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TALE-induced immunity against the bacterial blight pathogen *Xanthomonas oryzae* pv. *oryzae* in rice

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Abstract

Transcription activator-like effectors (TALEs) are proteins produced by plant pathogenic *Xanthomonas* spp. TALEs exhibit a conserved structure and have the ability to directly bind to the promoter region of host target genes where they activate transcription. TALEs in *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), the causal agent of bacterial blight (BB) in rice, play important roles in triggering resistance (ETI) and susceptibility (ETS) for rice immunity. This review briefly describes rice resistance breeding in China, TALE properties and their roles, BB resistance (*R*) and susceptibility (*S*) genes in rice, the arms-race between TALEs and TALE-targets, and strategies for breeding disease-resistant crops. A systematic overview of the complex roles of TALEs are presented along with ongoing efforts to breed crops with durable and broad-spectrum resistance to the pathogenic bacterium.

Keywords: Rice, Bacterial blight, *Xanthomonas oryzae* pv. *oryzae*, TALE, Resistance, Susceptibility

Background

Rice is one of the most fundamental staple crops worldwide, and provides sustenance and nutrition for over half the global population. Efforts to stabilize rice production is a matter of great urgency in the face of complex environmental challenges and the growing global population. However, bacterial blight (BB), caused by *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), can easily spread in irrigated environments and result in a 10–50% reduction in crop yields (Mansfield et al. 2012). There is a general consensus that breeding rice varieties with durable and broad-spectrum resistance to *Xoo* is the most effective and environmentally-sustainable strategy to prevent losses caused by BB (Jiang et al. 2020). On the other hand, *Xoo* may evolve decoys or new virulence effectors to evade resistance gene recognition and suppress the resistance triggered by effectors (ETI), resulting in effector-induced susceptibility (ETS). These decoys or effectors are quite often related with transcription activator-like effectors (TALEs) that are injected into rice plants via the bacterial-encoded type III secretion system (T3SS) (White and Yang 2009; Xu et al. 2017; Timilsina et al. 2020; Xu et al. 2022). In this review, we focus on rice resistance breeding in China, the host-encoded resistance (*R*) or susceptibility (*S*) genes to BB, the characteristics and functions of TALE proteins, and recent approaches to breed rice varieties with broad-spectrum BB resistance. Our review concludes with a summary of recent research on TALE-induced immunity to BB and future control strategies.

BB resistance breeding in China

BB is a major disease in rice across the globe, and the first recorded observation was noted in 1884 by Japanese farmers (Ou 1985). Since the 1950s, BB has been

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reported in most Asian countries including India, Philippines, China, Korea, Thailand, Vietnam, and Sri Lanka where rice is cultivated (Ou 1985). BB has been regarded as one of the most devastating diseases of rice worldwide (Liu et al. 2014; Ji et al. 2018). In China, BB was initially observed in the 1930s in Jiangsu and Zhejiang provinces, and in the 1960s, BB quickly spread in irrigated fields and reduced rice production and grain quality primarily as a result of large-scale cultivation of semi-dwarf and high-yielding rice varieties (Zhang 2009). Over the past decades, intermittent epidemiology of BB on rice have been recorded in 28 provinces of China, especially in south of the Yangtze River and the Jianghuai Plain where climate conditions are more tropical than the northern areas of the country.

Breeding for BB resistance began in the late 1960s in China, and approximately 9.6% of indica rice varieties bred between 1960 and 1970 were resistant to BB, including Shuangzhuzhan that is resistant to both BB and rice blast (Zhang 2007). The *R* gene *Xa4* conveys resistance to the majority of *Xoo* races, and indica rice varieties such as Zhuzhan, BG90-2, IR20, IR22, IR26, IR30, and IR36 were utilized to develop BB-resistant cultivars (Zhang 2009). The *Xa3* resistance gene was primarily used for breeding japonica rice several decades ago (Cao et al. 2007). The wide use of *Xa4* and *Xa3* in the breeding of hybrid and conventional rice cultivars in China led to a well-controlled BB, and the disease rarely occurred in rice fields for two decades from 1980 to 2000 (Zhang 2009). However, the large-scale cultivation of rice varieties with *Xa4* and *Xa3* resistance on the other hand promoted the evolution of new pathogenic strains and races of *Xoo* and contributed to the breakdown of resistance not just in China (Mew et al. 1992; Quibod et al. 2016). Indeed, these cultivation practices have led to outbreaks of BB, and an example is that rice cultivar Xiushui 11 carrying the resistance gene *Xa3* is susceptible to BB (Zhang 2007).

Continually in the late 1990s, *Xa7*, *Xa21*, *xa5*, and *Xa23* were adopted to enrich the reservoir of resistance genes by molecular marker-assisted selection and transgenic technology (Huang et al. 2012; Luo et al. 2012; Chukwu et al. 2019; Tian et al. 2019; Chen et al. 2021; Joe et al. 2021; Luo et al. 2021; Wei et al. 2021). Although the deployment of these resistance genes initially reduced the occurrence of BB, ongoing changes in climate and continuous evolution of *Xoo* caused a resurgence of BB in some parts of China. For example, after a large-scale rainstorm in Hunan Province in 2017, BB broke out in paddy fields of approximately 0.667 M hm^2 (Li et al. 2013b; Chen et al. 2019; Chukwu et al. 2019; Jiang et al. 2020).

