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TALEs as double-edged swords in plant–pathogen interactions: Progress, challenges, and perspectives

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ABSTRACT

Xanthomonas **species colonize many host plants and cause huge losses worldwide. Transcription activator-like effectors (TALEs) are secreted by** ***Xanthomonas*** **and translocated into host cells to manipulate the expression of target genes, especially by** ***Xanthomonas oryzae*** **pv.** ***oryzae*** **and** ***Xanthomonas oryzae*** **pv.** ***oryzicola*****, which cause bacterial blight and bacterial leaf streak, respectively, in rice. In this review, we summarize the progress of studies on the interaction between** ***Xanthomonas*** **and hosts, covering both rice and other plants. TALEs are not only key factors that make plants susceptible but are also essential components of plant resistance. Characterization of TALEs and TALE-like proteins has improved our understanding of TALE evolution and promoted the development of gene editing tools. In addition, the interactions between TALEs and hosts have also provided strategies and possibilities for genetic engineering in crop improvement.**

Key words: *Xanthomonas*, TALEs, rice, resistance, susceptibility, interaction

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INTRODUCTION

Plants have developed different kinds of immunity systems to cope with the continuous threat of various pathogens throughout their lifetimes. The interactions between plants and pathogens are sophisticated, and they can take place at different levels. Usually, the first line of plant immunity is controlled by membrane-anchored receptors that recognize pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs); therefore, they are called pattern recognition receptors (PRRs). The defense reactions triggered by these PRRs are called PAMP-triggered immunity (PTI) (Jones and Dangl, 2006; van Wersch et al., 2020). Because of the conservation of PAMPs or MAMPs, the response level of PTI is commonly non-specific but weak, and it is sometimes called basal resistance (Zhang and Wang, 2013). Pathogens can overcome PTI by secreting special protein effectors into plant cells. Many plants have also developed another line of defense mediated by resistance (*R*) genes. *R* genes can recognize corresponding effectors and initiate severe resistance reactions in a process called effector-triggered immunity (ETI) (Jones and Dangl, 2006; van Wersch et al., 2020).

Among the diverse plant pathogens, *Xanthomonas* is an important genus and contains many species that can colonize a large number of host plants worldwide (Timilsina et al., 2020). In rice, *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*) are two major pathovars that cause bacterial blight (BB) and bacterial leaf streak (BLS), respectively, and lead to great losses in production (Nino-Liu et al., 2006). *Xanthomonas campestris* pv. *vesicatoria* (*Xcv*) causes bacterial spot disease in tomato and pepper, and *Xanthomonas citri* subsp. *citri* (*Xcc*) can cause canker in citrus fruit (Timilsina et al., 2020).

During infection, many effectors are secreted into host cells by *Xanthomonas*. There are several secretion systems in *Xanthomonas*, such as the type II secretion system (T2SS) and type VI secretion system (T6SS). However, the type III secretion system (T3SS) is considered to be the primary system for pathogenesis (Timilsina et al., 2020). Most of the secreted effectors are translocated into plant cells through the T3SS, and they are therefore also known as type III secreted effectors (T3SEs). T3SEs are grouped into many families based on differences in protein structure. Among them, the transcription activator-like effectors (TALEs) are the most special family; they can induce the expression of host target genes in the nucleus (Boch and

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Bonas, 2010). In addition to TALEs, some T3SEs are also called *Xanthomonas* outer proteins (Xops), except for AvrBs1 and AvrBs2, because of their avirulence function (White et al., 2009; Timilsina et al., 2020).

The first TALE to be characterized was AvrBs3 from *Xcv*, which triggers *Bs3*-mediated resistance in pepper (Bonas et al., 1989). AvrBs3 homologs were then found in *Xoo*, *Xoc*, *Xcc*, and other *Xanthomonas* species (Swarup et al., 1991, 1992; Hopkins et al., 1992; Yang and White, 2004). Some less-related homologs have also been reported in *Ralstonia solanacearum*, which causes plant disease in tropical areas (Schandry et al., 2016). Most TALEs are extremely similar in structure. They are composed of a conserved N-terminal region, a central repeat region (CRR), and a conserved C-terminal region. The type III translocation signal sequence is located in the N-terminal region, whereas the nuclear localization signal (NLS) sequences are in the C terminus, together with the transcriptional activation domain (AD). The CRRs usually contain nearly identical repeats but differ in number and arrangement. The repeat variable diresidues (RVDs) at positions 12 and 13 are involved in direct interaction with host DNA in a specific way, the RVD code (Boch et al., 2009; Moscou and Bogdanove, 2009; Deng et al., 2012; Mak et al., 2012). TALEs can bind to effector binding elements (EBEs) in the promoters of host genes and activate their expression (Figure 1) (Timilsina et al., 2020).

Some sequenced *Xanthomonas* genomes contain fewer than six TALEs, and some TALE-encoding sequences even exist in plasmids (Scholze and Boch, 2011). However, the genomes of *Xoo* and *Xoc* contain more TALEs, usually more than 10, with a maximum of 28 (Scholze and Boch, 2011). This is consistent with TALEs having a more important role in infection for *Xoo* and *Xoc* than for other species. Some studies have shown that many BB and BLS resistance genes are directly related to the process of TALE-mediated host gene induction (Zhang and Wang, 2013). Studies of the interactions between rice and *Xoo* or *Xoc* have greatly expanded our understanding of TALEs and facilitated similar studies of other host–*Xanthomonas* interactions (Timilsina et al., 2020). TALEs are key components that lead not only to susceptibility but also to resistance in many plants.

TALEs MANIPULATE HOST GENE EXPRESSION FOR VIRULENCE

It is evident that TALEs provide a great ‘‘arsenal’’ for *Xanthomonas* to control host gene expression. Target gene expression may contribute to disease symptoms, such as chlorosis, or benefit the reproduction and spread of the bacteria (Kay et al., 2007). Some target genes are so critical for pathogenicity that they are called susceptibility (*S*) genes (Figure 1; Table 1) (Yang et al., 2006).

