Chapter

Disease Resistance and Susceptibility Genes to Bacterial Blight of Rice

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Abstract

Rice (*Oryza sativa* L.) is a valuable resource for understanding the complex processes controlling yield and value-added traits. Bacterial blight (BB) is a vascular disease of rice, caused by strains of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and provides insight, both practical and basic, into the concepts of susceptibility and resistance. Basic knowledge has been empirically and, more recently, intentionally exploited for broad and durable resistance to the disease. Bacterial blight involves representatives of most classes of resistance genes (*R* genes) and pathways for basal plant immunity. The study of BB also revealed novelties not observed in other models, possibly due to the long history of rice cultivation and the constant disease pressure. Conspicuous are the recessive *R* genes that target the notorious type III Transcription Activator-like effectors (TALes) of *Xoo*. Results indicate that pathogen and host are currently in a battle over a small patch of ground involving TALes function. At the same time, analyses of rice disease physiology are adding to a growing body of knowledge for plant disease processes and to how these processes are intertwined with disease susceptibility. The basic processes of BB present rich targets for the rapid advances in genome editing.

Keywords: *Xanthomonas oryzae* pv. *oryzae*, rice, recessive resistance, TAL effector, genome editing, CRISPR

1. Introduction

World population is expected to rise beyond 9 billion by 2050 [1]. Rice (*Oryza sativa*) is a staple food crop world-wide, providing about one fifth of the calories consumed by humans [2]. In particular, rice accounts for 35–75% of the calories consumed by more than 3 billion in Asian countries alone and planted on approximately 154 million hectares land annually [3]. Crop protection and food security go hand in hand, and breeding for resistance against crop diseases remains the essential ingredient for food security. Due to the labor-intensive nature of breeding, integrated disease control is often reduced to mere chemical control, leaving the very purpose of this environment-friendly approach in limbo. Advances in molecular tools in crop breeding, however, makes breeding an increasing sustainable effort in staying ahead of pathogen adaptation [4]. Bacterial blight (BB) of rice is a widespread vascular disease caused by *Xanthomonas oryzae* pv. *oryzae*

(*Xoo*). Epidemics can severely reduce grain yield due to collapse of the entire crop [5]. BB was first characterized in the late nineteenth century [6]. Introduction of resistance (*R*) genes into rice cultivars is considered as the best option for *Xoo management*. A total of 42 *R* genes have been identified in rice against *Xoo, and the number continues to grow* [7–9]. Due to co-evolution and selection pressure between *Xoo* and rice, these *R* genes are selective in their efficiency against specific *Xoo* strains or races, which are sets of strains that share incompatibility on defined sets of *R* genes [10].

2. Post genomic era and rice grain protection

Advancements in genomics, referring here to DNA and RNA analyses, is as beneficial to crop protection as is to other discipline of biology. Rice MetaSysB, an open source which provides detailed information about BB-responsive genes, is based on the global expression analysis. The database provided 7475 unique genes and 5375 simple sequence repeats, which were responsive to *Xoo* in rice [11]. Such information is based on the compatible and incompatible rice-*Xoo* interactions. In another example, 454 and 498 differentially expressed genes were reported as exemplified by the incompatible and compatible rice-*Xoo* interactions, respectively, using cDNA microarray [12]. Genomics also provides functional information of genes up- and downstream of candidate resistance genes in the defense signal pathway, as is done in near-isogenic rice lines introgressed with *Xa39*, an as yet uncharacterized BB resistance gene [13].

Multiple rice and *Xoo* genomes have been sequenced, either in draft or complete form [14–23], paving the way to identify functional connections between host and pathogen genes. The functional validation of the candidate genes is helping develop new rice varieties by introduction of the gene of interest through traditional breeding, marker assisted breeding, or genetic engineering approaches [3]. BB disease resistance is overcome by the emergence of more virulent strains of *Xoo*. Whole genome sequencing of 100 *Xoo* strains from India revealed that these strains were distinct from African and US *Xoo* strains [24]. Based on the reaction towards ten major resistance genes of rice, 46 out of the 100 strains were grouped into 11 pathotypes [24].

