Host and Pathogen Factors Controlling the Rice-X*anthomonas oryzae* Interaction[C]

Frank F. White* and Bing Yang

Department of Plant Pathology, Kansas State University, Manhattan, Kansas 66506 (F.F.W.); and Department of Genetics, Development, and Cell Biology, Iowa State University, Ames, Iowa 50011 (B.Y.)

Rice (*Oryza sativa*) cultivation represents a world laboratory for investigation into bacterial diseases of rice, in particular, and host-parasite interactions, in general, at the molecular, genetic, and genomic levels. The crop, in its various forms, has been under intense cultivation for more than 6,000 years, resulting in the selection of a wide variety of traits and germplasm (Khush, 1997). Tremendous molecular and genetic resources have also been developed in recent years. The species can be genetically manipulated by *Agrobacterium tumefaciens*-mediated transformation (Krishnan et al., 2009). Against this backdrop, bacterial blight is an important disease of rice and present throughout much of the rice-growing regions (Ou, 1985; Mew et al., 1993; Fig. 1). *Xanthomonas oryzae* pv *oryzae* (Xoo) is the causal agent and a member of the γ-proteobacteria and, like many other proteobacteria, depends, in part, on a type III secretion system for pathogenicity (Swings et al., 1990; Zhu et al., 2000). The bacterium invades the xylem tissue, either through wounds or water pores, leading to systemic infection. Bacterial streak of rice is caused by the closely related pathovar *X. oryzae* pv *oryzicola* (Xoc), which, in contrast to Xoo, is limited to the intervascular regions, giving the disease the characteristic leaf streaking (Niño-Liu et al., 2006). Bacterial streak can also cause severe losses, although the disease tends to be tropical and is more sporadic than blight (Niño-Liu et al., 2006). This review will highlight recent advances in our knowledge of bacterial blight and, to a lesser extent, bacterial streak with regard to the host-bacteria interaction and the peculiar exploitation of a family of type III effectors. We will also provide speculation and thought as to how these findings might relate to classical analyses of disease resistance and susceptibility as well as a discussion of prospects for future research.

RESISTANCE AND SUSCEPTIBILITY GENES TO XOO

Bacterial blight is subject to control by genetic resistance, and rice has representatives of the two major classes of resistance genes (R genes) against the disease, which are given the prefix *Xa* for *Xanthomonas* (Table I). *Xa21* is an R gene introgressed into rice from the related species *Oryza longistaminata* and was the first R gene for bacterial blight as well as the first R gene of the receptor kinase (RLK) class to be cloned (Song et al., 1995). *Xa21* confers resistance to many strains of Xoo, which is known as broad resistance (Ronald et al., 1992; Wang et al., 1996). RLKs have subsequently been shown to play a major role in a number of signaling pathways in plants, including innate immunity (Morillo and Tax, 2006). The prototypic RLK has a multidomain structure and includes an extracellular leucine-rich repeat (LRR) domain, which serves as the receptor for specific extracellular molecules, a transmembrane domain, and an intracellular kinase domain. *Xa21D*, a member of the multicopy locus that includes *Xa21* and confers partial resistance, has only portions of the prototypic protein and likely functions through intermolecular interactions (Wang et al., 1998). Other, more recently cloned, members of the RLK family include *Xa26* (and *Xa3*, the same locus by a different name), which also provides broad resistance to a somewhat different strain profile (Sun et al., 2004).

RLK receptors, as a class, respond to a variety of molecules, both exogenous elicitors and endogenous signaling factors. With regard to innate immunity in rice, the molecules produced by Xoo and recognized by XA21 or XA26 have not been fully characterized. However, genetic analyses indicated that the elicitor is likely to be a sulfunated peptide that is secreted through a type I system (da Silva et al., 2004). In Arabidopsis, RLK receptors that signal innate immunity have been shown to respond to bacterial flagellin (FLS2) and elongation factor Tu (EFR; Gomez-Gomez and Boller, 2000; Zipfel et al., 2006). FLS2 and EFR were not formally identified as R genes but as components of the pathogen-associated molecular pattern-triggered immunity (PTI) response (Gomez-Gomez and Boller, 2002; Zipfel et al., 2004). Thus, *Xa21*, *Xa26*, and other RLKs are likely to represent genetic components of the PTI surveillance pathway of rice and related species.

Xa1 represents the second major class of R genes, the nucleotide-binding site (NBS)-LRR group (Yoshimura

* Corresponding author; e-mail fwhite@ksu.edu.

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www.plantphysiol.org/cgi/doi/10.1104/pp.109.139360

Figure 1. Bacterial blight and bacterial streak of rice. Left, Bacterial blight in an experimental field plot in Korea, 2006. Right, Bacterial streak from a test inoculation (courtesy of Dr. A. Bogdanove).

et al., 1998). *Xa1* expression is elevated upon bacterial infection and, as such, represents one of the cases in which R gene regulation is coordinated with other pathways for defense responses (Yoshimura et al., 1998; Zhang and Gassmann, 2007). *Rxo1* from maize (*Zea mays*) is a member of the NBS-LRR gene family and confers broad resistance to Xoc isolates upon transfer to rice (Zhao et al., 2005). *Rxo1*-mediated resistance is triggered by strains containing the type III effector gene *avrRxo1* from Xoc (Zhao et al., 2004). Although rice has relatively large numbers of NBS-LRR genes, *Xa1* remains the only endogenous NBS-LRR gene identified for bacterial resistance (Monosi et al., 2004). *Xa1* is effective against some Xoo isolates in Japan but is not effective against most strains from the Philippines. The gene for the elicitor signal from the pathogen has also not been identified for *Xa1*.

