosaccharide elicitor-binding protein (CEBiP), the major chitin-binding protein in rice cells, shows high-affinity chitin-binding activity (63). CEBiP is an RLP that contains a transmembrane domain and two LysM motifs. CEBiP lacks an intracellular kinase domain, suggesting that at least one additional component is required to transduce chitin-triggered signals within the cell. Indeed, a second protein, the LysM RLK protein OsCERK1 (chitin elicitor receptor kinase 1), cooperates with CEBiP and functions as a crucial component for chitin-triggered immunity in rice (103). In rice cells treated with chitin oligosaccharides, OsCERK1 and CEBiP heterodimers form a plasma membrane receptor complex (120). Two additional LysM domain–containing proteins, LYP4 and LYP6, also bind chitin (89). Knockdown of *CEBiP*, *OsCERK1*, *LYP4*, or *LYP6* expression results in reduced chitin-triggered immune responses and leads to compromised resistance against *M. oryzae*. CEBiP, OsCERK1, LYP4, and LYP6 all contain at least one LysM domain, suggesting this domain is important for perception of chitin oligosaccharides in rice (63).

Peptidoglycan–LysM Domain Protein-Mediated Immunity

Bacterial peptidoglycan (PGN), a major cell wall component in both gram-positive and gram-negative bacteria, is a carbohydrate PAMP that is structurally related to chitin (52). Although AtCERK1 in *Arabidopsis* was initially identified as a chitin receptor (103), a recent study suggests that AtCERK1 senses both PGN and chitin (156). AtCERK1 associates with two PGN-binding LysM proteins (LYM1 and LYM3). Similarly, LYP4 and LYP6, the rice homologs of LYM1 and LYM3, bind PGN in rice cells (89). Silencing of *LYP4* or *LYP6* compromises PGN-induced

defense responses in transgenic rice, resulting in enhanced susceptibility to *X. oryzae* pv. *oryzae* (89). It is not yet known whether OsCERK1 interacts with LYP4 or LYP6 as a PGN coreceptor. However, LysM-containing proteins (LYPs) likely play a key role in binding to PGN in rice.

Xa21-Mediated Immunity

The RLK gene *Xa21* was first isolated as a rice *R* gene that confers resistance to diverse *X. oryzae* pv. *oryzae* strains (135). A sulfated peptide called axY^{S}22, which was derived from the *X. oryzae*–secreted protein Ax21, was proposed to trigger *Xa21*-mediated resistance by binding to the LRR domain of the XA21 protein (76). Because this peptide is present in most *Xanthomonas* species, Ax21 was considered a PAMP and XA21 a PRR (76). However, recent evidence has demonstrated that the peptide axY^{S}22 is not the ligand of XA21 (77). Although the nature of its ligand remains unclear, XA21 is still discussed as a putative PRR based on its predicted structural characteristics.

The *Xa21*-mediated signaling network has been studied extensively. Five XA21-binding proteins (XBs), including an ATPase (XB24), an E3 ubiquitin ligase (XB3), a PP2C phosphatase (XB15), a WRKY62 transcription factor (TF) (XB10), and an ankyrin-repeat protein (XB25), play an important function in regulating the rice defense response against *X. oryzae* pv. *oryzae* (20, 62, 113, 118, 153). The diversity of structure and function of these XBs demonstrates the complexity of the XA21-mediated signaling network. XB24 catalyzes the autophosphorylation of serine and threonine residues on XA21, a modification that is essential to keep XA21 in an inactive form (20). XA21 kinase disassociates from XB24 and is activated upon recognition of pathogen invasion (20). This activation triggers numerous downstream events, including cleavage and recruitment of the XA21 kinase domain to the nucleus (114). XA21-mediated immunity signaling is attenuated by the phosphatase 2C protein XB15, which dephosphorylates the autophosphorylated XA21 in a temporal- and dosage-dependent manner (113). The N-terminal portion of XB25 physically interacts with the transmembrane domain of XA21 through the binding to transmembrane and positively charged domain (BTMP) repeats of XB25 (62). Downregulation of *Xb25* results in reduced levels of XA21 and compromised XA21-mediated resistance. Several endoplasmic reticulum (ER)-localized chaperones that copurify with XA21 are necessary for XA21-mediated resistance, presumably because they ensure the folding and stability of XA21 (115). Thus, multiple and diverse proteins are involved in XA21 activation and signaling after pathogen recognition.

SIGNALING EVENTS DOWNSTREAM OF PAMP RECOGNITION

Balancing Growth and Defense: OsSERK2 and SPL11

In *Arabidopsis*, SERK (somatic embryogenesis receptor kinase) family proteins regulate the function of multiple plasma membrane (PM)-localized receptor kinases, including hormone and immune receptor kinases (27, 80). The most well-studied member, SERK3, also referred to as BAK1 (brassinosteroid insensitive 1 associated kinase 1), was initially identified as a positive regulator of the brassinosteroid (BR) hormonal signaling pathway. BAK1 is a ligand-independent coreceptor of RLKs such as FLS2, EFR, and PEPR1 (69), and acts as a central regulator of PTI triggered by diverse PAMPs.

The rice genome was originally reported to contain four *SERK* genes and several additional genes encoding SERK-like proteins (131). One of these, *OsBAK1* (Os08g0174700, reannotated as Os08g07760 in the Rice Genome Annotation Project; **http://rice.plantbiology.msu.edu/**) was proposed to be the ortholog of *Arabidopsis BAK1* based on phylogenetic analysis and partial restoration of function in the *Arabidopsis br-1* BR receptor mutant (78). Recently, Chen et al. (23)

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argued that the rice genome encodes only two SERK proteins (OsSERK1: Os08g07760 and OsSERK2: Os04g38480) and provided functional and biochemical evidence that *OsSERK2*, not *OsSERK1*, is the closest functional ortholog to *AtBAK1* in rice (23). Nonspecific silencing of *OsSERK1* and *OsSERK2* and several other SERK-like genes compromises resistance to *M. oryzae* (116), whereas overexpression of *OsSERK2*, originally named *OsSERK1* (56), increases resistance to *M. oryzae* (56).

In addition to mediating fungal resistance, OsSERK2 positively regulates immunity to *X. oryzae* pv. *oryzae* mediated by OsFLS2, XA21, and XA3 (23). OsSERK2 and XA21 form a heteromeric complex in planta and phosphorylate one another. OsSERK1 is also important for PTI-mediated bacterial disease resistance; the conserved *X. oryzae* pv. *oryzae* effector protein Xoo2875 [also called XopAA (154)] targets OsSERK1 to inhibit rice resistance to *X. oryzae* pv. *oryzae* (163). Expression of *Xoo2875* in rice results in a BR-insensitive mutant phenotype and increased susceptibility to an *X. oryzae* pv. *oryzae hrpX* mutant (163). Thus, although both OsSERK1 and OsSERK2 may play essential roles in regulating development and receptor kinase-mediated immunity, only OsSERK2 has been shown to do so through direct interaction with rice immune receptors.

Plants have evolved several repertoires of genes that regulate both defense and developmental signals. *Spotted leaf 11* (*Spl11*) encodes an E3 ligase protein that negatively regulates programmed cell death (PCD), innate immunity, and flowering in rice (149, 174). The *spl11* mutant develops lesion mimics and enhanced non-race-specific resistance to both *X. oryzae* pv. *oryzae* and *M. oryzae*. Its *Arabidopsis* ortholog, *PUB13*, a U-box E3 ligase gene, also encodes a regulator of cell death, innate immunity, and flowering in *Arabidopsis*; PUB13 mediates polyubiquitination of FLS2 to attenuate PTI (84, 92, 174). PUB13 requires phosphorylation by BAK1 to function (92). Like PUB13, SPL11 functions in PTI regulation in rice (71, 175). Mutations in *Spl11* showed increased levels of PTI markers in response to rice blast fungus elicitors, including increased oxidative stress, defense-related gene expression, and hydrogen peroxide (H_2O_2) accumulation (71, 175). However, whether SPL11 regulates rice PTI signaling through interactions with OsFLS2 and OsSERK proteins remains unclear. Together, OsSERK2 and SPL11 illustrate how plants must balance developmental processes between growth and defense.