Many well-known *S* genes belong to the *SWEET* gene family, which is well characterized in the rice–*Xoo* pathosystem. PthXo1 from *Xoo* was the first reported TALE that can bind to the EBE of a *SWEET* gene in rice, *OsSWEET11* (previously called *Os8N3*/*Xa13*) (Chu et al., 2006; Yang et al., 2006; Moscou and Bogdanove, 2009; Yuan et al., 2011). Later, AvrXa7, PthXo3, TalC, and Tal5 were found to bind to the promoter of *OsSWEET14* (previously called *Os11N3*), but this gene may not be the major *S* gene for TalC-mediated virulence (Antony et al., 2010; Yu et al., 2011; Streubel et al., 2013; Blanvillain-Baufume et al., 2017). *OsSWEET13* (previously called *Os12N3* or *Xa25*) was found to be the target gene of PthXo2 (Liu et al., 2011; Zhou et al., 2015). *OsSWEET12* and *OsSWEET15* have also been found to function as *S* genes during infection by *Xoo*, which carries the artificial TALEs ArtTAL12 and ArtTAL15 (Streubel et al., 2013). These five genes can be grouped into the unique clade III of the *SWEET* gene family (Streubel et al., 2013). For some time, the function of SWEET proteins was unclear. However, studies using HEK293T cells and oocytes produced a breakthrough and showed that these *SWEET* genes participate in sucrose efflux. The bacteria hijack these host glucose transporters in the phloem, and this process improves their nutrient uptake and multiplication (Chen et al., 2010, 2012).

Similar results have also been found in other pathosystems. $TAL20_{Xam668}$ from *Xanthomonas axonopodis* pv. *manihotis* (*Xam*) binds to the EBE in the promoter of *MeSWEET10a* in cassava (Cohn et al., 2014). In the interaction between *Xanthomonas citri* subsp. *malvacearum* (*Xcm*) and cotton, Avrb6 from *Xcm* can bind to the EBE of *GhSWEET10* in the A and D genomes (Cox et al., 2017). The *upa* (upregulated by AvrBs3) gene *upa16* encodes a homolog of SWEET protein (Kay et al., 2009; Gupta et al., 2021). These studies revealed conservation during the evolution of different *Xanthomonas* species.

Besides the *SWEET* genes, other kinds of genes can also be targeted. AvrBs3 can induce several *upa* genes in pepper. Among them, *upa20* encodes a helix-loop-helix domain-containing transcription factor, and its upregulation can lead to hypertrophy (Kay et al., 2007). AvrHah1 in *Xanthomonas gardneri* has been reported to induce two *S* genes, *bHLH3* and *bHLH6*, resulting in water-soaked lesions in tomato (Schwartz et al., 2017). PthA4, an important TALE in *Xcc*, directs gene expression of a specific transcription factor-encoding gene, *CsLOB1*. Similar induction has been found for PthAw, PthA*, PthB, and PthC from different *Xcc* strains (Hu et al., 2014). Ectopic expression of *CsLOB1* can induce pustule formation in citrus fruit (Duan et al., 2018). Recently, Tal8 from *Xanthomonas translucens* pv. *undulosa* (*Xtu*) has been found to activate the expression of *TaNCED_5BS*, which encodes a rate-limiting enzyme in abscisic acid (ABA) synthesis in wheat (Peng et al., 2019).

In rice, there are also many non-*SWEET*-encoding *S* genes during infection with *Xoo* and *Xoc*. *OsTFIIAγ1* encodes the γ subunit of the general transcription factor IIA and is the target of PthXo7 from *Xoo* strain $PXO99^{A}$ (Sugio et al., 2007). Induction of *OsTFIIAγ1* is essential for *Xoo* multiplication on *xa5*-carrying rice (Ma et al., 2018b). *OsTFX1*, which encodes a basic leucine zipper (bZIP) transcription factor, can be induced by PthXo6 and $TalB_{MAI1}$ (Sugio et al., 2007; Tran et al., 2018). $TalB_{MAI1}$ can also activate another transcription factor gene, *OsERF#123*, for susceptibility to African *Xoo* strains (Tran et al., 2018). In rice–*Xoc* interactions, the sulfate transporter gene *OsSULTR3;6* is one of the targets of Tal2g and a major *S* gene for BLS (Cernadas et al., 2014).

The diversity of *S* gene products is probably related to differences in the infection or dispersal of diverse pathogens. For example, *Xoo*

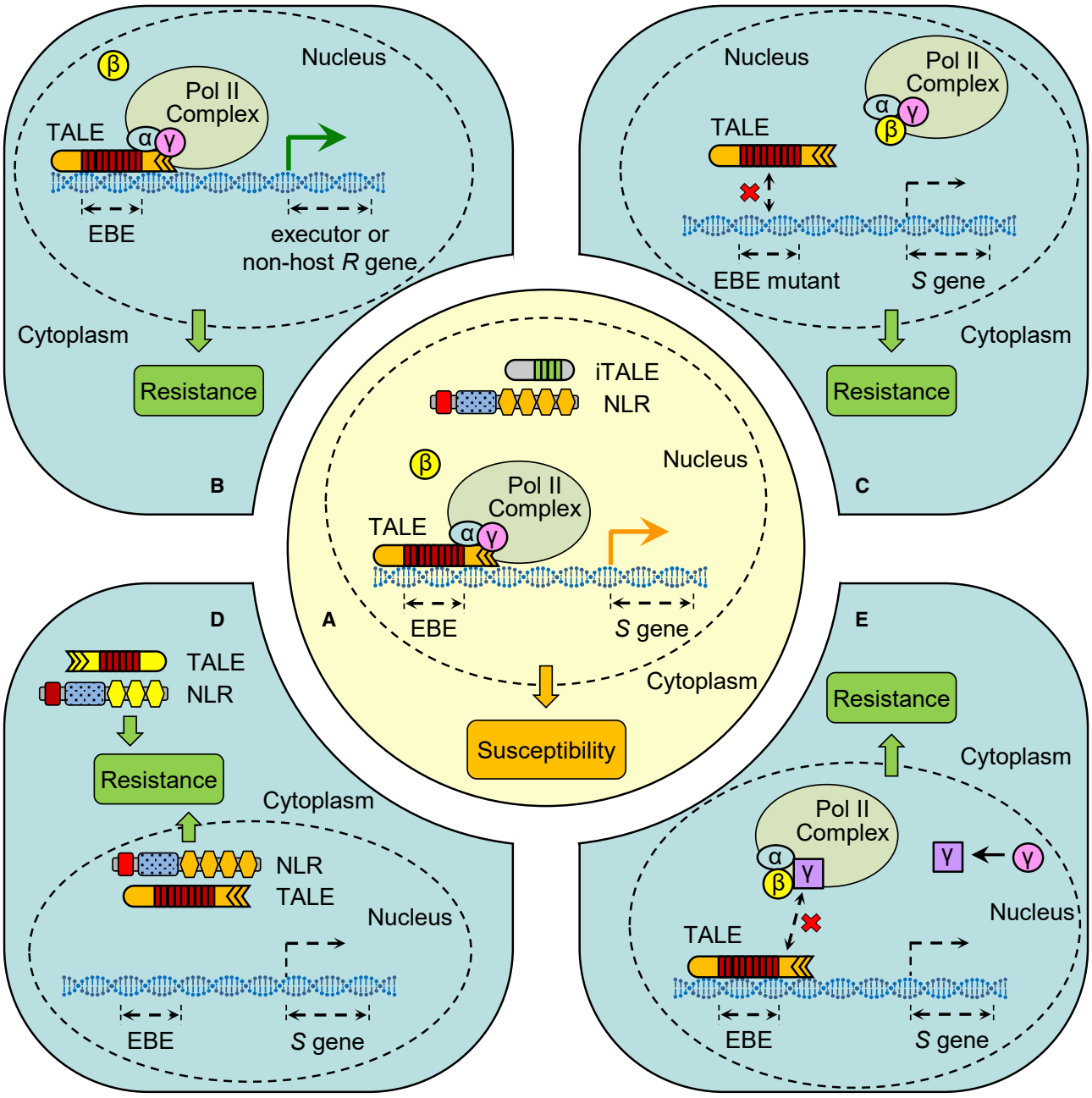

Figure 1. Models of interactions between TALEs and host genes or proteins.