Xa27 confers broad resistance and is representative of an unusual class of dominant R genes in rice (Gu et al., 2004). Upon analysis, *Xa27* differed remarkably from other R genes in that specificity is based on differential gene expression (Gu et al., 2005). Identical open reading frames are present in resistant and susceptible cultivars but are only expressed in resistant cultivars upon bacterial infection. No function or conditional expression for the susceptible allele of *Xa27* has been determined. The product of *Xa27* is unrelated to any other class of R protein and has two related open reading frames on chromosome 6, although whether these related genes are functional is unknown. *Xa27* is only expressed upon inoculation with Xoo strains harboring the type III effector gene *avrXa27* (Gu et al., 2005). XA27 protein appears to be toxic to rice and initiates a resistant reaction upon expression (Gu et al., 2005; Tian and Yin, 2009). When fused to a pathogen-nonspecific-inducible rice *OsPR1* promoter, *Xa27* conferred resistance to compatible and incompatible strains of the pathogen alike. Localization studies of XA27 indicate that the protein is secreted into apoplastic space and associated with both the plant membrane and cell walls upon gene induction during resistance (Wu et al., 2008; Fig. 2). Two additional, as yet uncharacterized, R genes of rice have similar requirements for the transcription activation

Table I. *Cloned R genes of rice*

Gene	Class	Comments (Product Localization; Resistance Profile; Function)	Cognate Elicitor/Effector	References
Xa21	RLK	Extracellular, membrane, and intracellular domains; kinase; broad resistance	Unknown small extracellular molecule	Song et al. (1995), da Silva et al. (2004)
Xa26	RLK	Similar to *Xa21*; same locus as *Xa3*; broad resistance	Unknown	Sun et al. (2004), Xiang et al. (2006)
Xa1	NBS-LRR	Cytoplasm; narrow resistance	Unknown	Yoshimura et al. (1998)
Rxo1	NBS-LRR (maize)	Cytoplasm; broad resistance; transferred to rice from maize	AvrRxo1	Zhao et al. (2004, 2005)
Xa27	T3 TAL effector-inducible	Membrane and cell wall; novel protein; broad resistance	AvrXa27	Gu et al. (2005)
xa5	Missense mutant of TFIIAγ5; small subunit of TFIIA transcription factor complex	Nuclear; broad resistance	Unknown	Iyer and McCouch (2004), Jiang et al. (2006)
xa13	Promoter mutants of *Os8N3*; nodulin 3 family	Membrane; unresponsive to S gene to T3 effector	PthXo1	Chu et al. (2006), Yang et al. (2006)

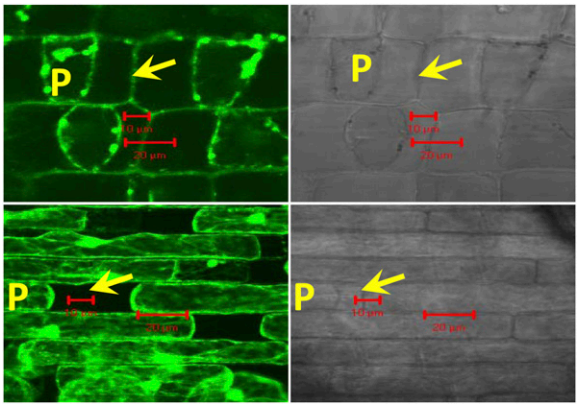

Figure 2. Localization of XA27::GFP. XA27 fused to GFP is found associated with cell plasmalemma and cell wall when cells are plasmolyzed (top). A GFP control is shown at bottom. A complete description of the approach is provided by Wu et al. (2008). P, Plasmolyzed plant cell. Arrows indicate adjoining plant cell wall. Photographs are courtesy of Z. Yin.

domain and nuclear localization signal motifs of the corresponding transcription activation-like (TAL) effectors as required for AvrXa27-mediated induction of *Xa27* (Hopkins et al., 1992; Zhu et al., 1998; Yang et al., 2000). Cloning and analysis of these R genes will reveal whether the effectors and R gene expression have similar features to *Xa27* (Porter et al., 2003; Chen et al., 2008; Gu et al., 2008).