OsRAC1 Defensome-Mediated Immunity

The Rac/Rop small GTPases are a plant-specific Rho subfamily involved in diverse signaling processes, including growth, development, immunity, and hormone responses (104, 161). Many recent studies of Rac/Rop proteins have revealed how they function in rice immunity. The rice small GTPase OsRac1 participates in PTI induced by fungal pathogen-derived PAMPs, such as chitin and sphingolipids (111, 138). Similar to the rapid phosphorylation of the plant PRRs FLS2 and BAK1 after flagellin treatment, OsRac1 is activated at the plasma membrane of rice protoplasts within minutes of exposure to chitin or sphingolipids (2), suggesting that OsRac1 activation is a key early response to diverse microbial pathogens of rice. Strikingly, OsRac1 is also activated by direct interaction with the rice NB-LRR-type R protein Pit and is required for Pit-mediated immunity to the rice blast fungus (65), suggesting that OsRAC1 is required for both PTI and ETI in rice. OsRAC1 is at the center of a protein defensome network that comprises numerous receptors, mitogen-activated protein kinases (MAPKs), guanine nucleotide exchange factors (GEFs), chaperones, and other proteins (**Figure 2**) (19, 66, 70, 87, 106, 143, 162). GEFs function to control the activity of Rho GTPases, which play important roles in plant development and defense. OsRAC1 is bound and activated by two known GEFs, OsSWAP70A and OsRacGEF1. OsSWAP70A is a Dbl (diffuse B-cell lymphoma)-homology (DH) domain-containing GEF (162), and when the *OsSWAP70A* gene is silenced, ROS (reactive oxygen species) production is reduced

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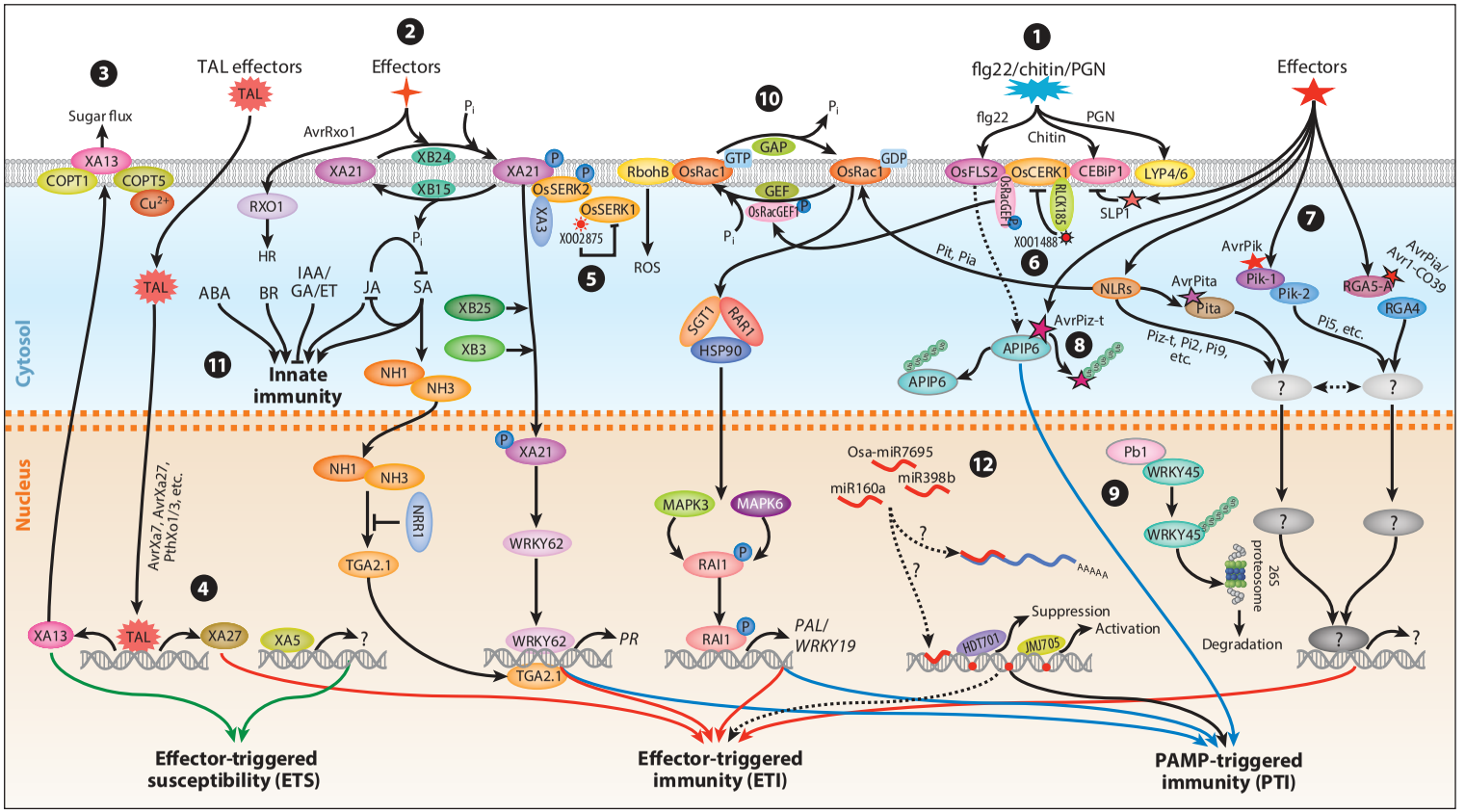

and chitin-induced defense gene expression is suppressed (162). OsSWAP70 likely regulates immune responses through activation of OsRAC1; however, this has not yet been demonstrated.

OsRacGEF1, a PRONE (plant-specific Rac/Rop nucleotide exchange factor) GEF, interacts directly with both OsRAC1 and the PAMP receptors OsCERK1 and OsFLS2 (2). Upon chitin treatment, the chitin receptor CEBiP dimerizes with OsCERK1, which phosphorylates OsRacGEF1 and, in turn, activates OsRac1 (2). Protein trafficking and transport are usually important for defense activation (7). The complex formed by the interactions between OsRacGEF1 with OsCERK1 and chaperones is transported from the ER to the plasma membrane, where it