3. The genetic context of rice-*Xoo* interaction

Many BB-resistance genes in modern rice germplasm were selected long before the concepts of modern plant breeding were established, and a rich assortment of major dominant and recessive *R* genes has been identified by genetic and molecular studies (**Table 1**).

Perhaps the best known of these genes, *Xa21* represents the receptor kinase (RLK) class of *R* genes. *Xa21* was originally introgressed into rice from the related species *O. longistaminata* and confers resistance to a broad range of *Xoo* strains [25]. *Xa26*, another cloned member of RLK gene family, also confers broad resistance with a somewhat different strain profile [26]. The cognate elicitor for Xa21 has been reported [27]. However, for *Xa26* has not been identified.

RLKs play a central role in disease immunity pathways in plants, largely via the characterization of the bacterial flagellin receptor FLS2 and the related receptor EFR in *Arabidopsis* [28, 29]. A typical RLK consists of an extracellular receptor domain comprising of leucine-rich repeats (LRRs), a transmembrane domain, and an intracellular kinase domain [30]. As a class, RLKs have great potential for

Gene	Class	Comments	Cognate elicitor/ effector	Ref
Xa21	RLK[1]	extracellular, membrane and intracellular domains; kinase; broad resistance	RaxX	[25, 27]
Xa26	RLK	similar to *Xa21*; same locus as *Xa3*; broad resistance	Unknown	[26]
Xa1, *Xo1*	NBS-LRR[2]	cytoplasm; narrow resistance	Multiple TALes	[31–33]
Xa4	WAK[3]	narrow	unknown	[40]
Xa27, *Xa23*, *Xa10*	TAL effector inducible	membrane and cell wall; novel protein; broad resistance	AvrXa27, AvrXa23, AvrXa10	[37–39]
xa5	Missense mutant of *TFIIAγ5*; small subunit of TFIIA transcription factor complex	nuclear; broad resistance	TALe interference	[51, 53, 54]
xa13	promoter mutants of *OsSWEET11*; nodulin 3 family	membrane; unresponsive to PthXo1	PthXo1	[42, 47]
xa25, *OsSWEET13*^{Kit}	promoter mutant of OsSWEET13, nodulin 3 family	TATA box polymorphisms; unresponsive to PthXo2	PthXo2	[44, 52]

[1]*RLK, receptor linked kinase.*
[2]*NBS-LRR, nucleotide binding site, leucine-rich repeat.*
[3]*WAK, wall-associated kinase.*

Table 1.
Cloned R genes to bacterial blight of rice.

enhancing resistance to BB in rice and in other disease complexes of crop plants *Xa21*, *Xa26*, and other RLKs represent genetic components of the pathogen-associated molecular patterns (PAMPs)-triggered immunity (PTI) surveillance pathway in rice. Improvements in the rationale design of RLK receptor specificities, and screening for novel genes in germplasm or wild relatives could lead to general application for broad and durable resistance.

The nucleotide binding site-LRR (NBS-LRR) is another large class of *R* gene, represented in rice toward *Xoo* by *Xa1* and *Xo1* [31–33]. XA1 and XO1 recognize multiple TALe, and *Xoo* strains have adapted TALes, the so-called iTALes, that are truncated and inhibit the function of XA1 and XO1 [32, 34].

Specific TALe-dependent *R* genes governing dominant resistance in rice against *Xoo* are known as executor (*E*) genes. *E* genes are distinct from classical *R* genes, whose transcriptional activation by TALes of *Xoo* trigger immunity, leading to dominant resistance [35]. *Xa27* represents the E genes class of dominant *R* genes and confers broad resistance to BB in rice [36]. Although not expressed in susceptible host, *Xa27* is expressed only upon inoculation with *Xoo* strains harboring the TALe gene *avrXa27* [37]. The protein is localized to apoplastic space, cell membrane and cell wall, and when expressed under a pathogen-nonspecific inducible rice *OsPR1* promoter, conferred constitutive resistance to both compatible and incompatible

strains alike [37]. The rice *R* genes *Xa10* and *Xa23* have similar requirements for the transcription activation domain and nuclear localization sequence (NLS) motifs of the corresponding TALes for their induction [38, 39].