Two recessive R genes have been characterized from rice. The R gene *xa5* confers broad resistance and, oddly, is an allele of the gene for the γ or small subunit of the transcription factor TFIIA (Iyer and McCouch, 2004; Jiang et al., 2006). The recessive allele is not a null allele but differs from the susceptible form by a single codon substitution of Val at position 39 to Glu. TFIIA, consisting of α-, β-, and γ-subunits, is involved in stabilizing the binding of the TATA box-binding protein complex (TFIID) to the TATA box of gene promoters (Hieb et al., 2007). The TFIIA components are highly conserved across the eukaryotes but are not required for transcription of all genes. Rice is unusual in comparison with human and yeast in having two loci for TFIIAγ (Iyer and McCouch, 2004). One gene is on chromosome 5 (*TFIIAγ5*, *xa5*) and the other is on chromosome 1 (*TFIIAγ1*). The proteins are closely related but not identical. The fact that the *TFIIAγ5* message is present at greater levels based on hybridization analyses of leaf tissue indicates that TFIIAγ5 is likely the predominant form of the proteins in rice (Iyer and McCouch, 2004; Jiang et al., 2006; Sugio et al., 2007). The presence of two genes raises the question of whether or not rice or an ancestral relative adapted to bacterial infection by duplication of an ancestral gene for TFIIAγ. *xa5* may provide effective resistance to bacterial infection while maintaining the necessary functionality for normal rice gene expression under most circumstances. TFIIAγ1 may be needed under some other, as yet unknown, conditions or developmental state, and maintenance of a second gene may have a fitness advantage. However, no evidence has been reported that indicates that *xa5* has a detrimental effect under any field or experimental conditions. Additional recessive rice R genes await characterization and may prove as equally fascinating as *xa5* (Iyer-Pascuzzi and McCouch, 2007).

Another recessive resistance gene, *xa13*, has been identified by map-based cloning (Chu et al., 2005, 2006). Like *xa5*, the recessive allele is not a null mutant and encodes a protein related to *MtN3*, encoding nodulin 3 (N3) protein of *Medicago truncatula*. The *MtN3* gene was first identified in EST libraries of *M. truncatula* root nodules (Gamas et al., 1996). The dominant allele *Xa13* was also named *Os8N3* due to the location on rice chromosome 8 and the similarity to *MtN3*, and that name is used throughout this review (Yang et al., 2006). *Os8N3* is a member of a moderately large gene family consisting of 17 to 20 members in rice. Arabidopsis (*Arabidopsis thaliana*) also has an 18-member MtN3 family, and the family is also conserved across kingdom boundaries, with related genes in mammals, insects, nematodes, and filamentous fungi, although not to the same degree as TFIIAγ (Chu et al., 2006; Yang et al., 2006; Guan et al., 2008; B. Yang and F.F. White, unpublished data). The critical difference between resistant (*xa13*/*xa13*) and susceptible plants is the elevated expression of *Os8N3* during bacterial infection in susceptible plant genotypes and the absence of *Os8N3* induction during bacterial infection in the resistant genotypes (Yang et al., 2006; Yuan et al., 2009). Knockdown of *Os8N3* expression by inhibitory RNA also results in resistance to some bacterial strains, but, unlike *xa13* genotypes, silenced plants have low pollen viability and reduced numbers of viable seeds (Chu et al., 2006; Yang et al., 2006). Thus, *xa13* confers resistance due to a lack of elevated *Os8N3* expression during bacterial infection. *Os8N3*, therefore, is a susceptibility (S) gene that is exploited by Xoo, and the *xa13* resistance is a naturally occurring allele, actually a series of alleles that "fix" a genetic disease vulnerability in the plant developmental pathways (Yang et al., 2006). Bacterial strains that induce *Os8N3* expression are virulent, and those strains that normally induce *Os8N3* but not the *xa13* allele are incompatible. The *xa13* gene appears to have been a valuable allele in rice cultivation, as the resistance has occurred in various forms in a variety of cultivars (Chu et al., 2005). The simplest variant is present in 'BJ1', where the difference between the resistant and susceptible alleles is a single nucleotide change in the promoter region of the gene. Other variants have more apparent complex alterations, including multiple base changes and/or insertions in the *Os8N3* promoter region (Chu et al., 2006). Further expression analysis of *Os8N3* and the various *xa13* alleles will provide important insights into the intricacy of host genes that have adapted for disease resistance while maintaining normal developmental processes. Despite the number

of alleles, *xa13* is not as broad as the resistance provided by *Xa21*, *Xa27*, and *xa5*, and many strains from China, the Philippines, Japan, and Korea are compatible on *xa13* lines (Yang et al., 2006).

The number of strains that are compatible on plants containing *xa13* illustrates that Xoo can and has adapted to *xa13* alleles as well as other R genes in the host. Studies of the basis of compatibility and incompatibility between rice genotypes and strains of the pathogen have been conducted in the hope that insight may be gained into the factors that affect R gene breadth and durability, which here is defined loosely as the time the R gene is effective against extant populations of pathogens.

TYPE III EFFECTORS IN XOO

Despite all the resources, only two pathogen genes for elicitors that correspond to cloned R genes for bacterial blight or streak of rice have been cloned: *avrXa27* from Xoo as the cognate elicitor gene for *Xa27* and, if the heterologous *Rxo1* gene from maize is included, *avrRxo1* from Xoc (Table II). Both genes encode substrate proteins that are secreted through the bacterial type III secretion system (T3SS) and are generally known as type III (T3) effectors, which are fully reviewed in this issue. A functioning T3SS is required for pathogenicity of both Xoo and Xoc and serves to secrete multiple T3 effectors into the host cells. Although not all are associated with phenotypic effects for virulence, T3 effectors function, in general, as virulence factors in pathogenicity. A subset of the T3 effectors, including AvrXa27 and AvrRxo1, can serve as the cognate elicitors (avirulence proteins) for specific R genes in many plant systems. Two additional cognate T3 effector (avirulence) genes that have been cloned are *avrXa7* and *avrXa10*, corresponding to the R genes *Xa7* and *Xa10*. Five additional T3 effectors from Xoo have known contributions to virulence under the appropriate conditions (Table II). These genes are *pthXo1*, *pthXo2*, *pthXo3*, *pthXo6*, and *pthXo7*. The gene *avrXa7*, in addition to *Xa7*-dependent elicitor activity, is also a virulence factor. Four additional T3 effectors were derived under a laboratory setting from *avrXa7* (Table II; Yang et al., 2005). Two genes, named *pthXo4*