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Figure 2

Rice innate immunity signaling pathways triggered by the bacterial blight and fungal blast pathogens. (1) Two major rice receptor-like kinase (RLK) pattern recognition receptor (PRR) proteins, OsCERK1 and OsFLS2, perceive the pathogen-activated molecular patterns (PAMPs) chitin and flg22, respectively, to trigger a rice PAMP-triggered immunity (PTI) response. OsCERK1-dependent PTI signaling requires its dimerization with the receptor-like protein (RLP) CEBiP1. CEBiP1 directly binds with chitin. OsFLS2 binds to PAMP flg22. (2) The rice RLK R protein XA21 mediates immune signaling in response to infection by the bacterial blight pathogen [*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)]. Co-components, including XB24, XB15, XB3, and XB25, are required for activation of XA21-mediated signaling. After XA21 activation by phosphorylation, the XA21 kinase domain is cleaved and transported into the nucleus, where it binds to the transcription factor (TF) WRKY62 and further triggers defense gene expression. XA21 also interacts with the RLK protein OsSERK2, an ortholog of AtBAK1 that is involved in BR (brassinosteroid)-mediated immune responses. (3) The rice bacterial blight susceptible protein XA13 associates with two copper transport proteins, COPT1 and COPT5, or acts as a sugar transporter to regulate the distribution of copper or sugar flux in rice plants to modulate the susceptibility to bacterial blight. (4) R-protein XA27-mediated immunity is activated by the transcriptional activator–like (TAL) effector AvrXa27, which binds to the promoter of *Xa27*, inducing *Xa27* expression to result in immune activation. Several other TAL effectors, such as AvrXa7 and PthXo1/3, induce expression of rice susceptibility genes (members of the *SWEET* family: *Os8N3*, *Os11N3*, etc.) to facilitate bacterial infection. (5, 6) Two non-TAL *X. oryzae* pv. *oryzae* effector proteins, XOO2875 and XOO1488, target rice RLK proteins to suppress PTI. (5) XOO2875 directly interacts with OsSERK1, a positive regulator of rice PTI. (6) XOO1488 targets RLCK185 to suppress OsCERK1-mediated defense. (7) In rice–*Magnaporthe oryzae* interactions, three direct recognition models between Avr effectors and R proteins are characterized. AvrPita/Pita interactions represent the first model. In the second model, AvrPik-triggered immunity requires two nucleotide-binding (NB) domain, leucine-rich repeat (LRR)-containing receptor (NLR) proteins, Pik-1 and Pik-2, which form a heterodimer. AvrPik directly associates with Pik-1. The third model involves two different Avr effectors, AvrPia and Avr1-CO39, which are recognized by the same R protein Pia (RGA5-A and RGA4). Both AvrPia and Avr1-CO39 interact with RGA5-A. (8) AvrPiz-t relies on an indirect interaction to trigger Piz-t-dependent immunity. AvrPiz-t targets a RING (really interesting new gene) finger E3 ligase, APIP6, to modulate rice chitin- and flg22-mediated PTI signaling. AvrPiz-t is ubiquitinated by APIP6; APIP6 is also self-ubiquitinated for 26S proteasome-mediated degradation. (9) Pb1, another NLR protein, interacts with a TF, WRKY45; the degradation promoted by ubiquitination of WRKY45 is required for the Pb1-mediated effector-triggered immunity (ETI) response. Knowledge of downstream signaling events after the interactions of Avr effectors and NLR proteins remains limited. (10) The small G protein OsRac1 plays an integrating role in rice PTI and ETI signaling. OsRac1 is required for NLR protein Pit- and Pia-mediated ETI responses. OsRac1 also perceives chitin-triggered PTI signaling. In this case, after sensing the triggering of chitin, the PRR protein OsCERK1 activates OsRacGEF1, a guanine nucleotide exchange factor, by phosphorylation. OsRacGEF1 then triggers the activation of OsRac1 from a GDP (guanosine diphosphate)-bound to a GTP (guanosine triphosphate)-bound state. OsRac1 associates with multiple co-components (OsSGT1, OsRAR1, and HSP90) that are involved in diverse downstream defense activation. The GTPase-activating protein (GAP) is responsible for hydrolyzing active GTP-bound OsRac1 into inactive GDP form, but the GAP for OsRac1 remains unknown. OsRac1 interacts with RbohB to activate reactive oxygen species (ROS) generation. OsRac1 also activates MAPK3/6, then triggers TF RAI1 to induce defense related gene expression (e.g., *WRKY19*, *PAL1*, etc.). (11) The major phytohormones play critical roles in rice immune response modulation. IAA (indole-3-acetic acid), GA (gibberellic acid), and ET (ethylene) negatively regulate rice immunity, whereas ABA (abscisic acid), BR, JA (jasmonic acid), and SA (salicylic acid) play positive roles in rice immune response activation. SA activates two homologs of *Arabidopsis* NPR1-like proteins, NH1 and NH3 in rice, then induces the TF TGA2.1 to trigger *PR* (pathogenesis-related) gene expression. The NH1-interacting protein NRR1 negatively regulates SA-mediated defense signaling. (12) The rice microRNAs Osa-miR7695, miR160a, and miR398b positively regulate resistance to the rice blast fungus by activating defense-related gene expression, but how these microRNAs are involved in gene transcriptional or post-transcriptional modulation remains unclear. In addition, several histone modification-related proteins, such as HDT701 and JMJ05, are involved in resistance to both *M. oryzae* and *Xoo* by modulating defense-related gene suppression or activation. Abbrevations: HR, hypersensitive reaction; PGN, peptidoglycan.

forms a defensome complex with OsRac1 (2). The associations and relationships among CEBiP, OsCERK1, OsRacGEF1, and OsRac1 suggest that they are key components of the OsRac1 defensome and function as critical regulators of early immune responses in rice to pathogen invasion.

In addition to OsRacGEF1, another substrate of the OsCERK1 chitin receptor is the rice receptor-like cytoplasmic kinase (RLCK) protein OsRLCK185 (164). OsRLCK185 was originally identified as an interactor of the *X. oryzae* pv. *oryzae* type III effector Xoo1488 [also called XopY (154) in yeast-two-hybrid assays (164)]. Both overexpression of *Xoo1488* and silencing of *OsRLCK185* in rice suppressed peptidoglycan- and chitin-induced immune responses, including MAP kinase activation and defense gene expression (164). When it binds to chitin, OsCERK1 phosphorylates OsRLCK185, activating a MAPK cascade (164). Xoo1488 prevents phosphorylation of OsRLCK185, inhibiting MAPK activation (164). Whether OsRLCK185 directly regulates MAPK cascades remains unknown. Together, these results suggest that OsCERK1 directly phosphorylates both OsRacGEF1 and OsRLCK185 to mediate chitin- and peptidoglycan-induced downstream signaling in plant immunity (**Figure 2**).

Epigenetic Regulation Is Important for Rice PAMP-Triggered Immunity Signaling

Epigenetic modification, including DNA methylation and histone modification, is important in plant defense against pathogens (94). Two *Arabidopsis* histone deacetylase (HDAC) genes, *HDA19* and *SRT2*, regulate disease defense pathways (151, 181). In rice, RNAi silencing of the HDAC gene *HDT701* enhances resistance to both *M. oryzae* and *X. oryzae* pv. *oryzae*, whereas overexpressing the gene enhances susceptibility to both pathogens (37). Resistance levels in *HDT701*-silenced lines are closely associated with the enhanced expression of the defense-related genes *MAPK6* and *WRKY53* and elevated histone H4 acetylation levels of *CEBiP* and *OsFLS2* during rice blast infection (37). Methylation of histones is also important for rice defense; the rice histone H3 demethylase *JMJ705* is expressed in response to biotic stress and positively regulates resistance (81). Overexpression of *JMJ705* increases resistance to *X. oryzae* pv. *oryzae*, whereas mutation of the gene reduces resistance (81). Thus, although histone H4 acetylation by HDT701 negatively regulates rice defense response genes, histone H3 methylation by JMJ705 increases the defense response. It remains to be seen which of the numerous additional histone modifications that make up the histone code are important regulators of rice disease defense.