(A) TALEs induce expression of *S* genes in the host nucleus.

(B) TALEs induce expression of *R* genes (executor or non-host *R* genes) in the host (or non-host) nucleus.

(C) EBE mutations attenuate TALE-mediated *S* gene induction in the host nucleus.

(D) NLRs recognize TALEs and trigger resistance.

(E) A mutated TFIIA subunit cannot interact with TALEs, and TALE-mediated *S* gene induction is impaired in the host nucleus.

can spread into the xylem after entering through hydathodes or wounds (Nino-Liu et al., 2006). The *SWEET* genes induced by TALEs translate into sugar transporters in the phloem and translocate the sucrose necessary for *Xoo* (Chen et al., 2010, 2012). However, *Xoc* multiplies mainly in the substomatal cavity and intercellular spaces of the parenchyma (Nino-Liu et al., 2006). Thus, it prefers other types of *S* genes to *SWEET* genes in rice. Plant cell enlargement is an important disease symptom and contributes to the spread of *Xcv*. Induction of the *upa20* gene in pepper cells by AvrBs3 can lead directly to cell hypertrophy (Kay et al., 2007). Similar phenomena have been observed in the induction of *bHLH3*, *bHLH6*, and *CsLOB1*, which lead to water-soaked lesions and pustules in plants (Hu et al., 2014; Schwartz et al., 2017). In wheat, induction of *TaNCED_5BS* by Tal8 from *Xtu* increased the ABA content of infected leaf tissues. The elevated ABA levels can suppress the salicylic acid (SA)-mediated defense pathway and reduce transpiration rate and water loss, which, in turn, promotes the multiplication of *Xtu* (Peng et al., 2019).

S Genes		Encoding products	Host species	TALEs	Pathogen species	References
SWEET encoding	*OsSWEET11/ Os8N3/Xa13*	sugar transporter	rice	PthXo1	*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)	Chu et al., (2006); Yang et al., (2006); Moscou and Bogdanove (2009); Yuan et al., (2011)
	OsSWEET12	sugar transporter	rice	ArtTAL12	artificial TALE	Streubel et al., (2013)
	OsSWEET13/ Os11N3/Xa25	sugar transporter	rice	PthXo2	*Xoo*	Liu et al., (2011); Zhou et al., (2015)
	OsSWEET14/ Os11N3	sugar transporter	rice	AvrXa7, PthXo3, TalC, Tal5	*Xoo*	Antony et al., (2010); Yu et al., (2011); Streubel et al., (2013); Blanvillain-Baufume et al., (2017)
	OsSWEET15	sugar transporter	rice	ArtTAL15	artificial TALE	Streubel et al., (2013)
	MeSWEET10a	sugar transporter	cassava	$TAL20_{Xam668}$	*Xanthomonas axonopodis* pv. *manihotis* (*Xam*)	Cohn et al., (2014)
	GhSWEET10	sugar transporter	cotton	Avrb6	*Xanthomonas citri* subsp. *malvacearum* (*Xcm*)	Cox et al., (2017)
	upa16	sugar transporter	pepper	AvrBs3	*Xanthomonas campestris* pv. *vesicatoria* (*Xcv*)	Kay et al., (2009); Gupta et al., (2021)
Non-SWEET encoding	*upa20*	bHLH transcription factor	pepper	AvrBs3	*Xcv*	Kay et al., (2007)
	bHLH3, bHLH6	bHLH transcription factor	tomato	AvrHah1	*Xanthomonas gardneri*	Schwartz et al., (2017)
	CsLOB1	LOB transcription factor	citrus	PthA4, PthAw, PthA*, PthB, PthC	*Xanthomonas citri* ssp. *citri* (*Xcc*)	Hu et al., (2014)
	TaNCED_5B	9-*cis*-epoxycarotenoid dioxygenase	wheat	Tal8	*Xanthomonas translucens* pv. *undulosa* (*Xtu*)	Peng et al., (2019)
	OsTFIIAγ1	γ subunit of the general transcription factor IIA 1	Rice	PthXo7	*Xoo*	Sugio et al., (2007)
	OsTFX1	bZIP transcription factor	Rice	PthXo6, $TalB_{MAI1}$	*Xoo*	Sugio et al., (2007); Tran et al., (2018)
	OsERF#123	AP2/ERF transcription factor	Rice	$TalB_{MAI1}$	*Xoo*	Tran et al., (2018)
	OsSULTR3;6	sulfate transporter	Rice	Tal2g	*Xanthomonas oryzae* pv. *oryzicola* (*Xoc*)	Cernadas et al., (2014)

Table 1. *S* genes targeted by TALEs.

Some *S* genes are so important that pathogens and plants co-evolve to overcome each other. With *OsSWEET13*, for example, there are several types of EBEs in various rice cultivars that respond to various PthXo2-like TALEs (Xu et al., 2019). In the japonica rice varieties Nipponbare and Kitaake, the $OsSWEET13_{Kit}$ EBE cannot be targeted by PthXo2, PthXo2.1, or PthXo2.2, but it is the target of $Tal5_{LN18}$ and $Tal7_{PXO61}$, which are PthXo2-like TALEs from *Xoo* strains LN18 and PXO61 (Zhou et al., 2015; Xu et al., 2019). In the indica rice variety IR24, the $OsSWEET13_{IR24}$ EBE can be recognized by PthXo2, PthXo2.1, and PthXo2.2 but not by $Tal5_{LN18}$ or $Tal7_{PXO61}$. There are also other types of *OsSWEET13* EBEs in a few varieties that cannot be bound by any of these PthXo2-like TALEs (Xu et al., 2019). The polymorphisms in these EBEs and PthXo2-like TALEs are the direct results of selection during rice–*Xoo* co-evolution.