Table II. *Type III effectors of Xoo and Xoc with phenotypic effects in rice*

T3 Effector	Strain	Cognate Host Gene(s)	References	Additional Comments[a,b]
AvrRxo1 (Xoc)	BLS256	*Rxo1* (maize)	Zhao et al. (2004)	No virulence activity
AvrXa7	PXO86	*Xa7*	Hopkins et al. (1992)	Major TAL effector; present also in T7174 and KXO85; *Xa7*-dependent avirulence activity
AvrXa7-Δ38	PXO99^A	*Xa7*	Yang et al. (2005)	Derivative of AvrXa7 with no virulence activity
AvrXa7-sacB50	PXO99^A	New unnamed R gene	Yang et al. (2005)	Derivative of AvrXa7 with no virulence or *Xa7*-dependent avirulence activity
AvrXa10	PXO86	*Xa10*	Hopkins et al. (1992)	No virulence activity
AvrXa27	PXO99^A	*Xa27*	Gu et al. (2005)	No virulence activity
PthXo1	PXO99^A	*Os8N3*	Yang and White (2004), Yang et al. (2006)	Present also in PXO71
PthXo2	JOX1	Unknown	Yang and White (2004)	Major TAL effector; also present in PXO71 and T7174
PthXo3	PXO61	Unknown	Yang and White (2004)	Major TAL effector
PthXo4	PXO99^A	Unknown	Yang et al. (2005)	Derivative of AvrXa7
PthXo5	PXO99^A	Unknown	Yang et al. (2005)	Derivative of AvrXa7
PthXo6	PXO99^A	*OsTFX1*	Sugio et al. (2007)	Virulence activity in all strains tested
PthXo7	PXO99^A	*OsTFIIAγ1*	Sugio et al. (2007)	Unique to PXO99^A; weak virulence activity in host with xa5 recessive resistance
PthXo8	PXO99^A	Unknown	B. Yang and F.F. White (unpublished data)	Virulence activity

[a]Virulence activity indicates contribution to virulence based on lesion length and bacterial population on the host plant. Avirulence activity indicates ability to elicit a resistance reaction on appropriate genotype of the host. [b]Major TAL effectors are defined by their loss due to mutation. Loss of major TAL effector gene, if the only one present in a strain, results in more than 80% virulence as measured by lesion length when compared with the wild type.

and *pthXo5*, have lost *Xa7*-dependent elicitor activity while maintaining virulence activity. A third gene, *avrXa7*-Δ38, retained *Xa7*-dependent activity without the accompanying virulence activity, and a fourth, *avrXa7-sacB50*, appears to have lost both avirulence and virulence activity but acquired avirulence activity on the otherwise susceptible rice line IR24. The new incompatible response was not observed on the rice line Nipponbare. Preliminary results indicate that a sixth gene, *pthXo8*, also contributes to the virulence of Xoo (B. Yang, unpublished data). With the exception of *avrRxo1*, all of the above T3 effectors are related to *avrBs3* and *pthA*, which were first identified in *X. campestris* pv *vesicatoria* and *X. campestris* pv *citri*, the causal agents of bacterial spot of pepper (*Capsicum annuum*) and citrus (*Citrus* species) canker, respectively (Bonas et al., 1989; Swarup et al., 1991). The AvrBs3/PthA-related T3 effectors have properties of transcription factors and possess eukaryotic nuclear localization signal motifs and a potent acidic transcription activation domain in the C-terminal portion (Van den Ackerveken et al., 1996; Zhu et al., 1998). The proteins have DNA-binding activity, and AvrBs3 can bind specific gene promoter sequences in vivo, as shown by chromatin immunoprecipitation and gel shift assays (Yang et al., 2000; Kay et al., 2007). Here, we refer to the family of T3 effectors as the TAL T3 effectors, and each protein has a series of highly conserved repeated sequence of amino acids (Fig. 3). The consensus repeat, in Xoo and Xoc, is 34 amino acid residues, although some repeats have single codon deletions or internal smaller repetitive portions. With some exceptions, the central repetitive region can be switched among the TAL effector family members while retaining the biological activity of the effector from which the repeat region is derived. Thus, some aspect of TAL effector specificity is dictated by the repetitive structure. The repeats may affect domain spacing as well as, perhaps, the maintenance of individual effector identity. The proteins are believed to function as dimeric proteins within the host (Gurlebeck et al., 2005). The closest structural relative of the repeat region is the so-called tetratricopeptide repeat, which is also approximately 34 amino acid residues in length and widespread in proteins of diverse function (Blatch and Lassle, 1999).