Cytosine DNA methylation, particularly of the promoter region, often plays a repressive role in modulating gene expression in response to stress. For instance, the promoter region of the XA21-like protein XA21G in rice cultivar Yamada-nishiki is cytosine hypermethylated, resulting in an inactive *R* gene (3). Conversely, a mutant line with complete demethylation of the *Xa21G* promoter region displays constitutive gene expression and gain of resistance to *X. oryzae* pv. *oryzae* infection (3). The effects of promoter methylation, however, are not always straightforward. The promoter region of rice blast resistance gene *Pib* is heavily cytosine-methylated in some cultivars, but in this case, promoter demethylation does not cause induced expression of the *Pib* gene during *M. oryzae* infection (86). Intriguingly, rice plants in which the *Pib* promoter is partially demethylated by 5-azacytidine treatment expressed *Pib* at reduced levels and were more susceptible to *M. oryzae* (86). Why hypermethylation of the *Pib* promoter enhances expression of the *R* gene and disease resistance is still unclear.

Function of MicroRNAs in the Regulation of Rice Immunity

Plants have evolved efficient defense strategies that include microRNAs (miRNAs) as post-transcriptional regulators of gene expression in plant immunity. In *Arabidopsis*, accumulation of the

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miRNA miR393 following perception of flg22 leads to negative regulation of transcripts for F-box auxin receptors and repression of auxin signaling; this results in increased resistance to bacterial pathogens (108). In addition, miRNAs can guide the cleavage of *R* genes in *Solanaceae* and *Leguminosae* species (79, 129, 177). In rice leaf tissues treated with an *M. oryzae* elicitor, expression of a set of miRNAs increased (15). Similarly, numerous known rice miRNAs that differentially respond to blast fungus infection were identified through deep sequencing (85). One novel miRNA, osa-miR7695, directly targets and compromises the expression of the rice natural resistance-associated macrophage protein 6 (*Nramp6*) gene (15). Transgenic rice plants overexpressing osa-miR7695, miR160a, or miR398b show increased resistance to *M. oryzae* infection (15, 85). Five up-expressed and two down-expressed miRNAs were identified in an RSV (rice stripe virus)-infected rice sample (51). These limited examples indicate that rice possesses a regulatory network that integrates miRNA function to regulate rice immunity against various pathogens.

EFFECTOR SUPPRESSION OF PAMP-TRIGGERED IMMUNITY

Bacterial and fungal pathogens suppress plant immunity through the secretion of numerous effector proteins that disrupt host defense signaling and/or increase susceptibility. Effector repertoires can be key determinants of the virulence level and host range of a pathogen. In addition to encoding 15 to 26 transcriptional activator–like (TAL) effectors (9), *X. oryzae* genomes are predicted to encode 18 to 26 non-TAL effectors (154), of which at least 16 of the latter are known to enter host cells (45). Computational estimates of the *M. oryzae* secretome predict thousands of secreted proteins (28), only a few of which have a known function (147). This section reviews recent developments toward understanding the function of secreted effectors in the development of rice blast and bacterial blight.

Secretion of Effectors

The major pathways for secretion and translocation of protein effectors from bacteria, fungi, and oomycetes have been recently reviewed (14, 47, 61). Bacterial effector secretion occurs through the type III secretion system, a needle-like apparatus that traverses the plant cell wall to deliver proteins directly into the cell. Although it was commonly accepted that filamentous fungal effectors are actively secreted via the conventional ER-Golgi secretory pathway, recent studies using pharmacological approaches indicate that distinct pathways are used for apoplastic versus cytoplasmic effectors. Secretion of apoplastic effectors from invasive hyphae of *M. oryzae* into the interface between the fungal and host membranes is sensitive to Brefeldin A (BFA) treatment, suggesting secretion occurs via the conventional secretory pathway (46). By contrast, cytoplasmic effectors preferentially accumulate in structures called the biotrophic interfacial complex (BIC), and this is insensitive to BFA treatment; this type of secretion occurs via a novel pathway that involves exocyst components and the Sso1 t-SNARE (46). The generality of this novel secretion pathway for other fungi is not known.

Mechanisms of Effector Function

Numerous bacterial and fungal secreted effectors suppress innate immunity. In systematic mutagenesis studies, deletion of only three of the *X. oryzae* non-TAL effectors, XopR, XopN, and XopZ, affected symptoms (24, 45, 133). Five other non-TAL effectors suppressed plant innate immunity after individual transgenic expression in planta (132, 163, 164). However, the specific molecular targets and mechanisms of most effectors remain elusive; other than the TAL effectors,

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the few *X. oryzae* effectors with known targets include Xoo2875/XopAA and Xoo1488/XopY, which target the OsSERK and OsRac1 innate immune pathways of PTI, respectively (163, 164). A third effector, XopN, interacts with the TF OsVOZ2 in the nucleus; mutagenesis of OsVOZ2 eliminated infection by the *X. oryzae* strain (24). XopN also interacted with OsXNP, a putative thiamine synthase with a hypothetical role in callose deposition. Interestingly, these interactors are different from those found for XopN in *Xanthomonas campestris*, suggesting XopN could have different targets in monocot and dicot hosts (24).

Effector Targeting of the Host Cell Proteasome to Suppress PAMP-Triggered Immunity

The plant ubiquitin 26S proteasome degradation system (UPS) plays important roles in the signal transduction of various cellular processes, including host immune responses to pathogen attack (38). Plant-pathogen effectors can manipulate or inhibit the host UPS as a virulence strategy (29, 38). In rice, the UPS is exploited by at least one fungal effector. The *M. oryzae* effector AvrPiz-t is translocated into host cytoplasm, where it interacts with and compromises function of the AvrPiz-t-interacting protein 6 (APIP6), a host RING finger ubiquitin E3 ligase (112). Interestingly, AvrPiz-t and APIP6 are both degraded via the UPS when transiently coexpressed in *Nicotiana benthamiana* (112). Silencing of *APIP6* in transgenic rice leads to reduced PTI hallmarks, including reduced chitin- or flg22-triggered ROS generation and defense gene expression, and enhanced susceptibility to *M. oryzae* (112). Thus, AvrPiz-t suppresses APIP6-dependent PTI. Of the eleven other AvrPiz-t interactors, three (APIP2, APIP8, and APIP10) also encode UPS proteins, indicating that AvrPiz-t could interfere with proteolysis through multiple targets.

Fungal Effector Mimicry of Chitin Receptors to Suppress Chitin-Induced PAMP-Triggered Immunity

While host LysM immune receptor proteins detect fungal-derived chitin to activate immunity, fungi employ LysM effectors to prevent the recognition of chitin by host immune receptors. This was first shown by analysis of the LysM effector Ecp6 in *Cladosporium fulvum* (12). Ecp6 prevents host recognition of chitin by competitive binding of the chitin fragments released from the pathogen during host colonization and is highly conserved in almost all fungi (12, 34). Slp1 (secreted LysM protein 1), the Ecp6 ortholog in *M. oryzae*, is a secreted protein with two LysM domains (102). Similar to Ecp6, *M. oryzae* Slp1 prevents chitin recognition by CEBiP via direct binding to chitin oligosaccharides released from the fungal cell wall. Mutation of *Slp1* compromises fungal pathogenicity; the *slp1* mutant is fully pathogenic on rice lines silenced for the *CEBiP* gene. These results show that Slp1 is a virulence determinant in *M. oryzae*. Recently, structural analysis of the LysM effector Ecp6 revealed that chitin binding is mediated by LysM1-LysM3 interdomain dimerization, which produces an ultrahigh affinity chitin-binding groove buried deeply within ECP6 (123).