SOME TALEs INDUCE *R* GENE EXPRESSION AND ACT AS AVIRULENCE FACTORS

Although plants do not have an adaptive immunity system, they have developed other mechanisms after long-term selection and domestication. Various *R* genes are the most important

R Genes		Encoded products	Host species	TALEs	Pathogen species	References
Executor *R* genes	*Bs3*	flavin-dependent monooxygenase (FMO) homolog	pepper	AvrBs3	*Xanthomonas campestris* pv. *vesicatoria* (*Xcv*)	Romer et al., (2007)
	Bs3-E	FMO homolog	pepper	AvrBs3Δ16	*Xcv*	Romer et al., (2007)
	Bs4C-R	unknown executor	pepper	AvrBs4	*Xcv*	Strauss et al., (2012)
	Xa7	unknown executor	rice	AvrXa7, PthXo3	*Xanthomonas oryzae* pv. *oryzae* (*Xoo*)	Chen et al., (2021); Luo et al., (2021); Wang et al., (2021)
	Xa10	unknown executor	rice	AvrXa10	*Xoo*	Tian et al., (2014)
	Xa10-Ni	unknown executor	rice	dTALE-Xa10-Ni	designed TALEs	Wang et al., (2017)
	Xa23	unknown executor	rice	AvrXa23	*Xoo*	Wang et al., (2015)
	Xa23-Ni	unknown executor	rice	dTALE-Xa23-Ni-1, dTALE-Xa23-Ni-2	designed TALEs	Wang et al., (2017)
	Xa27	unknown executor	rice	AvrXa27	*Xoo*	Gu et al., (2005); Romer et al., (2009)
Non-host *R* gene	*NbZnFP1*	C2H2-type zinc-finger protein	tobacco	AvrXa10	*Xoo*	Haq et al., (2022)

Table 2. *R* genes targeted by TALEs.

components of the plant defense process. In some cases, plants even use the EBE targeted by certain TALEs to initiate *R* gene expression (Figure 1; Table 2). These TALE-induced *R* genes usually do not encode products that directly participate in the recognition of corresponding TALEs. Instead, their products trigger a severe defense response and even cell death and are called executors (Bogdanove et al., 2010; Zhang et al., 2015).

Most of the reported executor *R* genes encode very small special proteins (113–164 amino acids [aa]) that have low similarity to known proteins. Rice *Xa27* is the first reported executor *R* gene; it harbors an EBE of AvrXa27 in its promoter compared with the recessive allele (Gu et al., 2005; Romer et al., 2009). A signal-anchor-like sequence in the N terminus is required for XA27 to localize to the apoplast and initiate resistance to *Xoo* (Wu et al., 2008). In the rice cultivar Nipponbare, there are another four homologs of *Xa27*, but none of them can confer resistance when induced by designed TAL effectors (dTALEs) (Li et al., 2013b). *Xa10* and *Xa23* are two homologous executor *R* genes in rice. They trigger resistance through the binding of two *Xoo* TALEs, AvrXa10 and AvrXa23, to the EBEs in their promoters (Tian et al., 2014; Wang et al., 2015). XA10 can form a hexamer and localize to the endoplasmic reticulum (ER) membrane. The XA10 hexamer may function as an ion channel and induce Ca^{2+} depletion in the ER, which results in a hypersensitive response (HR) in rice and tobacco (Tian et al., 2014). XA23 has about 50% identity to XA10 and triggers ER Ca^{2+} depletion and a strong HR in rice and tobacco (Wang et al., 2015, 2017). Because AvrXa23 is found in almost all *Xoo* strains, *Xa23* confers broad-spectrum resistance to BB in rice (Wang et al., 2015). In Nipponbare, there are two homologs of *Xa10* and *Xa23*; one is the recessive allele of *Xa23* (called *Xa23-Ni*), and the other is *Xa10-Ni*. These genes can confer disease resistance after induction of dTALEs and cause ER Ca^{2+} depletion and cell death in tobacco (Wang et al., 2017). *Xa7* has been cloned by three different groups and found to be another executor gene. *Xa7* can be activated by two TALEs, AvrXa7 and PthXo3, which bind to overlapping EBEs in its promoter (Chen et al., 2021; Luo et al., 2021; Wang et al., 2021). The predicted binding scores of *Xa7* EBEs for these two TALEs were at the same level or even better than those of *OsSWEET14* EBEs, which are also their targets. As a result, *Xa7* can effectively protect rice against many *OsSWEET14*-targeting Asian *Xoo* strains (Oliva et al., 2019; Chen et al., 2021; Luo et al., 2021). Induction of *Xa7* is greatly increased under high temperatures, which may be an advantage in rice breeding (Chen et al., 2021). There is an *Xa7* homolog in Nipponbare, but its role in disease resistance is unknown (Luo et al., 2021). Such an executor *R* gene also exists in pepper. *Bs4C-R* encodes a 164-aa executor and contains an EBE for *Xcv TALE-AvrBs4* in the promoter compared with the susceptible allele *Bs4C-S* (Strauss et al., 2012). Similar to XA10 and XA23, Bs4C-R also localizes in the ER membrane and triggers cell death when expressed in tobacco (Wang et al., 2018).

The only exception of the executor *R* gene is *Bs3* in pepper, which encodes an enzyme homologous to flavin-dependent monooxygenases (FMOs) (Romer et al., 2007). *Bs3* is just one of the genes targeted by AvrBs3, and it has an allele called *Bs3-E* that recognizes the truncated AvrBs3 AvrBs3Δ16 (lacking repeats 11–14). Both alleles can induce an HR in tobacco (Romer et al., 2007).

Bs3 and Bs3-E are also classified as group 1 executor proteins (G1EPs), and other executors are classified as group 2 executor proteins (G2EPs) (Ji et al., 2022). Although these executors trigger strong defense reactions and even an HR, the pathways in which they participate may be different. Bs3 has been hypothesized to participate in auxin biosynthesis because of its homology to YUCCA proteins in *Arabidopsis* (Romer et al., 2007). However, it was later found that SA and pipecolic acid (Pip), but not indole-3-acetic acid (IAA), were accumulated during Bs3-mediated cell death. SA and Pip are elicitors of systemic acquired resistance (SAR), and SA is also a downstream signaling compound in many PTI and ETI reactions (Kronauer et al., 2019). By