Xa4 is the latest and, again, an unusual *R* gene of rice to be characterized. The protein is a wall-associated kinase (WAK) and provides attributes other than enhanced resistance. Rice plants with XA4 are shorter and stiffer in comparison to plants lacking the gene [40]. Xa4 is race-specific, meaning many strains of *Xoo* are compatible on plants with Xa4. How Xa4 functions in resistance is unknown at present.

3.1 *SWEET* genes and recessive resistance

A class of major TALe-dependent susceptibility (*S*) genes for BB in rice encodes sugar transporters, thereby named as SWEET gene family [41]. Specific TALes, referred to as major TALes, transcriptionally activate the corresponding SWEET genes in rice during infection to promote the disease in a gene-for-gene susceptibility manner [42]. Although at least five SWEET genes of the clade III members can function as an *S* gene in BB, only three members are known to be targeted by extant strains of *Xoo* [42–47]. A member of the SWEET gene family, *OsSWEET14*, is induced by multiple distinct TALes, which include AvrXa7, PthXo3, Tal5 and TalC and are present in strains of different geographic origins and genetic lineages [43, 45, 46]. Similarly, PthXo2 drives *OsSWEET13* expression in the susceptible rice variety IR24 [44], and *OsSWEET11* is induced by the cognate PthXo1 [42]. The typical TALe possesses a central repetitive domain, a nuclear localization signal domain, and a transcription activation domain. The repetitive domain is responsible for binding of the TALe to a sequence motif called the effector binding element (EBE), which is commonly located in the promoter region of the respective *S* gene.

Mutated *S* gene alleles are proposed to be potentially more durable than dominant *R* genes [48, 49]. Identifying the promoter variant alleles of major *S* genes has been proposed in breeding for BB resistance [42, 47, 50–53]. Recessive resistance is due to the cognate TALe cannot bind to the promoter variants of the *S* gene. The gene *xa13*, for example, is a recessive resistance insertion allele of 14.8 kb DNA fragment in the promoter of *OsSWEET11* [42, 47]. *OsSWEET11* encodes a protein related to *MtN3* encoding nodulin 3 (N3) protein of *Medicago truncatula*. The gene was originally named *Os8N3* due to its location on rice chromosome 8 and the similarity to *MtN3* [42]. The critical difference between resistant (*xa13*/*xa13*) and susceptible plants is the elevated expression of *OsSWEET11* during infection in otherwise susceptible plant genotypes [42]. RNAi-mediated silencing of *OsSWEET11* plants was similarly resistant to *Xoo* strains that are solely dependent on PthXo1 for SWEET induction. Silenced plants, but not promoter variants, showed low pollen viability, corroborating the fact that *Xoo* hijacked otherwise developmentally important genes in rice for pathogenicity [42, 47]. Similarly, the TALe PthXo2 cannot bind to the EBE of *xa25*, a recessive allele of *OsSWEET13*, or the EBE region of *OsSWEET13* in japonica rice cultivars, owing to single nucleotide polymorphisms in the respective EBEs [51, 52].

The gene *xa13* is a naturally occurring allele, actually a series of alleles that protects the plant from a genetic disease vulnerability in the plant developmental pathways [42, 47]. However, *xa13* is not a broad resistance provided in comparison to *Xa21*, *Xa27* and *xa5*), and many strains from China, Philippines, Japan and Korea are compatible on *xa13* lines [51]. Compatibility is derived by acquisition of major TALes that target alternative SWEET promoters [43]. As yet, not major TALe has been identified that replaces PthXo1 for *OsSWEET11* expression.

The gene *xa5* also affects TALe-dependent function but does not act at a specific SWEET gene. The recessive allele encodes a variant of the γ or small subunit of the transcription factor TFIIA [54, 55], which confers broad resistance. The gene differs from the susceptible allele by a single codon substitution of valine at position 39 to glutamic acid. TFIIA, consists of α, β, and γ subunits, and is involved in stabilizing the binding of the TATA box binding protein complex (TFIID) to the TATA box of gene promoters. The TFIIA components are highly conserved across the eukaryotes. Rice has two loci for *TFIIAγ*-one gene is on chromosome 5 (*TFIIAγ5, xa5*) and another on chromosome 1 (*TFIIAγ1*) [54]. The proteins are closely related but not identical. *xa5* provides broad BB resistance and functions in inhibiting TALe function [51, 56]. However, *xa5* is not effective against strains with the TALe PthXo1 [51].