Effector Reprogramming of Host Gene Transcription: The *Xanthomonas* Transcriptional Activator–Like Effectors

Plant-pathogen TAL effectors activate expression of specific host susceptibility genes by binding the promoters, a unique strategy for pathogen virulence (67, 166). Promoter-binding specificity is mediated by a pattern of variable DNA-interacting amino acid residues found in the conserved tandem repeats of the central domain (8). TAL effector activation is not yet known to directly suppress

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plant innate immunity; although some effectors are computationally predicted to target SERK and MAPK pathway components in rice (49), this has not been validated experimentally. Rather, the current understanding of the *X. oryzae* TAL effector strategy is to create a favorable plant environment for the pathogen, thus increasing plant susceptibility in spite of innate immunity. The TAL effectors with the strongest virulence-promoting activity are activators of the SWEET family of sugar transporter genes, which are thought to favor bacterial growth by increasing sucrose availability in the xylem (18) or, in some cases, interacting with copper transporters to reduce copper toxicity in the xylem (172). At least five distinct TAL effectors that contribute to the virulence of different strains of *X. oryzae* pv. *oryzae* (PthXo1, PthXo3, AvrXa7, Tal5, and TalC) activate expression of either *OsSWEET11* or *OsSWEET14* from varying binding sites; *OsSWEET13* is also activated by some strains (reviewed in 17). Introducing TAL effectors engineered to activate other SWEET family members demonstrated that activation of *OsSWEET12* or *OsSWEET15* could also be an effective virulence strategy for *X. oryzae* (82, 136). Modulation of host SWEET gene expression appears to be a conserved strategy in plant pathogenesis, as these genes are also induced during infection with fungal pathogens and species of bacteria that do not harbor TAL effectors (18).

SWEET genes are not the only targets of *X. oryzae* TAL transcriptional activation; two TAL effectors with moderate virulence phenotypes activate TF genes (137), and several additional TAL effectors are predicted to target the RNA methylase *HEN1* and components of phosphate metabolism (49). *X. oryzae* pv. *oryzicola* is an important pathovar with large numbers of TAL effectors, none of which are known to activate *SWEET* genes (150). Hundreds of other genes are putative targets of TAL effectors with no characterized virulence role, and the diversity of TAL effectors in *X. oryzae* is still poorly characterized. Increased availability of pathogen genomes and host transcriptomes will likely soon uncover additional TAL effector mechanisms for promoting *X. oryzae* virulence and therefore new potential targets for resistance.

EFFECTOR-TRIGGERED IMMUNITY RECOGNITION AND SIGNALING IN RICE

Gene-for-Gene Resistance to *Magnaporthe oryzae* and *Xanthomonas oryzae*

The gene-for-gene concept first defined the recognition and interaction pattern between a pathogen and its host: when a single plant-pathogen *Avr* gene and the corresponding single host *R* gene are present, recognition occurs, leading to the activation of defense responses and culminating in resistance (42). Increasing knowledge of the molecular interactions between pathogens and their host plants has broadened the gene-for-gene concept. Direct interaction between *R*-gene and *Avr*-gene products, such as occurs between the blast R protein Pita and the corresponding effector AvrPita (59), are relatively rare. For most R-Avr pairs, the interactions leading to resistance are indirect, which fit into the guard and decoy models (148).

Approximately 100 rice *R* genes conferring resistance to *M. oryzae* have been named (125), and 23 of them have been cloned (**Table 3**). However, only five corresponding *Avr* genes have been cloned from *M. oryzae* (**Table 3**). The availability of five cloned rice *R*-gene and *M. oryzae Avr*–gene pairs (*Pita*/*AvrPita*, *Pik*/*Avr-Pik*, *Piz-t*/*AvrPiz-t*, *Pia*/*Avr-Pia*, and *Pi-CO39*/*Avr1-CO39*) has facilitated study of the molecular interactions governed by these five pairs.

The majority of cloned *M. oryzae R* genes are dominant NB-LRR genes (19). The exceptions are *Pi-d2*, which encodes an RLK protein (22), and the recessive *pi21*, which encodes a proline-rich protein with no known homolog (44). In contrast, 14 of the 37 identified *R* genes to *X. oryzae* pv. *oryzae* are inherited recessively, and only one of the seven cloned *R* genes (*Xa1*) encodes an NB-LRR-type protein. The other *X. oryzae* pv. *oryzae R* genes encode a diverse variety of protein

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Table 3 Cloned resistance genes in rice and avirulence effectors in fungal and bacterial pathogens

Resistance genes		Avirulence effectors		
***R* gene**	**Encoding protein**	***Avr* gene**	**Encoding protein**	**Pathogen**
Pib	NB-LRR	ND	Unknown	*Magnaporthe oryzae*
Pi-ta	NB-LRR	*AvrPi-ta*	224 AA secreted protein	
Pi9	NB-LRR	ND	Unknown	
Pi2	NB-LRR	ND	Unknown	
Piz-t	NB-LRR	*AvrPiz-t*	108 AA secreted protein	
Pi-d2	B-lectin RLK	ND	Unknown	
Pi33[c]	Unknown	ACE1	Polyketide synthase	
Pii[c]	Unknown	*AvrPii*	70 AA secreted protein	
Pi36	NB-LRR	ND	Unknown	
Pi37	NB-LRR	ND	Unknown	
Pikm[a]	NB-LRR	*Avr-Pik/km/kp*	113 AA secreted protein, five alleles (A–E)	
Pit	NB-LRR	ND	Unknown	
Pi5[a]	NB-LRR	ND	Unknown	
Pid3	NB-LRR	ND	Unknown	
Pid3-A4	NB-LRR	ND	Unknown	
Pi54	NB-LRR	ND	Unknown	
Pish	NB-LRR	ND	Unknown	
Pik	NB-LRR	Avr-Pik/km/kp	113 AA secreted protein, five alleles (A–E)	
Pikp	NB-LRR	*Avr-Pik/km/kp*	113 AA secreted protein, five alleles (A–E)	
Pia[a,b]	NB-LRR	*Avr-Pia*	85 AA secreted protein	
Pi-CO39[a,b]	NB-LRR	*Avr1-CO39*	89 AA secreted protein	
Pi25	NB-LRR	ND	Unknown	
Pi1	NB-LRR	ND	Unknown	
pi21	Proline-containing protein	ND	Unknown	
Pb1	NB-LRR	ND	Unknown	
ND	Unknown	PWL1	Unknown	
ND	Unknown	PWL2	145 AA secreted protein	
xa5	TFIIA transcription factor	*Avrxa5/PthXo7*	Unknown	*Xanthomonas oryzae* pv. *oryzae*
xa13	MtN3/saliva domain protein	*Avrxa13/PthXo1*	TAL effector	
Xa25	MtN3/saliva domain protein	ND	Unknown	
Xa3/Xa26	LRR-RLK	*AvrXa3*	TAL effector	
Xa27	Rice unique gene	*AvrXa27*	TAL effector	
Xa1	NB-LRR	ND	Unknown	
Os11N3 (*OsSWEET14*)	Homolog of nodulin MtN3	*AvrXa7*	TAL effector	

(*Continued*)

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Table 3 (*Continued*)

Resistance genes		Avirulence effectors		
***R* gene**	**Encoding protein**	***Avr* gene**	**Encoding protein**	**Pathogen**
Rxo1[d]	NB-LRR	*AvrRxo1*	Unknown	*X. oryzae* pv. *oryzicola*

[a]The function of these three *R* genes requires two NB-LRR members.
[b]These two *R* genes share the same NB-LRR gene locus.
[c]The gene has not been cloned yet.
[d]This gene was cloned from maize.
Abbreviations: AA, amino acid; NB-LRR, nucleotide-binding leucine-rich repeat; ND, not determined; RLK, receptor-like kinase; TAL, transcriptional activator–like.

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types (**Table 3**), illustrative of the complex and noncanonical nature of the rice–*X. oryzae* interaction. Below we discuss several patterns of R-Avr interaction in *M. oryzae* and *X. oryzae*: single *R-Avr* gene interactions (dominant and recessive), two *R* genes recognizing one *Avr* gene, and one *R* gene recognizing two *Avr* genes.