R Genes		Encoded products or key elements	Host species	TALEs	Pathogen species	References
EBE mutation	*xa13*	EBE mutation in the *OsSWEET11* promoter	rice	PthXo1	*Xoo*	Chu et al., (2006); Yuan et al., (2011)
	xa25	EBE mutation in the *OsSWEET13* promoter	rice	PthXo2	*Xoo*	Liu et al., (2011); Zhou et al., (2015)
	xa41(t)	EBE mutation in the *OsSWEET14* promoter	rice	AvrXa7, PthXo3, Tal5	*Xoo*	Hutin et al., (2015)
	AbLOB1	EBE mutation in *AbLOB1* promoter	(primitive) citrus	PthA4	*Xanthomonas citri* ssp. *citri* (*Xcc*)	Tang et al., (2021)
Mutated TFIIA encoding	*xa5*	mutated γ subunit of the general transcription factor IIA 5	rice	multiple TALEs	*Xoo*	Iyer and McCouch (2004); Jiang et al., (2006); Yuan et al., (2016)
	AbTFIIAγ	mutated γ subunit of the general transcription factor IIA	(primitive) citrus	N/A	*Xcc*	Tang et al., (2021)
NLR encoding	*Bs4*	TNL	tomato	AvrBs4 and derivatives	*Xanthomonas campestris* pv. *vesicatoria* (*Xcv*)	Schornack et al., (2004)
				Hax3, Hax4	*X. campestris* pv. *armoraciae*	Kay et al., (2005)
	Xa1, *Xa2* (*Xa1-2*), *Xa14*, *Xa31(t)*, *Xa45(t)*, *Xo1*	BED-NLR	rice	multiple TALEs, iTALEs/truncTALEs	*Xoo*	Yoshimura et al., (1998); Ji et al., (2016); Read et al., (2016); Ji et al., (2020); Read et al., (2020a); Zhang et al., (2020)
				multiple TALEs, iTALEs/truncTALEs	*Xanthomonas oryzae* pv. *oryzicola* (*Xoc*)	

Table 3. *R* genes attenuating TALE-mediated gene induction.

contrast, most of the G2EPs, except XA27, have been reported to localize in the ER, where they probably form calcium channels (Tian et al., 2014; Ji et al., 2022). The resulting ER Ca^{2+} depletion leads to a Ca^{2+} increase in the cytosol or mitochondria and then to cell death (Tian et al., 2014; Wang et al., 2017). Recent studies have shown that Ca^{2+} influx and then cell death also resulted from activation of the ZAR1 and NRG1.1 resistosomes, which form calcium-permeable channels in the plasma membrane (Bi et al., 2021; Jacob et al., 2021). Further studies are needed to determine whether certain components are shared by these two processes.

Many of these executor *R* gene-inducing TALEs are non-essential for the virulence of *Xanthomonas*, and they function mainly as avirulence factors. However, some TALEs, such as AvrBs3, AvrXa7, and PthXo3, are also involved in virulence determination and induce *S* gene expression (Marois et al., 2002; Yang and White, 2004). For hosts that harbor *R* and *S* genes corresponding to these effectors, immediate HR and cell death are triggered by *R* genes in infected cells to limit the spread of pathogens, and *S* genes in uninfected healthy cells can thus be protected from induction (Luo et al., 2021).

AvrXa10 has been reported to induce a non-host *R* gene, *NbZnFP1*, in tobacco (Haq et al., 2022). An EBE for AvrXa10 has been found in the promoter of *NbZnFP1*, and activation of *NbZnFP1* leads to cell death in tobacco and rice protoplasts (Haq et al., 2022). *NbZnFP1* encodes a C2H2-type zinc-finger protein that differs from XA10; its homolog has been identified in tomato, contains a similar EBE, and can also be activated by AvrXa10 (Haq et al., 2022). The discovery of *NbZnFP1* may increase research interest in non-host *R* genes in many other plants.

MUTATIONS OF KEY COMPONENTS INVOLVED IN TALE-MEDIATED GENE EXPRESSION LEAD TO PASSIVE HOST RESISTANCE

There is a significant difference between *Xanthomonas*–host interactions and other pathosystems, in that recessive *R* gene-mediated passive resistance plays an important part. This is especially notable in *Xoo*–rice interactions. A quarter of the cloned *R* genes for BB are recessive and related to the induction process of *Xoo* TALEs (Figure 1; Table 3).

The first class of recessive *R* genes are produced by mutations in the EBEs of some *S* gene promoters. In rice, promoter mutations in alleles of the three important *S* genes *OsSWEET11* (*Os8N3*/*Xa13*), *OsSWEET13* (*Os12N3*/*Xa25*), and *OsSWEET14* (*Os11N3*) cause them to become recessive *R* genes, *xa13*, *xa25*, and *xa41(t)* (Chu et al., 2006; Liu et al., 2011; Yuan et al., 2011; Hutin et al., 2015; Zhou et al., 2015). Before the RVD code was deciphered, sequence comparison of different *Xa13* and *xa13* alleles suggested that mutation in the sequence corresponding to the −69 to −86 promoter region of *Xa13* was the key determinant of resistance (Chu et al., 2006). This

region was later found to cover the EBE of PthXo1, an important virulence factor in some *Xoo* strains (Moscou and Bogdanove, 2009). Its mutations impair PthXo1 binding and cause loss of susceptibility to *Xoo*; namely, passive resistance (Yuan et al., 2011). Similar results have been found in studies of *xa25*. The *xa25* alleles from various rice cultivars contain polymorphisms in the EBEs of PthXo2 and its homologs, attenuating their binding and the subsequent upregulation of *OsSWEET13* expression (Liu et al., 2011; Zhou et al., 2015). Based on the information gained from cloning of *xa13* and *xa25*, promoter variants were screened in wild and cultivated rice, and a genotype carrying an 18-bp deletion right at the EBEs for AvrXa7, PthXo3, and Tal5 was found in a wild rice accession (Hutin et al., 2015). This deletion prevents *OsSWEET14* from being induced by these TALEs, and the allele was named *xa41(t)* (Hutin et al., 2015).