Rice cultivars containing single *R* genes have been planted for long periods of time over large areas, and the resistance conferred by some *R* genes has been overcome by *Xoo* strains that evolved during co-evolution with host plants (Wang et al. 2020; Lu et al. 2021). Our laboratory took more than two decades during 2000–2020 to collect *Xoo* strains from rice-growing areas in China, and the isolates were then inoculated onto near-isogenic lines (NILs) that contain single *R* genes, including *Xa3*, *Xa4*, *xa5*, *Xa7*, *xa13*, and *Xa23*, to see their compatibility or incompatibility with the NILs. The results clearly showed that rice lines carrying *Xa3* or *Xa4* were susceptible to multiple *Xoo* strains (Table 1), indicating that new physiological races or pathotypes of the pathogen have emerged in natural environments. Recently, *R* genes such as *xa5*, Xa7, and *Xa23* were incorporated into some rice varieties to improve their resistance to BB, however, the resistance has now been overcome by few strains (Table 1), implying that new *R* genes must be continually incorporated into rice varieties to avoid the long-term and large-scale failure of varieties with single dominant *R* genes.

TALEs determine *Xoo* virulence in rice

The rice genes conferring resistance and susceptibility can be activated by corresponding avirulence (*avr*) and virulence (*vir*) genes derived from the pathogen, respectively (Nino-Liu et al. 2006; Perez-Quintero and Szurek 2019). Since the defense response is genetically stimulated by interaction of *avr* gene products in *Xoo* with *R* gene products in rice, it has been coined gene-for-gene resistance (Flor 1971; Gabriel et al. 1986). Most *avr* and *vir* genes from *Xoo* are TALE genes (Tran et al. 2018; Mucke et al. 2019) with an exception of *raxX*. It interacts with *Xa21* and triggers *Xa21*-mediated resistance that is regarded as PTI (PAMP-triggered immunity) (Pruitt et al. 2015; Luu et al. 2019; Joe et al. 2021). The elucidated whole-genome sequences of different *Xoo* races show that 80% of the encoded genes have homology with genes in other *Xanthomonas* spp., and *Xoo*-specific genes, particularly TALE genes, are associated with virulence variation (Ochiai et al. 2005).

The highly-conserved TALE proteins, which are injected into host cells by the pathogen via the T3SS (Rossier et al. 1999; Tampakaki et al. 2004; Boch and Bonas 2010), contain a type-III secretion signal at the N-terminus, two or three nuclear localization signals (NLSs), an activation domain (AD), and a transcription factor binding domain (TFB) at the C-terminus. The TFB mediates a complex of TALEs with the plant gamma subunit of basal transcription factor TFIIA, which in turn activates the transcription of TALE-targeted genes in plant host (Yang and White 2004; Yuan et al. 2016).

Table 1 Pathotypes of Chinese *Xoo* isolates in near-isogenic rice lines containing different *R* genes

Strains	Rice lines						
	IR24	IRBB3 (*Xa3*)	IRBB4 (*Xa4*)	IRBB5 (*xa5*)	IRBB7 (*Xa7*)	IRBB13 (*xa13*)	CBB23 (*Xa23*)
GZ-10	R	R	R	R	R	R	R
AH-10	R	R	R	R	R	S	R
LN2	S	R	R	R	R	S	R
LN1	S	R	R	R	S	S	R
JL1	S	S	R	R	R	S	R
JS-137-1	R	R	S	R	R	S	R
YC12	S	S	S	R	S	S	R
KS-1-21	R	S	S	R	R	S	R
LN3	S	R	S	R	R	S	R
YC26	S	R	S	R	S	S	R
AH28	S	S	S	R	R	S	S
YC15	S	S	S	R	R	S	R
YN04-5	S	S	S	R	S	R	R
XZ40	S	S	S	R	R	S	R
YC19	S	S	S	R	S	S	R
JNXO	S	R	S	S	R	S	R
LYG50	S	S	S	S	R	S	R

S, susceptible (the lesion length of BB is more than 2 cm); R, resistant (less than 2 cm)

TALEs differ from each other by the number of 33–35 amino acid repeats and the composition of highly variable residues at positions 12 and 13 in each repeat, which are known as repeat variable diresidues (RVDs). The composition of RVDs determines the specificity of DNA binding to the host plant promoter regions called effector-binding elements (EBEs), following the code that confers DNA binding specificity to TALE RVDs. For example, HD, NI, and NG repeats have a strong preference for C, A, and T nucleotides, respectively (Boch et al. 2009; Moscou and Bogdanove 2009). Subsequently, the crystal structure of TALE proteins was determined by experimental and computational predictions and ultimately confirmed the preference of RVDs for specific nucleotides (Deng et al. 2012; Mak et al. 2012). Remarkably, two types of truncated *tal* genes were characterized in *X. oryzae* strains, initially assumed as pseudogenes and subsequently confirmed as truncated-TALEs or interfering TALEs (iTALEs). Compared with typical TALEs (tTALEs), iTALEs contain 45 or 129 bp deletions in the sequence encoding the N-terminal region and lack the C-terminal AD domains (Ji et al. 2016). Moreover, *tal3a*, which encodes a type A iTALE, retains two NLS sequences, whereas *tal3b*, a type B iTALE, has only one NLS. Experimental analysis confirmed that the unique structural features of iTALEs are essential for their suppressive function on *Xa1*-mediated resistance triggered by tTALEs (Ji et al. 2016; Read et al. 2016). Currently it has been confirmed that PthXo1, PthXo2, PthXo3, and AvrXa7 are major TALEs of *Xoo*, and a single major TALE gene contributes more than 80% virulence to the pathogen in rice as measured by lesion length when compared with the full virulence caused by the wild-type strains (White and Yang 2009).