One-to-One Gene-for-Gene Resistance

In *M. oryzae*, *Pita/AvrPita* and *Piz-t/AvrPiz-t* are examples of recognition of a single *Avr* gene by a single dominant *R* gene. The interaction of Pita and AvrPita was the first report of direct binding of a fungal Avr and plant R proteins (59) in a far-western blot assay. The physical interaction was disrupted by a single amino acid substitution in the Pita LRR region, suggesting the essential role of the Pita LRR domain for Avr-Pita recognition (59). Although the direct interaction between AvrPiz-t and Piz-t has not been detected, transgenic rice expressing AvrPiz-t in Piz-t background results in an HR, suggesting specific recognition occurs in this gene pair (C.H. Park & G.L. Wang, unpublished results).

In addition to resistance conferred by the NB-LRR *R* gene *Xa1*, other types of dominant genes confer resistance to *X. oryzae* pv. *oryzae*. *Xa21* (discussed above) and *Xa3/Xa26* both encode proteins with predicted LRR receptor kinase structures (140, 158). An RLK structural conformation suggests that Xa21 and Xa3/Xa26 could trigger a strong, race-specific form of PTI, but the ligands and mechanisms of these proteins remain to be discovered. AvrXa3 has been identified as a TAL effector, but a direct interaction between the extracellular LRR domain of Xa3/Xa26 and the intracellularly secreted AvrXa3 is unlikely (124). Like Xa21, Xa3/Xa26 functions in an expression-dependent manner, and it is possible that AvrXa3 triggers resistance by activating expression of *Xa3/Xa26*, resulting in an amplified resistance response to *X. oryzae* pv. *oryzae* infection (124).

Several other *X. oryzae* dominant *R* genes are known or suspected to be directly transcriptionally activated by TAL effectors. The most well-understood of these executor *R* genes (10, 58) is *Xa27*, which encodes an apoplast protein with no known biochemical function (50). The TAL effector AvrXa27 binds to the UPT (upregulated by TAL effectors) box in the promoter of *Xa27* to initiate *Xa27* transcription (122). The dominant *R* genes *Xa10*, *Xa7*, and *Xa23* are also triggered and likely transcriptionally activated by their corresponding TAL effector *Avr* genes, but the identity of these *R* genes is not yet known.

Finally, although no gene-for-gene resistance to the pathovar *X. oryzae* pv. *oryzicola* has been identified in rice, the maize NB-LRR gene *Rxo1* confers resistance to this pathovar when transgenically expressed in rice. Resistance is mediated by interaction with the AvrRxo1 protein, distributed widely among Asian strains of *X. oryzae* pv. *oryzicola* as well as in *Burkholderia andropogonis* and several other plant-pathogenic species (179). The fact that *Rxo1* functions in diverse plant taxa is

unusual (178), and the mechanistic basis for this is not known. However, these results demonstrate the feasibility of nonhost *R*-gene transfer between crops to provide a valuable tool to achieve durable disease resistance.

Gene-for-Gene Resistance Requiring Two NB-LRR Genes

In some cases, a single Avr protein may require two R proteins acting together, such as the RPP2A and B in *Arabidopsis*, to trigger disease resistance (39, 130). Thus far, three NB-LRR-type *R*-gene pairs (*Pik-1* and *Pik-2*, *Pi5-1* and *Pi5-2*, a locus called Pia or Pi-CO39 consisting of *RGA4* and *RGA5*) have been identified in rice, which confer *Pik*-, *Pi5*-, and *Pia/Pi-CO39*-mediated resistance, respectively (6, 16, 75, 110). None of these NB-LRR gene products alone can activate resistance in the presence of the corresponding Avr protein.

R gene *Pik* has at least six alleles (*Pik*, *Pikm*, *Pikp*, *Piks*, *Pikh*, and *Pi1*), and they confer different blast resistance spectra (57, 64). Strikingly, molecular characterization of four alleles, *Pik*, *Pikm*, *Pikp*, and *Pi1*, reveals that a pair of highly related NB-LRR genes (*Pik*:*Pik-1* and *Pik-2*; *Pikm*:*Pikm1-TS* and *Pikm2-TS*; *Pikp*:*Pikp-1* and *Pikp-2*; *Pi1*:*Pi1-5C* and *Pi1-6C*) are required for resistance function (57, 171, 176). The corresponding Avr effector *AvrPik* is also highly polymorphic, with different races encoding five distinct alleles (*Avr-Pik-A*, *B*, *C*, *D*, and *E*) (64). Each Avr protein interacts in yeast with only one of the two NB-LRR proteins required for resistance to *M. oryzae* (e.g., Pikp-1 to Avr-Pik-D; Pik-1 to Avr-Pik-D and -E; and Pikm-1 to Avr-Pik-A, -D, and -E); this suggests that the different *Avr-Pik* alleles recognize and interact with different *Pik* alleles/genes (64). Why two R proteins are required for signaling resistance is not known. It is possible that one R protein recognizes the effector protein, and the other R protein transduces immune signals to downstream components, leading to a resistance response.

Gene-for-Gene Resistance Responsive to Two Distinct *Avr* Genes

The blast resistance locus, *Pia*, consists of two adjacent NB-LRR-type *R* genes (*RGA4* and *RGA5*) that are oriented in opposite directions (110). Transient expression of both *Avr-Pia* and *Pia* in rice protoplasts causes rapid cell death, indicating a specific recognition between Avr-Pia and Pia in rice cells (110). Intriguingly, both *RGA4* and *RGA5* are found in the *Pi-CO39* resistance locus. *rga4* mutants are compromised in resistance to *M. oryzae* strains that contain the *Avr1-CO39* gene, whereas transgenic lines expressing both *RGA4* and *RGA5* regain the resistance. These findings suggest that the *RGA4* and *RGA5* gene pair also confers Pi-CO39 resistance (16). *RGA5* has two alternative transcripts, *RGA5-A* and *RGA5-B*, and both Avr1-CO39 and Avr-Pia, which share no sequence similarity, directly interact with RGA5-A but not with RGA5-B (16). Notably, Avr1-CO39 and Avr-Pia directly bind to a small C-terminal region in RGA5 that is related to the *Saccharomyces cerevisiae* copper-binding domain (ATX1/RATX1). This domain also occurs in another rice R protein, Pik-1, indicating that it may be a novel recognition domain that functions in recognition of diverse effectors. The mechanism by which RGA5 interacts with the different Avr effectors remains unknown.

Gene-for-Gene Resistance Conferred by Recessive *R* Genes

Most (22 out of 23) cloned blast *R* genes are functionally dominant. The exception is *pi21* (44), a recessive gene conferring non-race-specific durable resistance to a blast disease that has successfully been used in breeding (44). Dominant *Pi21* encodes a cytoplasmic proline-rich protein that consists of a putative heavy metal–binding domain and putative protein-protein interaction motifs (44).

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Wild-type *Pi21* acts by slowing host defense responses, whereas recessive *pi21*, with a deletion in a proline-rich motif, does not retard defense responses (44).

Pi21 is speculated to enable fungal growth in rice based on analogies with studies on *Arabidopsis*. In *Arabidopsis*, mutational analysis has shown that several genes, including *Pen2*, *NahG*, *Agb1*, *Pmr5*, and *Mlo2*, are important for nonhost resistance (NHR) to *M. oryzae*. Mutation of these genes in *Arabidopsis* significantly increases the penetration rate of *M. oryzae*; however, growth of the rice blast fungus within the penetrated cells is very limited (105). Interestingly, expression of *Pi21* in a *pen2NahG pmr5mlo2 Arabidopsis* mutant allows remarkably enhanced infectious hyphal elongation and spread, leading to the speculation that the lack of an ortholog of rice *Pi21* may contribute to *Arabidopsis* NHR to *M. oryzae* (105).