The AvrRxo1, on the other hand, is a novel protein of 421 amino acids with a variety of reported motifs, including a eukaryotic thiol protease active site, an ATP/GTP-binding site motif, nine *N*-myristoylation site motifs, and a putative nuclear localization sequence motif (Zhao et al., 2004). The functionality of the motifs has not yet been experimentally verified. Genes related to *avrRxo1* are fairly limited in distribution and present in *Acidovorax*, *Burkholdaria*, and *X. campestris* pv *vesicatoria* (Zhao et al., 2004; Thieme et al., 2005). However, related genes have not been detected in Xoo. Mutants of *avrRxo1* have not been generated; therefore, any virulence contribution to Xoc by *avrRxo1* is unknown.

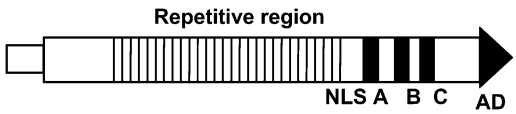

Figure 3. Prototypic TAL effector. Each TAL effector contains a central repetitive region of varying numbers of 34 amino acid repeat units (white boxes). The C-terminal region contains three nuclear localization signal motifs (NLS [A, B, and C]) and an acidic activation domain (AD).

IMPLICATION OF INTERACTION BETWEEN T3 EFFECTORS AND THE CORRESPONDING HOST GENES

Xa27 and *xa13* have provided insight into the diversity of resistance mechanisms in rice. The apparent reason for the broad activity of *Xa27* is the presence of *avrXa27* in a large number of strains from southeast Asia, including many strains from Korea, China, Japan, and the Philippines (Gu et al., 2004). At the same time, two lines of evidence indicate that strains of Xoo could defeat *Xa27*. First, *avrXa27* is present in a single copy, at least in the two strains that have been examined; therefore, simple loss or mutation of the gene converts incompatible strains to compatible strains on plants with *Xa27* (Gu et al., 2005; Ochiai et al., 2005). Second, mutation of *avrXa27* in the strain PXO99^{A} converts PXO99^{A} to compatibility on plants containing *Xa27* and does not lead to any detectible loss of virulence. Thus, the loss of *avrXa27* does not appear to have a fitness cost to the pathogen, and populations of Xoo without *avrXa27* could be expected to appear relatively rapidly should *Xa27* be deployed. *avrXa7*, unlike *avrXa27*, is an important virulence factor for some strains of Xoo, and loss of *avrXa7* can result in strains that are only weakly virulent (Bai et al., 2000; Yang et al., 2000). Several factors mitigate the argument that *Xa7*, by itself, would provide durable resistance due to the fitness cost for loss of *avrXa7* in the pathogen. One factor is that a variety of other TAL T3 effector genes are present in Xoo populations that do not have *Xa7*-mediated elicitor activity but can restore full virulence to strains missing *avrXa7* (Yang and White, 2004). We refer to interchangeable TAL effectors with regard to virulence activity as major TAL effectors. In addition to *avrXa7*, the major TAL effector genes in Xoo are *pthXo1*, *pthXo2*, and *pthXo3* (Yang and White, 2004). Loss of *Xa7*-dependent elicitor activity from *avrXa7* and concomitant retention of virulence activity has also been observed (Yang et al., 2005). Thus, evasion of *Xa7*-mediated resistance should, at least theoretically, be possible by deletion of the central repeats, as observed for *pthXo4*, by recombination among different TAL effector genes, as observed with *pthXo5*, or by horizontal transfer of alternate virulence factors (Yang et al., 2005). At the same time, field studies in the Philippines indicated that deploy-

ment of *Xa7* was durable in test plots for more than 10 years (Vera Cruz et al., 2000). Regardless of the possibility of race changes in the pathogen population, pyramiding R genes with cognate T3 effectors that are widespread in the pathogen populations should provide a degree of broad durable resistance.

TAL T3 effectors also are involved in recessive resistance. In the case of *xa13*, induction of the dominant allele *Os8N3* is mediated by the TAL effector PthXo1 (Yang et al., 2006). The gene *pthXo1* was first identified in Xoo strain PXO99^{A}, which coincidentally is also a strain that is incompatible on plants that are homozygous for *xa13* (Yang and White, 2004). PXO99^{A} cannot induce the *xa13* allele of *Os8N3* and does not grow as well in *xa13* plants in comparison with normal plants (Chu et al., 2005; Yang et al., 2006). The introduction of *avrXa7*, *pthXo2*, or *pthXo3* into PXO99^{A} restores virulence regardless of the presence of *pthXo1* (Yang et al., 2006). Thus, *xa13*-dependent resistance is only effective against strains that rely on *pthXo1* and is mimicked phenotypically by mutations in *pthXo1* of PXO99^{A} (Yang et al., 2006). The recessive resistance provided by *xa13* is phenotypically and qualitatively different from resistance provided by the dominant R gene *Xa7*, for example (Chu et al., 2004; Yang et al., 2006). Quantitatively, in terms of bacterial growth and lesion length, resistance mediated by *xa13* and *Xa7* are approximately equal (Bai et al., 2000; Yang et al., 2000, 2006). However, *Xa7* resistance is the result of the presence of the appropriate elicitor gene in the pathogen, while *xa13* is dependent on the absence of an effective virulence factor (Fig. 4). The *xa13* alleles are natural cases of mutations in loss of function for susceptibility, hence the classification of the dominant allele *Os8N3* as a S gene of the host and the target of the virulence factor PthXo1. The defeat of *xa13*-mediated resistance could theoretically involve induction of the *xa13* allele or targeting of alternative host genes that provide the same effect as *Os8N3*. Some variants of *xa13* are weakly inducible in young plants and concomitantly have greater susceptibility to PXO99^{A} as young plants (B. Yang, unpublished data). No strains have been identified that induced the *xa13* allele similar to PthXo1-mediated induction of *Os8N3*, nor have strains with alternate virulence TAL effectors been found that induce *Os8N3* in normal plants (Yang et al., 2006). The three aforementioned TAL effectors that restore virulence to PXO99^{A} compensate for PthXo1 by targeting alternative S genes (B. Yang and F.F. White, unpublished data).