Perhaps not all *SWEET S* genes are known or are not always induced in disease by *Xoo*. The Indian strain IX-80 was virulent but did not induce any known *SWEET* gene [57], suggesting an adaptation by the *Xoo* to relieve dependency on *SWEET* gene family. On the other hand, IX-80 remains TALe-dependent as the strain was not compatible on IR53 (*xa13*/*xa13*, *xa5*/*xa5*), a gene combination that blocks the xa5-compatible PthXo1 and all other major TALes at *OsSWEET14* and *OsSWEET14* [51].

4. Implication of interactions between TALes and the corresponding host genes

Due to the large reservoir of TALes in each strain of *Xoo* and the diverse roles of TALes in pathogenesis, the BB of rice represents an excellent plant/pathogen system for studying the biology of TALes. The apparent reason for the broad activity of *Xa27* and *Xa23* is the presence of the cognate TALes *avrXa27* and *avrXa23* in a large number of strains from southeast Asia, including Korea, China, Japan and the Philippines [37, 39]. On the other hand, the loss of *avrXa27*, *avrXa23*, or *avrXa10*, for that matter, does not appear to have an apparent fitness cost to the pathogen, and populations of *Xoo* may lose *avrXa27* if *Xa27* is widely deployed [37–39]. AvrXa7 is an important virulence factor for some strains of *Xoo*, and strains with AvrXa7 are incompatible on rice lines harboring the *Xa7*. In this case, loss of *avrXa7*, which is a major TALe for *OsSWEET14*, may result in strains that are weakly virulent or, essentially, nonpathogenic, if no other SWEET inducing TALes are present [43, 58]. A variety of other TALe genes are present in *Xoo* populations that can restore full virulence to strains missing *avrXa7* [59]. Evasion of *Xa7*-mediated resistance is possible by loss of the gene, rearrangement of the central repeats or recombination among different TALe genes [60, 61]. However, despite rapid adaptation of bacteria by genetic changes and gene flow, field studies in the Philippines indicated that deployment of *Xa7* was durable in test plots for more than 10 years [62]. Therefore, strains may have other limitations due to geographical location or rice genotype. Nevertheless, pyramiding broadly effective *R* genes with cognate TALes that are wide-spread in the pathogen populations should provide a degree of broad and durable resistance.

In the case of *xa13*, induction of the dominant allele *SWEET11* is mediated by the TALe PthXo1 [42]. However, strains of *Xoo* that solely rely on PthXo1 cannot induce *xa13* allele, and rice homozygous for *xa13* is symptomless. *xa13*-dependent recessive resistance is phenotypically and qualitatively different from resistance provided by the dominant *R* gene *Xa7* [42, 63]. Quantitatively, however, resistance mediated by *xa13* and *Xa7* are approximately equal with respect to bacterial growth and lesion length [42, 58, 64]. *Xa7* resistance is the result of the presence of the appropriate AvrXa7 in the pathogen and dominant, while *xa13* resistance is dependent on the absence of an effective virulence factor and recessive. The mechanism of XA7 mediated resistance is as yet unknown.

Type III effectors, in general, are hypothesized to interfere with host defense and defense signaling mechanisms. Strains of *Xoo* have other type III effectors, differing from TALes, and, therefore, not entirely dependent on TALes for suppression of host defenses [65]. *Xoo* strains lacking major TALes are still capable of causing water-soaking, if syringe inoculated, which is in contrast to type III secretion system (Hypersensitive reaction/pathogenicity or Hrp^-) mutants. Hrp^- mutant strains are incapable of secreting any type III effectors, including TALes, and are virtually symptomless [66]. The mechanism by which SWEET transporters condition susceptibility is unknown. One hypothesis is that the transporters allow cells to leak sucrose, providing the pathogen with nutrients. SWEET function may interfere with normal plant defense functions or, possibly, allow transport of other nutrients or disease promoting compounds [41]. However, little empirical evidence for the nutrition model exists at present.