Because TAL effectors function by activating susceptibility genes, plants can develop recessive resistance through loss-of-function mutations in TAL effector binding sites or TAL effector–recruited transcriptional machinery. Three of the seven cloned rice bacterial blight *R* genes, *xa5*, *xa13*, and *xa25*, function recessively. The recessive *xa5* allele encodes a mutated key component of the transcription preinitiation complex, the gamma subunit of transcription initiation factor IIA 5 (TFIIAγ5). The mutated TFIIAγ5 may abolish interaction between DNA-associated TAL effectors and the preinitiation complex, preventing susceptibility-inducing gene expression by the TAL effector *avrXa5* (93). These results suggest that TFIIAγ5 is essential for TAL effector function.

The rice recessive genes *xa25* and *xa13* encode alleles of OsSWEET13 and OsSWEET11, members of the aforementioned SWEET family of proteins, which is crucial for TAL effector-triggered susceptibility (90). In both cases, the resistant allele is derived from mutations in the UPT box required for TAL recognition. The recognition site mutation abolishes the ability of the effector to activate the susceptibility genes, conferring race-specific resistance against bacterial strains that express the corresponding TAL effectors.

The discovery of the code mediating TAL effector binding to specific DNA sequences has allowed the development of new biotechnological tools for targeted gene editing and activation (11), and has also opened up new opportunities for engineering resistance to both pathovars of *X. oryzae*. For example, engineering the *Xa27* promoter to contain the predicted target sites of six different TAL effectors resulted in the ability of all of the effectors to activate *Xa27*-mediated resistance, conferring resistance to strains of both pathovars harboring the effectors (58). Promoter editing to eliminate TAL effector binding sites has been used to engineer novel resistance to PthXo3 and AvrXa7, demonstrating another promising strategy for developing resistance to *X. oryzae* (83). Finally, although current understanding of resistance to TAL effectors is based on activation of executor *R* genes or lack of activation of susceptibility genes, plants have likely evolved additional mechanisms for resistance to TAL effectors. A study comparing the virulence effects of individual *OsSWEET*-activating TAL effectors in a TAL-free *X. oryzae* background showed that the virulence effects of TAL-mediated *OsSWEET* activation varies strongly by variety (150). Whether there are unknown mechanisms of resistance to *SWEET* gene–mediated susceptibility remains to be determined.

SIGNALING EVENTS UPSTREAM AND DOWNSTREAM OF PATTERN RECOGNITION RECEPTORS AND *R*-GENE ACTIVATION

Mitogen-Activated Protein Kinase Signaling

Mitogen-activated protein kinase (MAPK) cascades are well-established, highly conserved signaling modules and play pivotal roles in regulating both PTI and ETI. In the *Arabidopsis* genome, 20 MAPKs, 10 MAPK kinases (MAPKKs), and approximately 60 MAPKK kinases (MAPKKKs)

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have been identified based on sequence homology (100). A similar repertoire of MAPK cascade genes has been found in the rice genome. *BWMK1* (also named OsMPK12) was the first cloned MAPK gene in rice (54). BWMK1 interacts with and phosphorylates OsEREBP1, a rice AP2/EREBP family TF, a pivotal step in regulating resistance to *X. oryzae* pv. *oryzae* (25). OsEREBP1 is induced by *M. oryzae* infection, and overexpression of *BWMK1* in tobacco increases disease resistance to *Pseudomonas syringae* and *Phytophthora parasitica*, presumably as a result of increased expression of PR (pathogenesis-related) genes (25). These results indicate that the BWMK1-mediated MAPK cascade regulates rice innate immune responses to a wide range of pathogens. In addition to BWMK1, OsMAPK5, OsMAPK6, and OsBIMK2 also regulate rice defense responses. *OsMAPK5* is induced by *M. oryzae* infection, and RNAi silencing of the expression of *OsMAPK5* results in enhanced resistance to *M. oryzae*, *X. oryzae* pv. *oryzae*, and the bacterial panicle blight pathogen *Burkholderia glumae*, suggesting that OsMAPK5 negatively regulates disease resistance to a broad spectrum of pathogens in rice (160). Kinase activity of OsMAPK6 was induced by a *M. oryzae*–derived sphingolipid elicitor, and the OsMKK4-OsMAPK6 module in rice regulates the chitin-induced production of diterpenoid phytoalexins that defend against *M. oryzae* infection (87). Further studies showed that OsMAPK6 interacts with OsRac1 to coregulate cell death, ROS generation, and activation of PR gene expression (87). Moreover, OsMAPK6 is required for transduction of the NB-LRR protein Pit-mediated signaling by interacting with the OsRac1-RAR1-HSP90-STG1 complex (65). These results suggest that the OsMAPK6 MAPK cascade plays important roles in regulating both PTI and ETI in rice. In contrast to OsMAPK5 and OsMAPK6, overexpression of *OsBIMK2* in transgenic tobacco enhanced disease resistance against the fungal pathogen *Alternaria alternata* and against *Tomato mosaic virus* (134), suggesting that OsBIMK2 is a positive regulator of disease resistance. Although expression of *OsBIMK2* was induced shortly after inoculation with an incompatible isolate of *M. oryzae*, how it functions in the regulation of rice immunity is unknown.

Transcription Factor–Mediated Downstream Responses

PTI- and ETI-activated defense responses include physical cell wall reinforcement, antimicrobial chemicals (such as secondary metabolite phytoalexin accumulation), and expression of TFs (144, 169). TFs are master regulators of gene expression and are involved in diverse processes, including developmental control and initiation of stress and defense responses. Many rice TFs from different families, such as WRKY, MADS (MCM1, AGAMOUS, DEFICIENS, and SRF) box, and NAC (NAM, ATAF1,2, CUC2) are involved in responses to biotic and abiotic stresses as well as pathogen invasion (121). Accumulating research has provided knowledge of the mechanism of TF-mediated immunity regulation in rice.

OsWRKY Transcription Factors

More than 100 WRKY TFs have been identified in the rice genome (157), and many of them are involved in rice innate immune responses. For instance, a comprehensive expression analysis of *OsWRKY* genes revealed that the expression of many of the tested genes is increased in response to attack by numerous pathogens, including fungal (*M. oryzae* and *R. solani*) and bacterial (*X. oryzae* pv. *oryzae*) pathogens, and even an insect pest (white-backed planthopper *Sogatella furcifera*) (152). Four WRKY TFs (*WRKY28*, *WRKY62*, *WRKY71*, and *WRKY76*) specifically respond to *X. oryzae* pv. *oryzae* infection in rice. XB10/OsWRKY62 interacts with *Xa21* and negatively regulates XA21-mediated resistance to *X. oryzae* pv. *oryzae* (118). WRKY62 functions as a transcriptional repressor and suppresses *X. oryzae* pv. *oryzae* resistance when overexpressed (118). In contrast, overexpression of *OsWRKY30* in rice enhances resistance to *R. solani* and *M. oryzae*,

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presumably as a consequence of the activated expression of the jasmonate (JA) synthesis–related genes *LOX* and *AOS2* and of the defense genes *PR3* and *PR10* (117). OsWRKY45 is a transcriptional activator that plays an important role in rice resistance to both *M. oryzae* and *X. oryzae* pv. *oryzae* and is induced by chemical inducers such as benzothiadiazole (BTH), suggesting it is involved in the salicylic acid (SA) hormone signaling pathway (126). Moreover, OsWRKY45 has been shown to be regulated by the UPS. Treatment with a proteasome inhibitor in rice cells leads to accumulation of polyubiquitinated OsWRKY45 and increased expression of *OsWRKY45* target genes, suggesting that OsWRKY45 is constantly degraded by the UPS to suppress defense responses (96). CC (coiled-coil)-NB-LRR protein Pb1 confers rice durable resistance to *M. oryzae* by mediating OsWRKY45 degradation via the UPS (96). In addition, the direct interaction between Pb1 and OsWRKY45, as well as Pb1-dependent protection of OsWRKY45 from UPS degradation, is essential for Pb1-mediated blast resistance (96). These results indicate that UPS regulation plays an important role in OsWRKY45 degradation and transcriptional activity as well as in Pb1-mediated rice resistance to *M. oryzae* (96).