BB susceptibility genes activated by major virulence TALEs

Susceptibility (*S*) genes are genetically dominant in plants and their expression are induced by pathogen infection. The induction of *S* genes in turn is beneficial to pathogen nutrient acquisition and disease development. By contrast, the recessive resistance mediated by alleles of *S* genes, defined as recessive genes, differs from dominant form of resistance to BB in rice. The exocytosis function of SWEET (sugars will eventually be exported transporters) proteins is exploited by *Xanthomonas* to obtain nutrients required for bacterial colonization (Chen et al. 2010). For BB, TALEs activate not only *S* genes of the *SWEET* family (e.g., *OsSWEET11*, *OsSWEET13*, and *OsSWEET14*) but also transcription factor genes (e.g., *OsTFIIAγ1*, *OsTFX1*, and *OsERF123*) in rice (Table 2) (Yang et al. 2006; Sugio et al. 2007; Yu et al. 2011; Streubel et al. 2013; Tran et al. 2018). In the promoters of these *S* gene, there are EBEs that can be directly recognized and bound by *Xoo*-specific major virulence TALEs (Mak et al. 2012).

Table 2 Rice genes targeted by TALEs

TALE-targeted genes		Protein products	Matched TALEs	References
SWEET genes	*OsSWEET11* (*Xa13*)	Sugar transporter	PthXo1	Yang et al. 2006
	OsSWEET12	Sugar transporter	ArtTAL12	Streubel et al. 2013
	OsSWEET13 (*Xa25*)	Sugar transporter	PthXo2, PthXo2.2, $Tal5_{LN18}$, $Tal7_{PXO61}$	Zhou et al. 2015; Xu et al. 2019
	OsSWEET14 (*Xa41*)	Sugar transporter	TalC, Tal5, PthXo3, AvrXa7	Antony et al. 2010; Yu et al. 2011; Streubel et al. 2013
	OsSWEET15	Sugar transporter	ArtTAL15	Streubel et al. 2013
	OsSWEET11b	Sugar transporter	dTALe	Wu et al. 2022
Non-SWEET *S* genes	*OsTFIIAγ1*	Gamma subunit of rice basal transcription factor	PthXo7	Sugio et al. 2007
	OsTFIIAγ5	Gamma subunit of rice basal transcription factor	Multiple TALEs	Yang et al. 2016
	OsTFX1	bZIP transcription factor	PthXo6, $TalB_{MAI1}$	Sugio et al. 2007; Tran et al. 2018
	OsERF#123	AP2/ERF transcription factor	$TalB_{MAI1}$	Tran et al. 2018
Type-A NLR genes	*Xa1, Xa2, Xa14, Xa45, Xo1*	CNL	Multiple TALEs	Yoshimura et al. 1998; Ji et al. 2020; Zhang et al. 2020
Executor *R* genes	*Xa7*	Executor	AvrXa7, PthXo3	Chen et al. 2021; Luo et al. 2021
	Xa10	Executor	AvrXa10	Tian et al. 2014
	Xa23	Executor	AvrXa23	Wang et al. 2015
	Xa27	Executor	AvrXa27	Gu et al. 2005

OsSWEET11, also called *Xa13* or *Os8N3*, is targeted by PthXo1, and this is the first pair to confirm that *Xanthomonas* induces host susceptibility in a gene-for-gene manner (Yang et al. 2006). *SWEET14* (*Xa41* or *Os11N3*) can be targeted by AvrXa7 and PthXo3 from Asian *Xoo* strains, and TalC and Tal5 from Africa *Xoo* strains (Antony et al. 2010; Yu et al. 2011; Streubel et al. 2013). The susceptibility gene *SWEET13* (*Xa25* or *Os12N3*) can be activated by PthXo2 and PthXo2-like alleles that bind to variable EBEs in the promoter of the same gene (Zhou et al. 2015; Xu et al. 2019), suggesting a co-evolutionary relationship between rice and *X. oryzae*. *SWEET12*, *SWEET15*, and *SWEET11b* also belong to the third clade of SWEET family that can be induced by designer TALEs, thus causing BB in rice (Li et al. 2013a; Streubel et al. 2013; Wu et al. 2022). This implies that there are possibly uncovered TALEs targeting these *S* genes naturally.

Regarding rice transcription factors, PthXo6 and PthXo7, derived from $PXO99^{A}$ strain, target the rice bZIP transcription factor-encoding gene *OsTFX1* and the basal transcription factor-encoding gene *OsTFIIAγ1*, respectively (Sugio et al. 2007), and $TalB_{MAI1}$ from Africa strain binds to the promoter of AP2/ERF transcription factor coded by *OsERF#123* (Tran et al. 2018).