A typical *R* gene in the second class is the rice *xa5* gene, which encodes the gamma subunit of the basal transcription factor IIA 5 (TFIIAγ5) with a V39E amino acid change (Figure 1) (Iyer and McCouch, 2004; Jiang et al., 2006). The involvement of TFIIAγ5 in TALE-dependent gene expression was first reported when pyramiding *xa5* with *Xa27*. TFIIA$\gamma5^{V39E}$, which is encoded by the *xa5* gene, impairs AvrXa27-mediated induction of *Xa27* in double homozygotes (Gu et al., 2009). Later studies illustrated that the transcription factor binding (TFB) motifs in several TALEs can interact directly with TFIIAγ5 but not with TFIIA$\gamma5^{V39E}$, and this interaction is essential for the activation of host target genes, *S* genes, or executor *R* genes (Yuan et al., 2016; Ma et al., 2018a). Still, some strains can break through *xa5*-mediated resistance in nature. An *xa5*-compatible strain contains a PthXo1 homolog that can induce expression of *OsSWEET11* even in the presence of *xa5* (Carpenter et al., 2020). Other studies showed that TFIIAγ1, the homolog of TFIIAγ5, is recruited by some TALEs to upregulate target genes in the host (Ma et al., 2018b). In another *xa5*-compatible strain, PXO99^{A}, for example, PthXo7 can successfully activate gene expression of *TFIIAγ1*, and TFIIAγ1 then takes the place of TFIIAγ5 in TALE-triggered gene expression (Ma et al., 2018b). In addition, the large subunit of TFIIA in rice, OsTFIIA$\alpha\beta$, also participates in TALE-mediated gene expression. The TFB motifs of the TALEs reconstruct the basal transcription complex by competing with the OsTFIIAβ subunit for interaction with the OsTFIIA (α+γ) subcomplex, mimicking the function of the holo-OsTFIIA in gene transcription (Ma et al., 2018a). *OsTFIIA$\alpha\beta$*-RNAi rice plants also show increased resistance to *Xoo* and *Xoc*, similar to transgenic plants with suppressed *OsTFIIAγ5* expression (Yuan et al., 2016; Hui et al., 2019).

In addition to the *Xoo*–rice pathosystem, other *Xanthomonas–plant interactions also involve* target EBE mutations and TFIIAγ mutation. In Chinese box orange (*Atalantia buxifolia*), two substitutions in the EBE of the *AbLOB1* promoter markedly reduce its promoter activity in the presence of the corresponding TALE, PthA4. This EBE mutation contributes to *Xcc* resistance in *A. buxifolia* (Tang et al., 2021). The TFB motifs of *Xcc* TALEs can interact with CsTFIIAγ, and suppression of *CsTFIIAγ* leads to an obvious decrease in induction of the *S* gene *CsLOB1* and *Xcc* colonization in sweet orange (Huang et al., 2017). Natural variations in *TFIIAγ* revealed that AbTFIIAγ in *A. buxifolia* contains an amino acid residue change and compromises TALE-induced expression of *CsLOB1*, but the TFB motifs of *Xcc* TALEs can interact with AbTFIIAγ *in vitro* (Tang et al., 2021).

NLR PROTEINS ALSO RECOGNIZE TALEs FOR RESISTANCE

The total number of cloned plant *R* genes exceeds 300, and nearly two-thirds of them are nucleotide-binding domain and leucine-rich repeat-containing proteins (NLRs) (Kourelis and van der Hoorn, 2018). Most NLRs can be grouped into two classes based on their N-terminal sequence. If there is a Toll/interleukin receptor (TIR) domain, then the NLR is considered to be a TNL (TIR-NLR); if a coiled-coil (CC) motif is present, then it is a CNL (CC-NLR) (van Wersch et al., 2020). Many NLRs have been found to harbor additional integrated domains (IDs), such as WRKY, kinase, and BED zinc-finger domains; these are termed NLR-IDs (Le Roux et al., 2015; Kourelis and van der Hoorn, 2018; Marchal et al., 2018). NLRs that function in resistance to *Xanthomonas* species are comparatively rare. However, besides *Rxo1* in maize and *Bs2* in pepper that confer resistance to non-TALE avirulence factors, all other NLR-encoding genes recognize TALEs to trigger an immunity response (Figure 1; Table 3) (Schornack et al., 2004; Zhao et al., 2005).

The first characterized NLR–TALE interaction was between *Bs4* in tomato and AvrBs4 or its derivatives from *Xcv* (Schornack et al., 2004). *Bs4* encodes a typical TNL that is probably a cytoplasmic protein and also functions in potato and tobacco (Schornack et al., 2004). Later, it was found that Hax3 and Hax4, TALEs from the Brassicaceae pathogen *Xanthomonas campestris* pv. *armoraciae*, can also be recognized by *Bs4* (Kay et al., 2005).

In rice, several NLR-encoding genes allelic to *Xa1* have been reported recently that can trigger resistance to *Xoo* and *Xoc* in a TALE-dependent manner (Ji et al., 2016, 2020; Read et al., 2020a; Zhang et al., 2020). *Xa1* was cloned from the rice cultivar IRBB1 and encodes an NLR with a BED zinc-finger domain at the N terminus (Yoshimura et al., 1998; Marchal et al., 2018). Many rice *R* genes with different race-specific resistances for BB have been mapped to the *Xa1* locus; even the *Xo1* gene for BLS is reported to be located there (Triplett et al., 2016; Read et al., 2020b; Zhang et al., 2020). *Xa1* can recognize several TALEs and then initiate resistance to *Xoo*, and this process can be attenuated by a special class of TALEs called interfering TALEs (iTALEs) (Figure 1) (Ji et al., 2016). Similar results have also been found in studies of *Xo1*. *Xo1* recognizes diverse TALEs from *Xoo* and *Xoc* and then activates the resistance response, which can be suppressed by truncated TALEs (truncTALEs) (Read et al., 2016; Triplett et al., 2016). iTALEs and truncTALEs are the same TALEs; they lack the AD and some NLSs at the C terminus and have two deletions at the N terminus (Ji et al., 2016; Read et al., 2016). After *Xa2* (*Xa1-2*), *Xa14*, *Xa31(t)*, *Xa45(t)*, and *Xo1* were cloned, all of these genes were found to be *Xa1* allelic genes, but their predicted protein structures were different (Read et al., 2020a; Ji et al., 2020; Zhang et al., 2020). Obviously, other allelic genes, such as *Xa2* (*Xa1-2*), *Xa14*, *Xa31(t)*, and *Xa45(t)*, can also function in the same way as *Xa1* (Ji et al., 2020; Zhang et al., 2020). The differences in protein structure between these allelic genes mainly involve the numbers of central tandem repeats (CTRs)

Class	TALE-likes	Species	Target genes	Host species	References
RipTAL	Brg11 (RTL2)	*Ralstonia solanacearum*	*SlADC1/2*	tomato etc.	de Lange et al., (2013); Wu et al., (2019)
Btl (Bat)	Btl19-13	*Mycetohabitans* (formerly *Burkholderia*) *rhizoxinica*	N/A	*Rhizopus microsporus*	de Lange et al., (2014); Carter et al., (2020)
MOrTL	MOrTL1, MOrTL2	unknown marine bacteria	N/A	N/A	de Lange et al., (2015)
Mho TAL-likes	MhoF, MhoH	*Mycoplasma hominis*	N/A	human	Meygret et al., (2019)

Table 4. Characterized TALE-like proteins (TALE-likes).

and the existence of a linker or intervening motif whose function remains to be fully investigated (Zhang et al., 2020). Recently, a study showed that the resistance triggered by *Xa1* and the suppression mediated by iTALEs are independent of neither TFIIAγ1 nor TFIIAγ5 (Xu et al., 2021b). However, GFP-fused XA1 was found to be localized in the nucleus in rice, indicating that XA1 may interact with TALEs or iTALEs in the nucleus (Xu et al., 2021b).