Sequencing of *Xoo* genomes has revealed the full complement of TALes is now known [17–23]. The individual TALe 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 12^{th} and 13^{th} codons. Strains of the Asian lineage contain upwards of 16–19 TALe genes in each genome [18]. The large numbers of TALe genes in these species may reflect the evolutionary investment in utilizing the TALes for virulence and are essential, to the ecological niche these bacteria occupy. The maintenance of a large repertoire of TALe genes may increase the frequency of recombination between, and diversity of TALecgenes within the pathogen population [60]. Pathogen may then adapt faster to the changing host genotypes as exemplified by the appearance of *pthXo5,* which avoids Xa7 recognition and appears to be a hybrid between *avrXa7* and *pthXo6* [61].

Not all TALE genes of *Xoo*, however, are just substrates for new major TALEs. Two other TALE genes from PXO99 strain of *Xoo*, in addition to *pthXo1*, contribute to virulence, known to elevate the expression of two host genes distinct from *SWEET11*. PthXo6 elevates the expression of *OsTFX1*, which contributes to approximately 35% of the disease [67]. Many strains induce *OsTFX1*. The gene *pthXo7* of PXO99 elevates the expression of *OsTFIIAγ1* and would appear to be an adaption to host genotypes containing the *xa5* allele of *TFIIAγ5* [67]. However, introduction of *pthXo7* to other strains does not restore full virulence on *xa5*/*xa5* plants and may provide only an incremental fitness benefit [67]. All Asian strains also carry a set of truncated TALes, the inhibitory or iTALes, which function to suppress *Xa1*-mediated resistance [32].

4.1 Executor *R* genes and super promoters

Xa10, *Xa23* and *Xa27* are representatives of the new class of E genes, so-named because the induction of these genes executes a response of programed cell death (PCD) in the host. *Xa10* induced PCD in plant species rice and *N. benthamiana,* and mammalian HeLa cells [38]. No cognate *S* genes for AvrXa10, AvrXa23, or AvrXa27 in compatible host cultivars have been reported, though the presence of AvrXa27 and AvrXa23 in many extant strains of *Xoo* may portend either a defeated function or an unknown cryptic function in *S* gene expression. Nonetheless, *E* genes hold great potential for broad and durable resistance in rice against extant *Xoo* population. A super promoter consisting of multiple EBEs, corresponding to specific TALes in extant population of *Xoo*, have been constructed (**Figure 1**). [68–70]. Addition of multiple EBEs to a pathogen strain specific rice BB resistance gene makes it effective against additional strains of *Xoo*. The EBEs of TALes PthXo1, PthXo6 and Tal9a when conjugated to E gene *Xa27*, showed resistance against PXO99 and a derivative strain lacking *AvrXa27* [68]. A similar scenario was