BB resistance genes capable of trapping *Xoo* avirulence TALEs

Rice utilizes multiple strategies to trigger defense responses that are intended to ward off pathogens (Ji et al. 2018). Pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) occur during pathogen infection (Jones and Dangl 2006; Ngou et al. 2022). To date, 47 BB resistance genes have been identified (Jiang et al. 2020; Xing et al. 2021), which can be grouped into the following five categories: receptor-like kinase genes (*Xa3*/*Xa26*, *Xa4*, and *Xa21*) (Song et al. 1995; Xiang et al. 2006; Hu et al. 2017), EBE-mutated alleles of *SWEET* genes (*xa13*, *xa25*, and *xa41*) (Chu et al. 2006; Liu et al. 2011; Hutin et al. 2015), executor *R* genes (*Xa7*, *Xa10*, *Xa23*, and *Xa27*) (Gu et al. 2005; Tian et al. 2014; Wang et al. 2015; Chen et al. 2021; Luo et al. 2021), *NLR* genes encoding nucleotide-binding leucine-rich repeat receptors (*Xa1*, *Xa2*, *Xa14*, *Xa45(t)*, *Xo1*, and *Xa47(t)*) (Yoshimura et al. 1998; Ji et al. 2020; Zhang et al. 2020; Xing et al. 2021), and basal transcription factor gene *xa5* (Iyer and McCouch 2004; Jiang et al. 2006). *Xa21* is the first cloned *R* gene, and the cognate avirulence gene product in the pathogen was ultimately identified as sulfated RaxX (Song et al. 1995; Pruitt et al. 2015). Except for RaxX that interacts with XA21 to trigger PTI, other avirulence genes identified in *Xoo* are all TALE genes so far as we know (Table 2). Actually the recessive *R* genes *xa13*, *xa25*, and *xa41* are unable to cause either ETI or ETS in rice, since the mutated EBE of these genes cannot be recognized by their ligand TALEs, resulting in a failure for the pathogen to colonize host rice (Chu et al. 2006; Liu et al. 2011; Hutin et al. 2015). Later, editing the EBEs of host *S* genes has been developed into a new breeding strategy aiming at breeding rice varieties with broad-spectrum disease resistance (Oliva et al. 2019; Xu et al. 2019).

Host plants also utilize executor and NLR-type *R* genes to trigger an effective immune response. Four executor *R* genes have been identified in rice including *Xa7*, *Xa10*, *Xa23*, and *Xa27* (Gu et al. 2005; Tian et al. 2014; Wang et al. 2015; Chen et al. 2021; Luo et al. 2021). Executor *R* genes encode small, diversiform proteins that are trapped and transcriptionally activated by TALEs (Zhang et al. 2015); these genes share no sequence homology with other known BB resistance genes. The first NLR-type *R* gene cloned from rice is *Xa1*, which encodes nucleotide-binding site (NBS) and leucine-rich repeat (LRR) domains (Yoshimura et al. 1998). *Xa1*-mediated resistance can be triggered by multiple TALE proteins but inhibited by iTALEs (Ji et al. 2016; Read et al. 2016). XA1 is localized to plant nuclei, and *Xa1*-mediated resistance is independent of the basal transcription factors OsTFIIAγ1 and OsTFIIAγ5 (Xu et al. 2021). Allelic forms of *Xa1*, namely *Xa2*, *Xa14*, *Xa45(t)*, and *CGS-Xo1*$_{11}$, have been recently cloned, which are also activated by TALEs and inhibited by iTALEs (Ji et al. 2020; Zhang et al. 2020). Approximately 95% of sequenced *Xoo* Asian strains contain iTALEs, and consequently, *Xa1*-type resistance is limited (Ji et al. 2020). Although XA1 interacts in the nucleus with TALEs and a rice transcription factor OsERF101 via the XA1 BED domain to trigger BB resistance (Yoshihisa et al. 2022), how the iTALEs suppress *Xa1*-mediated defense in rice is still unknown.

Another type of BB resistance genes, the recessive *xa5*, encodes naturally-occurring V39E variant of the gamma subunit of basal transcription factor (TFIIAγ5, also called Xa5) (Iyer and McCouch 2004; Jianget al. 2006). Xa5 directly binds to the TFB region of TALEs to form a complex, facilitating the transcription of TALE-activated genes (Yuan et al. 2016). The mutant variant *xa5* cannot interact with TALEs or iTALEs, reducing the expression of TALE-driven *S* or/and *E* genes (Ma et al. 2018; Xu et al. 2021). However, TALEs can recruit OsTFIIAγ1 to compensate for the absence of OsTFIIAγ5 in rice, explaining the reason that PthXo7-containing strains overcome *xa5* resistance in rice (Table 1) (Ma et al. 2018).

Transcriptional complexes of TALEs with rice TFIIAγ

Deciphering the TALE code provides the basis for identifying TALE target genes in rice via computational predictions and experimental analyses (Boch et al. 2009; Mak et al. 2012). *Xoo* utilizes the T3SS to secrete TALEs, which are subsequently transported into the host nucleus to form a complex by binding with the promoter region of their target genes. This complex is essential for TALE-activated gene expression (Szurek et al. 2001; Perez-Quintero and Szurek 2019). Xa5 is a key component of the eukaryotic transcription complex, which is required for expression of *S* genes and executor *R* genes in rice (Yuan et al. 2016; Ma et al. 2018). OsTFIIAγ1 encoded by chromosome 1 is another gamma subunit of the basal transcription factor (Jiang et al. 2006). Consistent with Xa5, TALEs also interact with TFIIA*γ*1 but show a lower binding affinity. In the absence of Xa5, susceptibility genes were still induced when TFIIA*γ*1 was activated by PthXo7 (Ma et al. 2018). The complexes formed by TALEs and basal transcription factors (TFIIA*γ*) in host induce the expression of *S* genes, leading to disease susceptibility. In other words, genome-editing of these two *OsTFIIA*γ genes could be used to impair the expression of susceptibility genes (Huang et al. 2017; Ma et al. 2018). Interestingly, TALE-triggered and iTALE-suppressed *Xa1* resistance is independent of these two TFIIAγ factors, suggesting a novel mechanism for NLR *Xa1*-mediated resistance to BB (Xu et al. 2021).