TALE-LIKE PROTEINS BIND DNA SIMILARLY TO TALEs

In addition to TALE, its homologs, the TALE-like proteins (TALE-likes), have been reported in different microbes. The most well-characterized TALE-likes are some T3SEs from the soil-borne plant pathogen *R. solanacearum* that have almost the same modular architecture as TALEs and are called *Ralstonia* injected protein TALs (RipTALs) (Cunnac et al., 2004; de Lange et al., 2013; Li et al., 2013a). Unlike TALEs, RipTALs contain additional NLSs in the N-terminal region (Li et al., 2013a). The tandem repeats of RipTALs are commonly composed of 35 aa residues and mediate DNA recognition with an RVD code similar to that of TALEs (de Lange et al., 2013). However, the diversity of the repeat region is significantly limited, and cross-activation has been found between different RipTALs and predicted EBEs (Schandry et al., 2016). The RipTAL Brg11 (formerly called RTL2) has been reported to target the tomato (*Solanum lycopersicum*) arginine decarboxylase 1/2 (*SlADC1/2*) genes (Table 4) (Wu et al., 2019). Coincidentally, the EBE for Brg11 is part of the conserved ADC box, which represses transcription of *SlADC1/2*, and Brg11 induces truncated but active *SlADC1/2* mRNAs (Wu et al., 2019). Accumulated arginine decarboxylase can increase putrescine levels in tomato and inhibit the growth of the niche competitor *Pseudomonas syringae* (Wu et al., 2019). Brg11 is a unique effector because it activates a host target gene that is neither an atypical *S* gene nor an *R* gene but benefits the pathogen because of its metabolic function (Wu et al., 2019).

Some TALE-likes are less homologous to TALEs but retain the ability to bind DNA (de Lange et al., 2014, 2015). *Mycetohabitans* (formerly *Burkholderia*) *rhizoxinica*, an endosymbiotic bacterium of the plant pathogen *Rhizopus microsporus*, harbors *Burkholderia* TAL-like (Btl; formerly called Bat) proteins (de Lange et al., 2014; Carter et al., 2020). Btl proteins (Btls) can mediate sequence-specific DNA recognition with the same RVD code as TALEs, but they lack the N and C termini of the TALEs in structure, especially the AD (de Lange et al., 2014; Carter et al., 2020). However, Btl19–Btl13 have been reported to alter the transcriptome and improve the stress tolerance of the host fungus (Table 4) (Carter et al., 2020). Two TALE-likes were even discovered in unknown marine bacteria; they are called marine organism TALE-likes (MOrTLs) (de Lange et al., 2015). Like Btls, MOrTL1 and MOrTL2 are also structurally truncated but bind DNA in accordance with the RVD code (Table 4) (de Lange et al., 2015).

It has been reported that some TALE-likes exist in the human pathogen *Mycoplasma hominis* (*Mho*), which is also endosymbiotic with a human pathogenic protozoan, *Trichomonas vaginalis* (Meygret et al., 2019). The Mho TALE-likes MhoF and MhoH also lack the N-terminal and C-terminal structure of TALEs but share structural similarities with the CRR of TALEs (Table 4) (Meygret et al., 2019).

The natural function of some TALE-likes is unclear, but they are probably of common evolutionary origin and have been well characterized for use in DNA or genome modification (de Lange et al., 2013, 2014, 2015). Their discovery has also expanded our perception of the evolution of TALEs, which is not limited to the pathogen–plant system.

GENETIC MODIFICATION FOR RESISTANCE IMPROVEMENT BASED ON AN UNDERSTANDING OF TALEs

Accumulated research on *Xanthomonas*–host interactions has facilitated the improvement of plant disease resistance. The gene editing tool TAL effector nuclease (TALEN) is a chimeric protein composed of customized CRR repeats from TALEs for target DNA recognition and the catalytic domain of *Fok*I for target DNA cleavage. Its function is largely based on the RVD code of TALEs (Christian et al., 2010). Besides TALEN, the most popular and comparatively simple method is the CRISPR-Cas9 system. After genetic modification, new traits can be introduced into organisms by site-directed mutagenesis or replacement. Both technologies have developed significantly in recent years and have been used in plant breeding research.

A common gene editing strategy for resistance improvement is the modification of EBEs for important TALEs (Figure 2). Before *xa41(t)* was cloned, rice plants with site-directed mutations in the EBEs for AvrXa7, PthXo3, or Tal5 of *OsSWEET14* were generated using TALENs, and the homozygous plants were resistant to *Xoo* strains that carried these TALEs (Li et al., 2012). Later, modifications in the EBEs of *OsSWEET14* were reported in the rice cultivars Kitaake, Zhonghua 11, and Super Basmati using

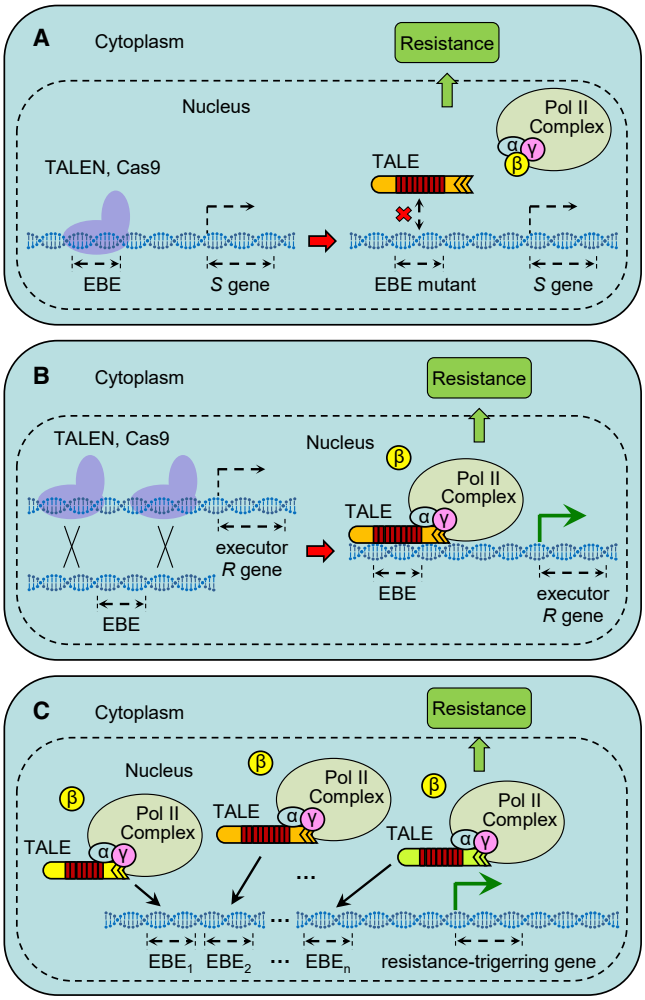

Figure 2. Models of genetic engineering for resistance improvement based on an understanding of TALEs.