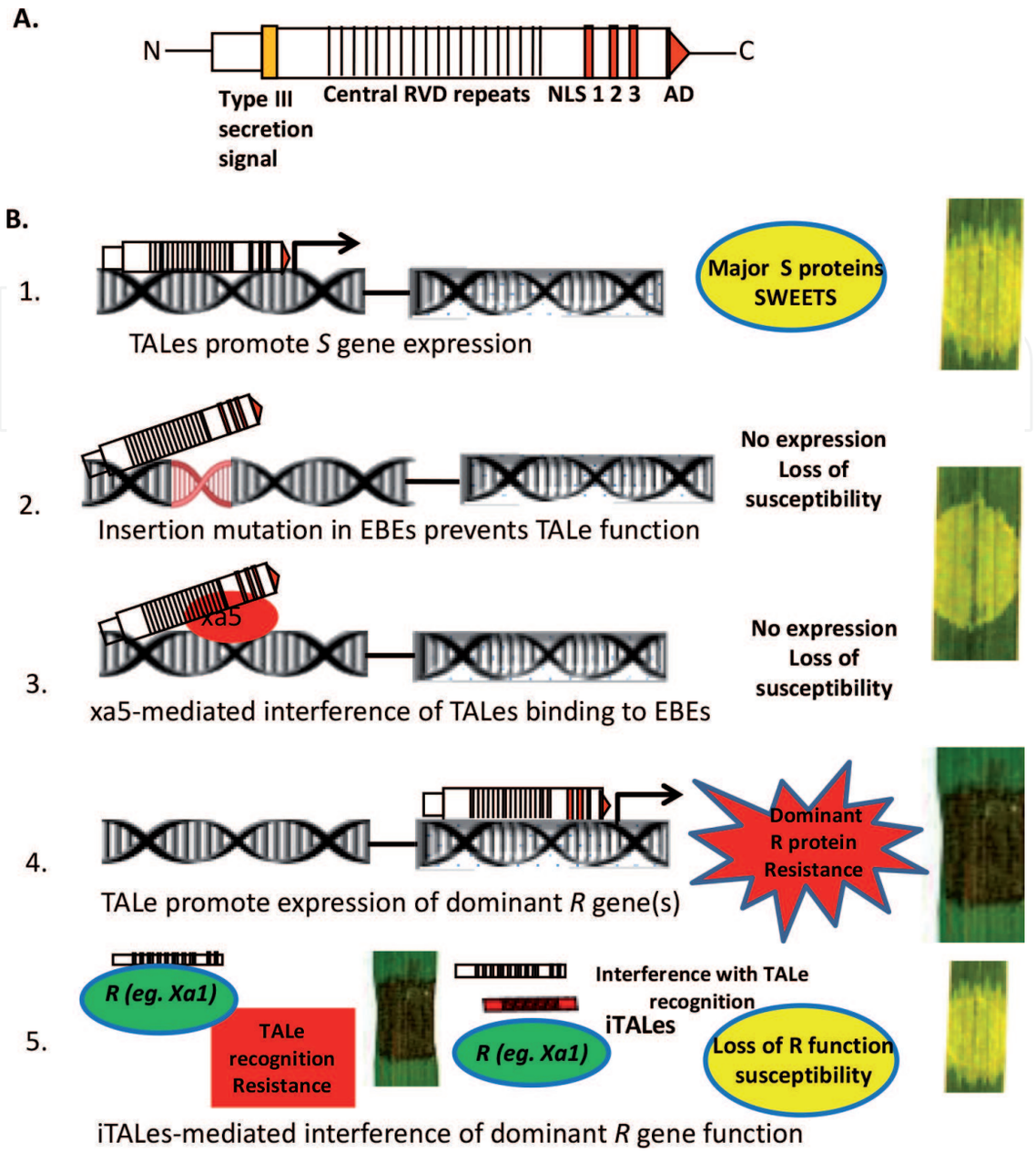

Figure 1.
Xoo TALe-dependent resistance and susceptibility in BB of rice. (A) Schematic of typical TALe from Xoo and (B) five types of TALe interactions affecting outcome of Xoo and rice interaction.

accomplished using E gene *Xa10* [69]. The study suggested that broad-spectrum and potentially durable resistance is possible by stable integration of an E gene engineered in a way to respond to multiple TALes from different strains or even different pathogens. Design of a super promoter, however, needs to be done carefully. Risk that an added EBE might coincidently contain a *cis* regulatory element could induce the E gene expression in response to particular stimuli and cause cell death without challenge by TALes. Amended promoters should be tested thoroughly before deployment.