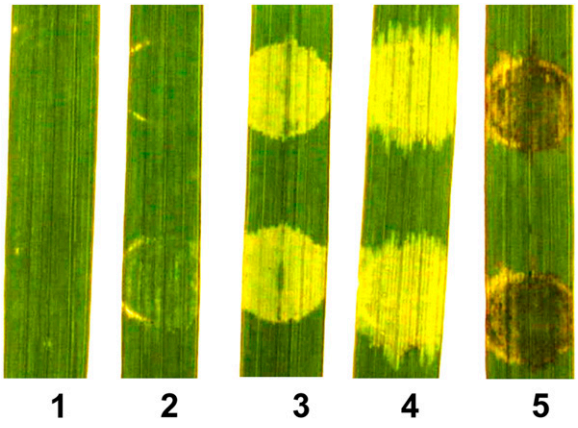

Figure 4. Diverse host responses to Xoo challenge in rice. Leaves were inoculated with water or Xoo by needleless syringe. Leaf 1, Mock inoculation; leaf 2, response to T3SS nonpathogenic mutant of PXO99^{A}; leaf 3, recessive R gene response (note the lack of streaking up and down the leaf blade); leaf 4, fully susceptible response (wild-type strain); leaf 5, PXO99^{A} (*avrXa7*; response to dominant R gene *Xa7*). Photographs were taken with back lighting, and yellow zones are indicative of water soaking.

PthXo1, AvrXa7, PthXo2, and PthXo3 are major virulence T3 effectors in the bacterial blight system, and the targeted host genes are major S genes. Strains lacking at least one of the major T3 effectors are severely debilitated for virulence, as measured by the standard leaf-clipping assays, display similar phenotypes, and, as noted above, compare favorably to results with dominant resistance genes. At present, the reason for resistance or lack of virulence is unclear and undoubtedly related to the benefit to the pathogen that is provided by the expression of the N3 gene in rice. T3 effectors, in general, are hypothesized to interfere with host defense and defense signaling mechanisms. Of course, in the broadest definition, any factor that promotes virulence can be interpreted as an interference with host defense. The question remains whether the major TAL T3 effectors of Xoo are "wrecking balls" and interfere with many normal host functions by expropriating normal developmental pathways or "guided missiles" designed to interfere with a specific host function related to immunity or, alternatively, beneficial functions unrelated specifically to immunity. One model for TAL effectors has proposed that the effectors enhance the spread of the bacteria from local infection sites (Yang et al., 1994; Iyer-Pascuzzi et al., 2008). Os8N3 protein, which is membrane localized, may, for example, result in loss of tissue integrity, allowing release of the bacteria into uninfected tissue (Chu et al., 2006). Alternatively, Os8N3 may promote greater bacterial growth due to leakage of nutrients into extracellular spaces, and consequently, the bacteria may grow to higher titers within the host. Future experimentation regarding bacterial physiology within the host as well as studies involving ectopic expression of S genes will provide insight into these models or provide new hypotheses to test. Xoo strains lacking the major TAL effectors are not nonpathogenic and are still capable of causing water-soaked symptoms if syringe inoculated. The ability to cause water soaking is in contrast to T3SS mutants, which are incapable of secretion of any T3SS effectors. T3SS-deficient mutants are virtually symptomless (Fig. 4). Utilization of the N3 family, based on existing evidence, is unique to the bacterial blight system. Xoc also contains multiple TAL effector genes, but infection

does not lead to *Os8N3* expression, indicating that, if the effectors play similar roles in heterologous systems, the targets of the effectors are likely to be different (A. Bogdanove, B. Yang, and F.F. White, unpublished data).