(A) EBE mutations of essential *S* genes generated by gene editing tools for resistance improvement.

(B) EBE replacement generated by gene editing tools in recessive alleles of executor *R* genes for resistance improvement.

(C) Promoter traps designed for multiple TALEs and fused to resistance-triggering genes to trigger resistance.

TALEN and the CRISPR-Cas9 system, improving resistance to many *Xoo* strains (Blanvillain-Baufume et al., 2017; Zafar et al., 2020; Zeng et al., 2020). Recently, engineered plants that carry modifications in EBEs of multiple *OsSWEET* genes have been reported and show broad-spectrum resistance to *Xoo* (Eom et al., 2019; Oliva et al., 2019; Xu et al., 2019; Ni et al., 2021). This strategy is also helpful for resistance to other *Xanthomonas* species. To obtain *Xoc*-resistant rice plants, mutations were successfully generated in the EBE of the promoter of *OsSULTR3;6*, a well-characterized TALE-induced *S* gene in BLS disease (Xu et al., 2021a; Ni et al., 2021). In citrus fruit, the EBE for the *Xcc* TALE PthA4 was mutated, and the homozygous plants showed a significant reduction in canker symptoms (Peng et al., 2017).

Another strategy is knocking in the EBEs for specific TALEs in the recessive alleles of executor *R* genes, which harbor the same open reading frames as the corresponding dominant alleles but not the same EBEs in many plants (Figure 2). Very recently, after CRISPR-Cas9-mediated gene replacement, the EBE for AvrXa23 was added to the promoter of the susceptible *xa23* allele in the rice cultivar Nipponbare. The progenies showed high and broad-spectrum resistance to *Xoo* because AvrXa23 is widespread in various strains (Wang et al., 2015; Wei et al., 2021).

A promoter trap is also an option in some cases (Figure 2). An engineered *Xa27* construct was generated by adding six EBEs for *Xoo* and *Xoc* TALEs in the promoter region. The *Xa27* gene can be activated by these TALEs, and the transgenic plants are resistant to many *Xoo* and *Xoc* strains (Hummel et al., 2012). Five different tandemly arranged EBEs for multiple TALEs were also constructed in the promoter of *Xa10* and transformed into the rice cultivars Nipponbare and 93-11, and the transgenic plants showed broad-spectrum resistance to many *Xoo* strains (Zeng et al., 2015). Similarly, a total of 14 EBEs for distinct TALEs were introduced into the promoter of the pepper *Bs3* gene and then fused to the *Xanthomonas* effector-encoding gene *avrGf1*, which can trigger an HR in orange. Transient transformation in citrus leaves showed that the engineered cassette conferred resistance to multiple *X. citri* strains (Shantharaj et al., 2017). Theoretically, the more EBEs added, the better the effect that may be expected for a broad resistance spectrum and durability. However, possibly because of the position, the farther the EBE was from the transcriptional start site, the weaker the induced expression. Thus, there is probably a limit for the EBEs engineered into the promoter of an *R* or *R*-like gene (Hummel et al., 2012; Zeng et al., 2015).

FUTURE CHALLENGES AND PERSPECTIVES

TALEs are unique and essential effectors in *Xanthomonas* species. Usually, their main functions focus on inducing plant genes for pathogenicity and pathogen fitness. Sometimes, plants can mimic the target EBEs for certain TALEs and then initiate an executor or non-host *R* gene-mediated defense response. Mutations of key components involved in TALE-mediated *S* gene expression, such as promoter EBEs or TFIIA subunits, lead to failure of pathogen infection and passive resistance in the host. In addition, plants have evolved some NLRs to recognize multiple TALEs. Accumulated and ongoing research on *Xanthomonas* and TALEs has made them a special model pathosystem and has facilitated our understanding of the diverse interactions between pathogens and plants. Studies of TALEs and characterization of TALE-likes from other microbes have also led to the development of genetic engineering tools. These tools, in turn, have assisted with resistance improvement in breeding. With the help of gene editing technology, we face a new future for the control of plant disease.

However, *Xanthomonas* and host plants evolve with each other in nature; thus, challenges always exist in breeding. The first concern about TALEs is that they could probably rearrange their CRRs, enabling them to bind to new EBEs to reactivate EBE-engineered *S* genes or avoid the induction of EBE-engineered executor *R* genes in plants. This is supported by a report showing that many PthXo2-like TALEs bind to various EBEs of

OsSWEET13 in different rice cultivars (Xu et al., 2019). Tal7b, an AvrXa23-like TALE from the Chinese *Xoo* strain AH28, has been found to contain various RVDs and overcome *Xa23*-mediated resistance by avoidance of trapping by the EBE for AvrXa23 (Xu et al., 2022). Also, there is the possibility that TALEs may target more than one gene in the host genome. After the EBE for TalC was mutated, rice plants did not show increased resistance to *Xoo* carrying TalC, although induction of *OsSWEET14* was impaired (Blanvillain-Baufume et al., 2017). Sometimes, the genome background makes things even more complex. *OsSWEET14* knockout mutant plants showed resistance to the African *Xoo* strain AXO1947 that contains TalC in the rice cultivar Zhonghua 11, in contrast to results obtained in the Kitaake background (Zeng et al., 2020).

Because multiple TALEs can be recognized by NLRs like XA1 or Bs4, rearrangement or deletion of their CRRs does not affect recognition, and TALE-recognizing NLRs are therefore potential tools for disease resistance (Schornack et al., 2004; Ji et al., 2016; Triplett et al., 2016). Although it was reported that *Xa1*- and *Xo1*-mediated resistance could be attenuated by iTALEs or truncTALEs, some strains can still trigger resistance in the presence of iTALEs or truncTALEs (Ji et al., 2016; Read et al., 2016; Zhang et al., 2020). Thus, recognition between these NLRs and TALEs or iTALEs may be more sophisticated than expected. The structures of CNL and TNL have shown that they form resistosomes for immunity (Wang et al., 2019; Ma et al., 2020). When detailed high-order structural information on TALE-recognizing NLRs is available, engineered NLRs that confer a broader resistance spectrum will be possible.

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