4.2 Targeted genome regulation and editing

Central to TALe function is the discovery of the DNA recognition cipher of TALEs [71, 72]. The central domain of a TALe, also known as binding domain, consists of variable number of tandem repeats, each consisting 33–35 amino acid residues. The 12th and 13th amino acid residues (known as repeat variable di-residues, RVDs)

of each repeat preferentially binds to the respective nucleotides in the EBEs of target gene, such that HD, NG, NI and NN bind to C, T, A, and G, respectively in the effector binding elements (EBEs) of the promoter of a target gene [71–73]. The TALe recognition code allowed custom-engineer of DNA binding domains, also called designer TALes (dTALes), with novel specificity to the user-chosen DNA sequences [74–76]. dTALes provide a useful tool box to transiently activate host genes of interest for their functional analysis and assess the associated effect on host phenotype and physiology during rice-*Xoo* interaction. TALENs are fusions between dTALes and the nuclease domain of restriction enzyme FokI [77–80]. Other C-terminal domains have also been used [81]. Target site recognition and TALEN dimerization triggers a double-strand break (DSB) and generates small random insertions or deletions at the cleavage site, resulting in an edited sequence. CRISPR-Cas editing approaches have circumvented the need to construct dTALes and achieved wide general use, including editing of rice genes [82–84].

5. Prospects for engineered broad and durable resistance in rice to BB

Traditional resistance breeding has identified many useful *R* genes and introgressed the genes into elite cultivars. Further, development of molecular markers allows the pyramiding of multiple genes into single lines. The development of designer TALENs and CRISPR-Cas genome editing brings greater flexibility and rapidity to the development of resistant germplasm. A continuous provision of novel *R* genes in breeding programs is possible. Of course, the adoption and utility of different approaches is dependent on the regulatory climate. Introduction of novel or alien genes may be prohibitive in the foreseeable future. Classification of genome editing techniques will also vary depending on the individual country. In the rice system, our understanding allows numerous approaches for the enhancement of resistance beyond classical breeding. TALe biology, specifically, can be exploited (**Figure 2**). Least intrusive is targeted genome editing of *S* genes. *OsSWEET14* is targeted by unrelated TALEs, AvrXa7, PthXo3, Tal5 and TalC from different *Xoo* strains and which in some cases overlap their EBEs [43, 45, 46]. *OsSWEET14* was made unresponsive to TALEs AvrXa7 and Tal5, when their respective EBEs were mutated using TALENs in otherwise susceptible rice cv. Kitake [85, 86]. Thus, recessive resistance obtained by the genome editing of *OsSWEET14* is expected to be broad and contribute to durability given the apparent few major TALes in the extant population. Future efforts will be to target all EBE/*S* gene combinations in single elite lines. Fusion of EBEs to a variety of R and E genes has

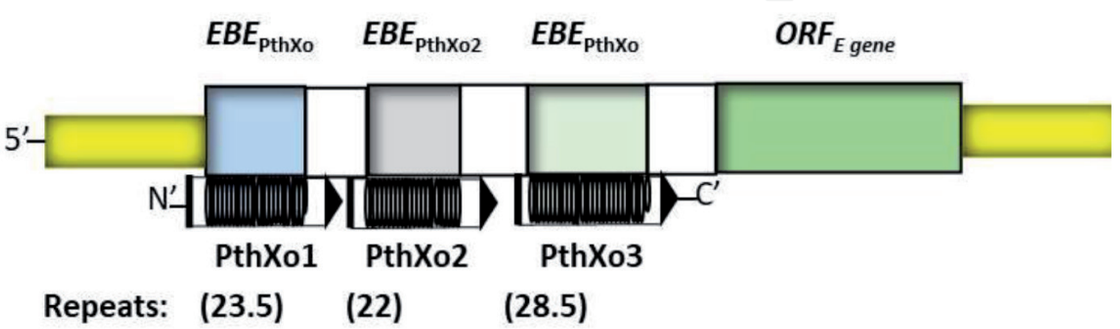

Figure 2.
Super promoters: pyramiding of EBEs of multiple TALEs upstream of an E gene for broad and durable resistance. Subscript of each EBE corresponds to the respective TALEs. Blocks under each EBE represent the respective TALes with blunt ends as their N termini, and arrowheads as their C-termini flanking the binding repeats in center.

been demonstrated to provide resistance [68, 87]. The functional specificity of an E gene can be broadened by linkage to general inducible defense genes [69, 88]. Approaches are not limited to TALe-associated responses. The RLK immunity receptor EFR from *Arabidopsis* [89, 90], as well as XA21/EFR fusion proteins function in rice [91]. Thus, the sky is the limit for the engineering of broad and durable resistance in rice to BB.

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