The arms race between TALEs and TALE-targets

The co-evolution of *Xoo* and rice has led to scenarios where they compete in attempts to co-opt TALEs to combat against each other. Initially, pathogens utilize TALEs to bind to the promoter of *S* genes, and this is necessary for establishing and stabilizing the parasitic relationship between host and pathogen (Boch et al. 2009; Yu et al. 2011). Host plants may respond by evolving executor *R* genes and/or modifying TALE-targeted EBEs (e.g., *xa13*, *xa25*, and *xa41*) or eukaryotic basal transcription factors (e.g., *xa5*) to subvert the pathogen (Jiang et al. 2020). In an effort to evade host resistance, pathogens inject new virulence factors into host cells. New TALEs transcriptionally activate *S* genes and regain the ability to weaponize TALEs (Streubel et al. 2013). Consequently, TALEs represent a double-edged sword for effector-triggered susceptibility (ETS) and ETI (Fig. 1). The typical example is that two alleles of AvrXa7 and PthXo3 are not only the avirulence factor trapped by the EBE of *Xa7* gene for triggering ETI (Chen et al. 2021; Luo et al. 2021) but also the major virulence factors targeting *OsSWEET14* for activating ETS (Hutin et al. 2015; Zaka et al. 2018).

The co-evolution between TALEs and their targets in host plants also occurs in nature, resulting in TALE variants and multiple TALE-binding EBEs. For instance, PthXo2, PthXo2.1, and PthXo2.2 from *Xoo* strains JXO1, PXO339, and PXO163, respectively, bind to the same EBE sequence in *OsSWEET13*$_{IR24}$ (Zhou et al. 2015). Subsequently, it was reported that two other PthXo2-like TALEs, Tal5$_{LN18}$ and Tal7$_{PXO61}$, also induce the expression of *SWEET13* but recognize and bind to different EBEs in the *OsSWEET13* promoter, and correspondingly, the host rice has evolved ten EBE variants in the promoter of *OsSWEET13* to avoid being recognized by PthXo2-like TALEs (Xu et al. 2019). Similarly, AvrXa23C of seven AvrXa23 alleles is not trapped by the EBE of *Xa23*, resulting in the loss of *Xa23* resistance in rice fields (Xu et al. 2022).