The genomic sequences are available for three strains of Xoo and one strain of Xoc (Lee et al., 2005; Ochiai et al., 2005; Lu et al., 2008; Salzberg et al., 2008). The full complement of TAL T3 effectors are now known for two strains of Xoo and one strain of Xoc, and both pathogens are unusual due to the high number of TAL effector genes within their individual genomes. Xoo strains PXO99^A and MAFF311018 (also named T7174) have 19 and 17 genes, respectively, organized in nine and eight regions of their respective genomes (Ochiai et al., 2005; Salzberg et al., 2008; Fig. 5). The individual genes are distinguishable on the basis of the number of repeats in the central repetitive region and by polymorphisms within each repeat sequence, particularly at the 12th and 13th codons. A comparison of the repetitive regions of PXO99^A and MAFF311018 indicates a high degree of rearrangements and shuffling of the genes at all of the loci, to the point where only three genes of 17 in MAFF311018 are identical (Salzberg et al., 2008). The large numbers of TAL effector genes in these species may reflect the evolutionary "investment" the strains have in utilizing the TAL effectors for virulence. The major contribution to virulence by *pthXo1*, for example, corroborates the view that the genes, as a class of T3 effectors, are important, maybe essential, to the ecological niche these bacteria occupy. Yang and Gabriel (1995) proposed that maintenance of a large repertoire of TAL effector genes may increase the frequency of recombination between genes and, as a consequence, increase the diversity of TAL effectors within the pathogen population. Populations with greater diversity of effector genes may then adapt faster to changing host genotypes. The maintenance of high gene numbers may even be exacerbated by rice breeding and R gene deployment by farmers over the millennia. The gene *pthXo5*, for example, gained virulence function by recombination of the original *avrXa7* and a chromosomal gene of PXO99^A, now known to be *pthXo6* (Yang et al., 2005; Sugio et al., 2007). Some of the genes are apparent pseudogenes, in the sense that a number of the genes are truncated in comparison with known functional genes (Salzberg et al., 2008). Pseudogenes could still serve as recombination substrates for generating new effector genes. Remarkably, Xoc strain BLS256 has 28 TAL effector genes, and the evidence also indicates that none are identical and most are unique with respect to repetitive region sequence. The profiles of changes in host gene expression upon infection by Xoc also appear different (A. Bogdanove, unpublished data). Differences in TAL effector gene effects have been observed between Xoo and Xoc, indicating possible differences in TAL effector utilization for host adaptation (Makino et al., 2006).

While many may serve as recombination substrates, the TAL effector genes of PXO99^A are not simply substrates for new major TAL effectors. Three TAL effector genes, in addition to *pthXo1*, are known to have contributions to virulence (Table II), and two are known to be associated with the elevated expression of two host genes distinct from *Os8N3*. The gene *pthXo6* is responsible for the elevated expression of a gene named *OsTFX1* (AK108319) and located on chromosome 9 of rice. A mutant of PXO99^A in *pthXo6* suffered a loss of approximately 35% in the lengths of leaf lesions and a 50% reduction in bacterial population per leaf (Sugio et al., 2007). Ectopic expression of *OsTFX1* in rice abrogated the need for *pthXo6* in the pathogen but did not make the plants more susceptible to PXO99^A (Sugio et al., 2007). *OsTFX1* is a member of the large bZip family of transcription factors, and the function of *OsTFX1* in a normal plant is unknown. Ectopic expression of the gene, other than compensating for the presence of *pthXo6* in the pathogen, did not cause any phenotypic abnormalities in the transgenic plants (Sugio et al., 2007). Elevated expression of *OsTFX1* may provide a good diagnostic tool for Xoo, as all strains examined were capable of inducing the gene. Xoc, at least on the basis of a single strain, was unable to induce *OsTFX1*. *pthXo7* is associated with the elevation of *OsTFIIAγ1* and has only been found in Xoo strain PXO99^A (Sugio et al., 2007). Loss of *pthXo7* in PXO99^A has no measurable effect on strain virulence in susceptible rice plants. In addition to compatibility on plants with the recessive *xa13*, PXO99^A is also one of the few strains known to be compatible with the other recessive resistance gene *xa5*. One model for the resistance provided by *xa5* is that the alternate TFIIAγ^{xa5} may not function properly with the TAL effectors and interfere with TAL effector function. In turn, PXO99^A may have adapted, in part, to *xa5* by

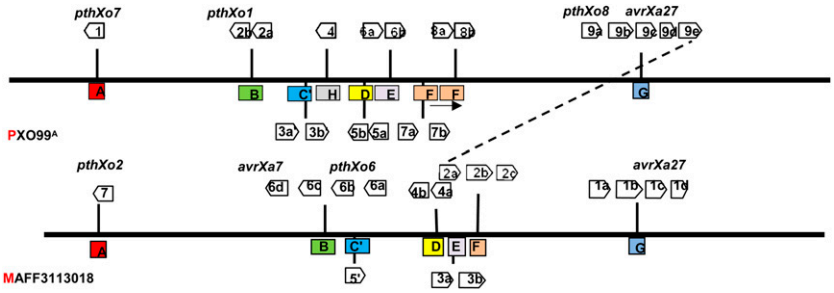

Figure 5. Genomic positions of TAL effector genes in two strains of Xoo. Genes are labeled and identified by biological function and name, where assigned (adapted from Salzberg et al. [2008] and Ochiai et al. [2005]). The dashed line indicates the location of the PXO99^A TAL effector gene 9e in MAFF3113018. Apostrophes after gene letters indicate truncated genes. Colored boxes indicate gene clusters. [See online article for color version of this figure.]

boosting the level of TFIIAγ1. A small effect on virulence was found upon transfer to a strain (PXO86) that is incompatible on plants with *xa5*, suggesting that *pthXo7* may be an adaptation to host genotypes containing the *xa5* allele of *TFIIAγ5* (Sugio et al., 2007). However, *pthXo7* does not confer on PXO86 the same level of growth on *xa5* plants in comparison with PXO99^{A}; therefore, it does not appear to be the sole or even the principal reason for the ability of PXO99^{A} to cause significant disease in the presence of *xa5* (Sugio et al., 2007). It should also be noted that the growth of PXO99^{A} is reduced in plants with the *xa5* gene for resistance, which again points to the uniqueness of the *xa5* mechanism for resistance. One also cannot, at this point, rule out the possibility of virulence factors and R genes in rice that are adapted specifically to the TFIIAγ^{xa5} subunit. In the future, *xa5* may be considered not only as an R gene, because it also has characteristics of a quantitative trait locus and a resistance modifier/suppressor gene.