OsWRKY13 is a transcriptional repressor that directly suppresses two TFs (SNAC1 and WRKY45-1) and autoregulates the balance of its own expression through binding to two *cis*-elements of its native promoter in response to drought and disease stresses (159). The expression of *OsWRKY13* is induced in vascular tissue where bacteria proliferate and in guard cells where SNAC1 mediates drought resistance via promoting stomatal closure (159). Taken together, these results suggest that OsWRKY13 regulates the antagonistic cross talk between drought and disease resistance pathways.

MADS-Box and OsNAC Transcription Factors

MADS-box TFs play a critical role in several aspects of plant growth and development. Seventy-five MADS-box genes have been identified in the rice genome (5). The expression pattern of MADS-box TFs in different tissues and their response to abiotic stress have been intensively studied (165). A total of 155 putative *OsNAC* TF genes have been identified in the rice genome (109). Nineteen of thirty-four nonredundant, differentially expressed *OsNAC* TF genes in seedlings treated with RSV (*Rice stripe virus*) or RTSV (*Rice tungro spherical virus*) were upregulated, whereas fifteen were downregulated (109). *ONAC122* and *ONAC131*, two NAC TF genes, were recently shown to play an important role in rice resistance to *M. oryzae* through regulation of the expression of defense-related genes (139).

Hormone Signaling–Mediated Defense Pathways

Plant hormones, including SA, JAs, and ET (ethylene), as well as growth-controlling hormones such as auxin, GAs (gibberellic acids), BRs, and ABA (abscisic acid), act as signals to trigger and mediate a diverse array of plant immune responses. The advances of molecular mechanisms and roles of various hormones in rice immunity during the past decade have been summarized in a recent excellent review (167).

Rice hormones, such as SA, JA, GA, ABA, and BR, are active regulators of immune responses (36, 60, 99). For example, brassinolide (BL)-treated rice plants are resistant to *M. oryzae* and *X. oryzae* pv. *oryzae* infection (107). Rice seedlings treated with exogenous JA resulted in activation of defense gene expression and induction of local resistance against *M. oryzae* (99). Additionally, a number of rice hormonal signaling pathway components, including DELLA and JAZ, share many conserved features for cross talk. The DELLA family proteins [with five members in *Arabidopsis* and, in contrast, only one member in rice (SLR1)] repress transcription of GA-responsive genes and function as key regulators of GA signaling (40). GID1 (GA insensitive dwarf1) is a GA receptor

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that interacts with SLR1 when binding to bioactive GAs (145). The *slr1* mutant compromises disease resistance to *X. oryzae* pv. *oryzae*, suggesting it is playing a positive regulation role in disease resistance in rice (168). Interestingly, the *slr1* mutant reduces JA sensitivity and was required for the induction of JA-responsive genes such as *OsMPK7* (168), indicating that SLR1 serves as a main target of JA-mediated growth inhibition and immunity. Therefore, the DELLA protein SLR1 functions in growth and immunity at least partially through its cross talk with the JA signaling pathway in rice.

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SUMMARY POINTS

1. Rice interactions with the fungus *M. oryzae* and the bacterium *X. oryzae* pv. *oryzae*, which cause two of the most devastating rice diseases, are the most advanced models for understanding rice-pathogen molecular interactions.
2. PTI against bacterial and fungal pathogens is initiated in rice by RLK and RLP receptors that perceive chitin, lipopolysaccharide, peptidoglycan, or flagellin. These interactions trigger signaling events that are centrally regulated by SERK family coreceptor kinases, the OsRAC1 small GTPase, and many other regulators.
3. *M. oryzae* and *X. oryzae* suppress rice PTI through the secretion of numerous effector proteins. Characterized targets for *X. oryzae* include interfering with the OsSERK and OsRac1 pathways and binding to TFs, whereas *M. oryzae* targets include inhibiting the host cell proteasome and mimicking chitin receptors to prevent recognition.
4. TAL effectors secreted by *X. oryzae* generally activate expression of host genes that greatly favor bacterial growth rather than directly suppress induced host defenses; rice varieties have evolved resistance to several TAL effectors by accumulating mutations in TAL effector binding sites or by employing TAL effector–activated *R* genes.
5. ETI to *M. oryzae* is largely mediated by dominant NB-LRR genes acting alone or in pairs, whereas *X. oryzae* resistance is conferred by mostly non-NB-LRR genes, a third of which are recessive. Availability of cloned *R-Avr* gene pairs has facilitated the dissection of the molecular events involved in recognition and signaling at the early stages of pathogen infection.
6. As in dicot models, PTI and ETI signaling pathways in rice converge on downstream immune responses, such as ROS production, cell wall reinforcement, and defense gene activation; these are regulated by MAPK cascades, TFs, plant hormones, epigenetic modifiers, and small RNAs.

FUTURE ISSUES

1. What are the effector targets in rice? Although a few host targets of *M. oryzae* and *X. oryzae* pv. *oryzae* are characterized, the functions of most effector targets are unknown.
2. What are the immediate targets or partners of R proteins that activate strong defense responses? To date, only a few R-protein interactors or partners have been identified and characterized. Overcoming challenges in fusing R proteins with epitope tags and raising R protein–specific antibodies is needed to identify and confirm R-protein interactors.

3. What is the role of epigenetic control in rice immunity? *HDT701* and *JMJ705* are at present the only two epigenetic-related genes that are known to be involved in rice immunity. Improved disease evaluation methods are needed to detect the subtle effect of these types of genes in mutant, RNAi, or overexpressing plants.
4. What is the function of microRNAs in the regulation of rice immunity? Overexpression of osa-miR7695, miR160a, or miR398b in transgenic rice enhances resistance to *M. oryzae* (15, 85), but the mechanism underlying the phenotype is unclear. How these miRNAs are activated and regulated, and their association with important PTI and ETI components, are important areas of investigation.
5. How can pathogen avirulence genes be more efficiently identified? Although there are more than 100 *R* genes mapped in the rice genome for *M. oryzae* and *X. oryzae* pv. *oryzae*, only a dozen of the corresponding avirulence genes have been isolated from the pathogens. New approaches are needed to efficiently clone these genes for *R-Avr* gene interaction studies and for the prediction of *R* gene durability in the field.
6. What is the impact of the environment (increasing temperatures, changes in humidity, etc.) on rice *R* gene–mediated resistance to rice blast and bacterial blight?
7. How can we use the knowledge of pathogen effector and R-gene biology for practical disease control in rice? Although considerable progress in understanding rice pathosystems has been made in the past two decades, few of the breakthroughs have been translated to practical applications. Therefore, innovative measures to enhance host resistance are needed, including genome-targeted modification of susceptibility genes to *X. oryzae* pv. *oryzae* to develop new sources of resistance.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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