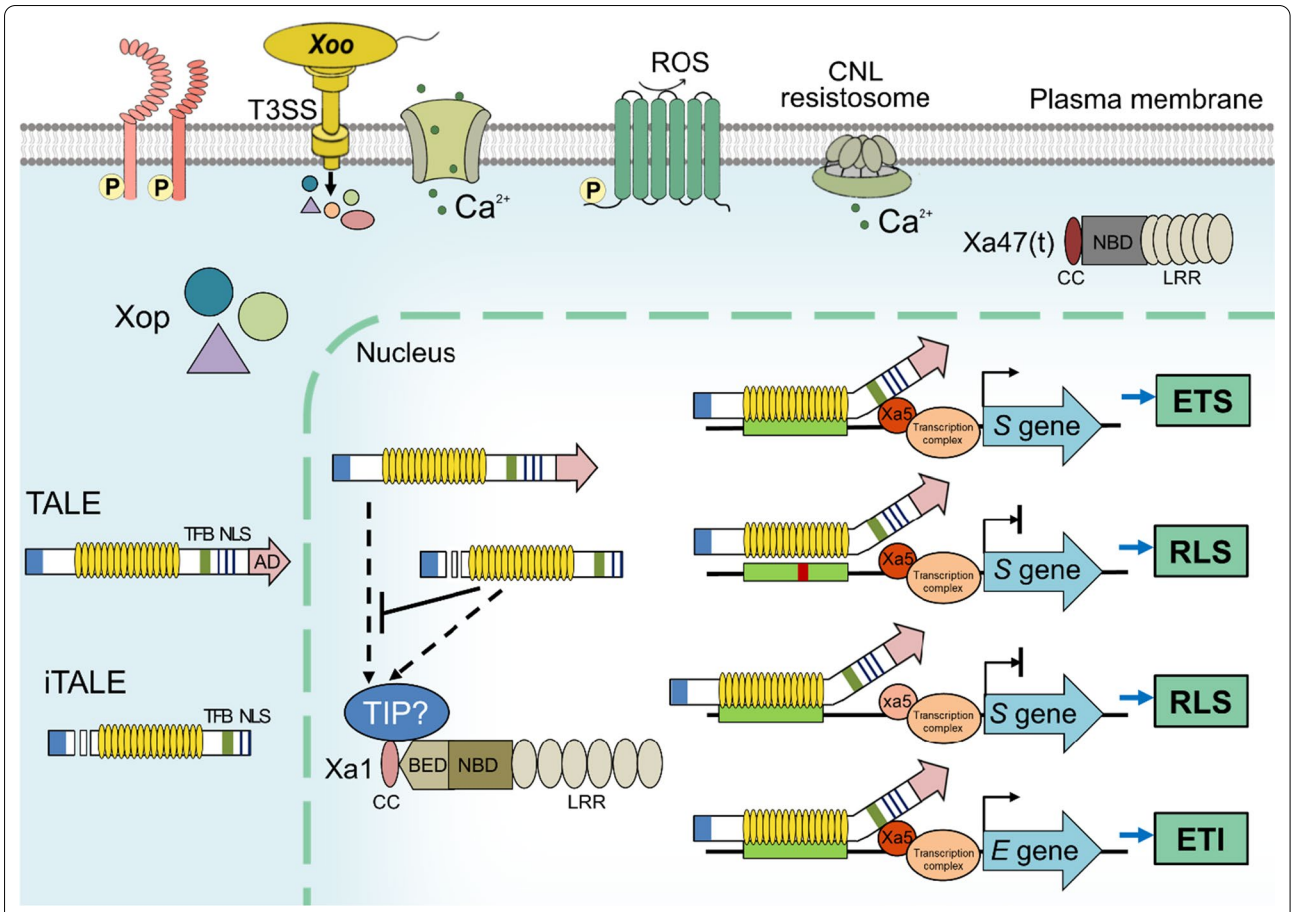

Fig. 1 Working model of rice immunity triggered by transcription activator-like effectors (TALEs) and Xops of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), the causal agent of bacterial blight (BB) in rice. Rice may use executor (*E*) genes to trap TALEs, or the BED domain of NLR-A type proteins (e.g., XA1 and its alleles) to recognize TALEs, or NLR-B type proteins (e.g., XA47) to recognize unknown type-III secretion effectors (T3SEs) for effector-triggered immunity (ETI) against *Xoo*. On the other hand, *Xoo* evolves iTALE to suppress XA1-mediated resistance via an unknown TIP1 in rice. These ETIs may have connection with calcium (Ca^{2+}) release and the burst of reactive oxygen species (ROS) for programmed cell death. Possibly, XA47 forms a resistosome like other coiled-coil NLR (CNL) proteins. Basically, *Xoo* secretes major virulence TALEs via the type-III secretion system (T3SS) to target the EBE (effector-binding element) of susceptibility (*S*) genes for ETS (effector-triggered susceptibility), and as a result to acquire nutrients from rice. This ETS may require unknown Xops to suppress PAMP-triggered immunity (PTI) via pattern-recognition receptors (PRR) on rice cell membrane. TALEs forms a complex with rice basic transcription factor OsTFIIAγ5 (Xa5) via a TFB domain to precisely activate the expression of *E* and *S* genes for ETI and ETS, respectively. If Xa5 mutated to *xa5*, the ETS turns to resistance by the loss of susceptibility (RLS). In addition, the disruption in EBEs of *S* genes makes rice acquire RLS. Xop, *Xanthomonas* outer protein; iTALE, interfering TALE; NLS, nuclear localization signals; AD, activation domain; TFB, transcription factor binding domain; TIP, TALE/iTALE interacting protein; NLR, nucleotide-binding leucine-rich repeat; CC, coiled-coil domain; BED, zinc-finger BED domain; NBS, nucleotide-binding site

The arms-race battle is also reflected in the activation and suppression of NLR-mediated resistance to BB. For example, typical TALEs (tTALEs) trigger *Xa1*-mediated resistance, which can be suppressed by iTALEs (Ji et al. 2016; Read et al. 2016). XA1, tTALEs, and iTALEs are localized to the host plant nucleus, suggesting that activation and inhibition of *Xa1*-mediated resistance occurs in host nuclei (Read et al. 2020; Xu et al. 2021). The contrasting functions of TALEs and their truncated variants (iTALEs) reveal the complex interactions underlying disease resistance and susceptibility in rice.

The interplay between TALEs and non-TALEs is unknown

Xoo type-III secretion effectors (T3SEs) include TALEs and non-TALEs, the latter are defined as *Xanthomonas* outer proteins (Xops) (Kay and Bonas 2009). Compared with TALEs, the contribution of non-TALEs to host plant susceptibility is poorly understood. In *Xanthomonas* spp., non-TALEs are involved in the disruption of plant defense signaling and the suppression of PTI (Buttner 2016). For example, XopK interacts and ubiquitinates somatic embryogenic receptor kinase 2 (SERK2) to inhibit PTI upstream of MAPK cascades (Qin

et al. 2018). In addition, XopP interacts with the U-box domain of rice ubiquitin ligase PUB44 to inhibit ligase activity and suppress peptidoglycan- and chitin-induced immunity (Ishikawa et al. 2014; Ichimaru et al. 2022); XopY interacts with the rice receptor-like cytoplasmic kinase OsRLCK185 to inhibit rice immunity (Yamaguchi et al. 2013); XopL catalyzes the ubiquitination of NbFd and induces defense-related response in plants (Ma et al. 2020); XopZ, XopN, and XopV suppress the peptidoglycan-triggered PTI response (Long et al. 2018); and XopN, XopQ, XopX, and XopZ suppress cell wall damage-induced immune responses in a functionally redundant manner (Sinha et al. 2013). However, it is still a mystery what are the core Xops necessary for *Xoo* to cause BB in rice in the presence of a single major virulence TALE.

The manners for rice to perceive TALEs

When TALEs function as transcription activators, rice perceives TALEs in host cells through DNA-protein interactions. For example, TALEs are trapped by executor *R* and *SWEET* genes via their EBEs (Zhang et al. 2015; Wu et al. 2022). The crystal structure of TALEs bound to DNA sequences was used to understand how RVDs recognize and bind to different nucleotides. For example, the RVD HD binds adenosine via hydrogen bonding, whereas NI binds thymine via van der Waals forces (Deng et al. 2012). The direct interaction between host gene promoters and TALE can be experimentally validated by gel retardation, chromatin immunoprecipitation, and glucuronidase assays (Romer et al. 2009; Streubel et al. 2013).