Research into the molecular basis of Xoo and Xoc interaction with the host promises to provide exciting new insights in the near future into the adaptations between pathogen and host. The full complement of host effects due to the T3 TAL effectors wait to be discovered as more genes, strains, and host genotypes are examined. More recently, the characterization of strains from West Africa has revealed new genotypes of both Xoo and Xoc and indicates that an ability to cause bacterial blight of rice may have arisen in at least three lineages of related bacteria (Gonzalez et al., 2007). The research has also uncovered a variety of novel R genes, and a further understanding of their function in host susceptibility and resistance will be forthcoming. As in other bacterial pathogen-host systems, the features of a host strategy to turn the mechanism of the virulence factors against the pathogen are beginning to emerge. Curiously, in the rice system, the pathogen gains advantage by expropriating the developmental control of host genes and subsequent induction of a membrane protein, in the case of Os8N3. The host, on the other hand, can foil the process by production of a separate membrane protein (XA27) that triggers a rapid defense response. The differential effects of the proteins and the components of the two consequences on host cell physiology await further investigations. XA27, on the basis of sequence relatedness, is unique to rice and, possibly, some relatives (Gu et al., 2004), and it is one of a number of genes that may have been "invented" through the evolutionary process for specific purposes (Xiao et al., 2009).

Our understanding of Xoo and Xoc virulence is far from complete. For example, a third TAL effector gene, named *pthXo8*, has been identified in PXO99^{A} with quantitative effects similar to *pthXo6*, and the host gene expression associated with *pthXo8* is under investigation. Preliminary evidence indicates that the effector is involved in manipulation of the small RNA pathways of the host. The curious and novel nature of the TAL T3 effectors sometimes distracts attention from the presence of multiple other T3 effectors in Xoo and Xoc genomes. Recent characterization of the genomic data from MAFF311018 indicates that at least 19 candidate T3 effector genes, in addition to the 17 TAL effector genes, are present in the genome (Furutani et al., 2009; Table III). Three of the T3 effector genes are

Table III. *Candidate non-TAL type III effectors of Xoo*

Modified from Furutani et al. (2009). Entries in the same row are related by sequence similarity. N, No similar sequence identified; NA, not annotated.

Xoo			*X. axonopodis* pv *citri* 306	*X. campestris* pv *vesicatoria* 85-10
MAFF311018[a]	KACC10331	PXO99^{A}		
XOO0037 (novel)	NA	PXO03356	N	N
XOO0103 (XopF)	XOO0074	PXO03413	XAC2785	XCV0414
				XCV2942
XOO0148 (AvrBs2)	XOO0168	PXO03330	XAC0076	XCV0052
XOO0315 (XopN)	XOO0343	PXO02760	XAC2786	XCV2944
XOO3150 (XopN)	NA	NA	XAC2786	XCV2944
XOO1488 (novel)	NA	NA	N	N
XOO1669 (conserved)	XOO1768	PXO01625	XAC3085	XCV3215
XOO2210 (conserved)	XOO4824	N	NA	N
XOO2877 (novel)	NA	PXO00236	N	N
XOO3803 (conserved)	XOO4033	PXO04172	XAC0601	XCV0657
XOO4134 (conserved)	XOO4391	PXO03819	XAC0277	XCV0285
XOO2402 (HopAS)	XOO2543	PXO01041	XAC2009	XCC2059
XOO3222 (XopP)	XOO3425	PXO02107	XAC1208	XCV1236
	XOO3426			
XOO2875 (XopX, HopAE)	XOO3022	PXO00234	XAC0543	XCV3785
XOO4042	XOO4287	PXO03702		XCV0572
XOO4208 (XopQ)	XOO4466	PXO03901	XAC433	XCV4438

[a]Previously identified candidate effectors are in parentheses. Conserved, Newly identified candidate effector and conserved in other species; novel, unique to Xoo.

novel to Xoo (Furutani et al., 2009). The value of RLK-type resistance in rice is evident through the investigations of *Xa21* and *Xa26* (Lee et al., 2006; Cao et al., 2007). At the same time, some Xoo strains are virulent in *Xa21* or *Xa26* plants (Lee et al., 1999, 2003; Jeung et al., 2006), and evidence from the case of FLS2 and related proteins indicates that PTI is also vulnerable to T3 effector interference (Gohre et al., 2008; Xiang et al., 2008; reviewed in more detail in this issue). Xoo and possibly Xoc appear to have built a lifestyle that is dependent on a single family of T3 effector genes. This strategy, while providing interesting insight to the vulnerabilities and driving forces of rice genome evolution, may also prove the Achilles' heel in future strategies for durable and broad resistance to bacterial blight and streak in rice.

ACKNOWLEDGMENT

We thank Dr. Zhongchao Yin for unpublished photographs.

Received April 1, 2009; accepted May 17, 2009; published May 20, 2009.

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