Rice plants may also perceive TALEs via NLR proteins and subsequently mount ETI. For example, TALEs containing various RVDs triggered *Xa1*-mediated resistance in a transcriptional activation-independent manner, while truncated iTALEs suppressed host resistance (Read et al. 2016). The structural differences between tTALEs and iTALEs suggest that the N-terminal deletion and the absence of the AD domain in iTALEs are critical for the activation and suppression of *Xa1/Xo1*- mediated resistance, respectively. the unique N- and C-terminal structures of iTALEs are essential for overcoming the resistance controlled by *Xa1* (Ji et al. 2016), and *Xa1*-mediated resistance is independent of rice transcription factor TFIIAγ (Xu et al. 2021). It is speculated that resistance mediated by *Xa1* and its alleles requires the N- and C-terminal regions of TALEs, rather than the central repeat regions; furthermore, the inhibition of NLR-type resistance by iTALEs supports this speculation. The resistance spectrum of *Xa1* and its alleles is greatly reduced by the presence of iTALEs in approximately 95% of Asian *Xoo* strains (Ji et al. 2020), and XA1 interacts with TALEs and OsERF101 via its BED domain to trigger BB resistance (Yoshihisa et al. 2022), which may be helpful to understand how iTALEs suppress *Xa1*-mediated resistance. *Xa47* represents another type of NLR gene and is predicted to localize to the host cytoplasm (Xing et al. 2021). The structure of Xa47 is very different from that of Xa1 localized to the nucleus (Xu et al. 2021). A recent report showed that a coiled-coil NLR (CNL) in Arabidopsis designated ZAR1 formed a calcium-permeable channel at the plasma membrane in its active oligomeric states and functioned as a resistosome (Bi et al. 2021). This resulted in plant innate immune responses (Fig. 1), including Ca^{2+} ion flux, production of reactive oxygen species (ROS), and cell death (Bi et al. 2021). Recently, another CNL gene *Xa47(t)* was identified. As a type-B NLR in rice, *Xa47(t)* confers resistance to *Xoo* via recognizing a yet unknown effector (Xing et al. 2021).

TALE-trapping EBEs upstream of executor *R* genes

Among the BB-resistant rice varieties in China, cultivars harboring *Xa23* exhibit the widest resistance spectrum (Table 1). *Xa23* is an executor-type *R* gene, and its broad spectrum of resistance imparts great breeding potential (Wang et al. 2020). The promoter regions of executor *R* genes contain EBEs that can be recognized and bound by TALEs. In rice, *Xa7*, *Xa10*, *Xa23*, and *Xa27* are trapped and activated by AvrXa7, AvrXa10, AvrXa23, and AvrXa27, respectively (Jiang et al. 2020; Chen et al. 2021; Luo et al. 2021). A recent study reported that the *Xoo* strain AH28, which produces the AvrXa23-like effector Tal7b, overcame *Xa23* resistance due to the varied RVDs, indicating that a co-evolutionary process between rice and *Xoo* leads to evasion of host resistance by pathogens (Xu et al. 2022). AvrXa10 was previously shown to transcriptionally activate *Xa10* in rice, resulting in a hypersensitive response (HR) and defense (Tian et al. 2014). AvrXa10 also elicited HR in the non-host plant *Nicotiana benthamiana* by targeting *NbZnFP1*; when *NbZnFP1* was overexpressed in rice protoplasts, cell death was observed (Haq et al. 2022). The rapid and strong defense response mediated by executor *R* genes indicates that executor (*E*) genes have great value for disease resistance breeding in rice. For example, the *E* gene *Xa23* was used to confer resistance to the BB-susceptible Nipponbare by deleting $EBE_{AvrXa23}$ using CRISPR/Cas9 technology (Wei et al. 2021).

EBE-editing rice provides durable resistance to TALE-containing *Xoo*

The resistance genes widely used in rice breeding to control BB, such as *Xa3*, *Xa4*, *xa5*, and *Xa23*, have failed to provide resistance in some rice-growing areas (Li et al. 2020) (Table 1). New *Xoo* strains have evolved in nature, imposing great challenges to BB-resistant rice cultivars bred in the past several decades. Some combined BB resistance genes, such as *xa5*+*Xa23* and *xa5*+*Xa7*, were introduced

into transgenic rice lines to help alleviate the breakdown of resistance (Chukwu et al. 2019). As mentioned elsewhere in this review, the PthXo7–containing strains without AvrXa23 or AvrXa7 would overcome *xa5*+*Xa23* or *xa5*+*Xa7* resistance. Thus, new rice breeding strategies to prevent resistance loss caused by co-evolutionary forces from host and pathogen are urgently needed. Among the tested *Xoo* strains, TALEs that function as major virulence factors have been identified, including PthXo1, PthXo2-like TALEs, and PthXo3 (AvrXa7) (Oliva et al. 2019), with *OsSWEET11*, *OsSWEET13*, and *OsSWEET14* as their recognized *S* genes, respectively. The promoter regions of *S* genes have been edited in rice to engineer broad-spectrum resistance to BB without introducing *R* genes (Oliva et al. 2019; Xu et al. 2019). This novel strategy shortens the breeding cycle. In other words, rice lines harboring homozygous mutations in *S* genes without transgenic elements can be obtained in the T_1 transgenic generation (Deng et al. 2020). Rice plants with triple mutations in *SWEET11*, *SWEET13*, and *SWEET14* are resistant to all the tested *Xoo* strains (Oliva et al. 2019; Xu et al. 2019). Thus, the process of engineering resistance in *S* genes, including *SWEET* and rice general transcription factor-encoding genes, will increase resistance without introducing *R* genes and will help clarify the mechanisms underlying *S* genes.

Another strategy is to utilize gene-editing technology to insert EBE sequences into executor *R* gene, by which rice cultivars with executor-mediated broad-spectrum resistance were obtained. For example, the EBE of *Xa23* was inserted into the susceptible rice cultivar Nipponbare that has no the EBE to trap AvrXa23, and the resulting transgenic line showed resistance to multiple *Xoo* strains (Wei et al. 2021). When combined with pathogen monitoring and intelligent planning of rice cultivars, this type of disease resistance might be deployed for long periods of time. However, it is important to mention that *E* gene-mediated resistance could be defeated by variants of trapped TALEs unless the underlying mechanisms on how the executors take functions are deciphered.

Concluding remarks and future perspectives

Xoo and its host rice represent a model system for studying plant-pathogen interactions, by which many innovative results have been obtained. As structurally unique pathogenic effectors, TALEs play a complex role in the co-evolution of *Xoo* and rice (Perez-Quintero and Szurek 2019). *Xoo* strains utilize surface-associated virulence factors and non-TALEs secreted via the T3SS to inhibit PTI in rice (Timilsina et al. 2020). TALE proteins are then injected into host cells and bind to EBE sequences at the promoter region of *S* genes. The subsequent expression of *S* genes further increases susceptibility to *Xoo* stains and helps the pathogen obtain nutrients for growth (Li et al. 2004; Yang and White 2004; Boch and Bonas 2010). Rice susceptibility to BB is mainly conferred by the *SWEET* family genes, which provide sucrose for growth of pathogenic bacteria (Streubel et al. 2013; Eom et al. 2015). Rice plants with genome-edited mutations in the EBEs of *SWEET* genes are resistant to BB, and this provides a new avenue for breeding BB-resistant rice (Oliva et al. 2019; Xu et al. 2019; Ni et al. 2021).

Of approximately 47 *R* genes to BB (Jiang et al. 2020; Xing et al. 2021), how the four executor *R* gene products (XA7, XA10, XA23, and XA27) lead to HR-like programmed cell death in rice is still unclear. We still do not know the *avr* genes in *Xoo* that match receptor-like kinases *Xa3*/*Xa26* and *Xa4* to trigger rice immunity. There are two types of NLR *R* genes. *Xa1* and alleles *Xa2*, *Xa14*, *Xa45(t)*, and *CGS-Xo1*$_{11}$ belong to the NLR-A type. Their encoding proteins that contain a BED domain and several leucine-rich repeats (LRR) (93 amino acids in length) are localized in rice nuclei (Read et al. 2020; Xu et al. 2021) (Fig. 1). It is still being explored to know how the resistance conferred by this NLR-A type is suppressed by *Xoo* iTALEs. XA47 is a NLR-B type protein without the BED domain (Xing et al. 2021) (Fig. 1). If the paired Avr of this type of resistance protein in *Xoo* is clear, the revealed mechanism of this NLR-type resistance shall be helpful in rice breeding programs.

Researchers across the globe utilize modern technology in an attempt to protect crops from pathogen infection. Breeding strategies aimed at developing rice varieties with durable and broad-spectrum resistance to BB can be divided into two general categories, that is, introducing *R* genes into cultivated rice varieties and increasing rice resistance to the pathogen by the loss of susceptibility (RLS). Although much has been accomplished in understanding the rice-*Xoo* interaction, many questions remain unanswered. For instance, is it possible to rearrange potential RVDs of a TALE to simultaneously activate at least two or more *R* genes in resistant rice varieties with different executor *R* genes for pyramiding breeding? What is the function of non-TALEs in TALE-triggered susceptibility on rice? Is an unidentified factor (TALE-interacting protein 1, TIP1) required for TALE-triggered and iTALE-suppressed *Xa1*-mediated resistance? And what is the underlying mechanism of iTALE-suppressed NLR-mediated resistance to BB? The *R* gene product XA1 could be recognized by multiple typical TALEs with diverse RVDs, which could attenuate the effect of TALE diversity and reduce the possibility of breakthrough resistance. The design of new effector recognition specificities in *R* genes, especially NLRs, via molecular engineering of integrated decoy domains has been reported to confer resistance to rice blast (Cesari et al. 2022) and might be applicable to BB. In summary, editing of the EBE of three *S* genes and the NLR genes have great

potential in breeding rice with durable and broad-spectrum resistance to TALE-containing pathogens.

Abbreviations
AD: Activation domain; *avr*: Avirulence gene; BB: Bacterial blight; BED: Zinc-finger BED domain; CC: Coiled-coil domain; CNL: Coiled-coil NLR; EBEs: Effector-binding elements; EPS: Extracellular polysaccharides; ETI: Effector-triggered immunity; ETS: Effector-triggered susceptibility; HR: Hypersensitive response; iTALE: Interfering TALE; LPS: Lipopolysaccharides; LRR: Leucine-rich repeat; NBS: Nucleotide-binding site; NLR: Nucleotide-binding leucine-rich repeat; NLS: Nuclear localization signals; PTI: Pathogen-associated molecular pattern (PAMP)-triggered immunity; RLS: Resistance by the loss of susceptibility; ROS: Reactive oxygen species; RVDs: Repeat variable diresidues; T3SS: Type III secretion system; TALEs: Transcription activator-like effectors; TFB: Transcription factor binding domain; tTALE: Typical TALE; *Xoo*: *Xanthomonas oryzae* pv. *oryzae*; Xops: *Xanthomonas* outer proteins

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Authors' contributions
GC designed the outline of the review. XX wrote the draft. XX, ZX, and LZ polished the manuscript. YL, JY, YW, YJW, and GC conducted some projects mentioned in this review. GC supervised the working group. All authors read and approved the final manuscript.

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