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

Biaoming Zhang, Xiaoyuan Han, Wenya Yuan* and Haitao Zhang*
State Key Laboratory of Biocatalysis and Enzyme Engineering, School of Life Sciences, Hubei University, Wuhan 430062, China
*Correspondence: Wenya Yuan (wyyuan@hubu.edu.cn), Haitao Zhang (zht@hubu.edu.cn)
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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). 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
TALEs lead to susceptibility and resistance

In rice, there are also many non-SWEET-encoding S genes during infection with Xoo and Xoc. OsSFTIIA-1 encodes the γ subunit of the general transcription factor IIa and is the target of PthXo7 from Xoo strain PXO99A (Sugio et al., 2007). Induction of OsSFTIIA-1 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 TaIC (Sugio et al., 2007; Tran et al., 2018). TaIBA1 can also activate another transcription factor gene, OsERF123, 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
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).

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.
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.

### Table 1. S genes targeted by TALEs.

| S Genes Encoding products | Host species | TALEs | Pathogen species | References |
|---------------------------|--------------|-------|------------------|------------|
| SWEET encoding OsSWEET11/ OsSN3/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/ OsSN3/Xa25 sugar transporter rice | PthXo2 | Xoo | Liu et al., (2011); Zhou et al., (2015) |
| OsSWEET14/ OsSN3 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 | TAL20Xam668 | 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, TalBMAI1 | Xoo | Sugio et al., (2007); Tran et al., (2018) |
| OsERF#123 AP2/ERF transcription factor Rice | TalBMAI1 | Xoo | Tran et al., (2018) |
| OsSULTR3;6 sulfate transporter Rice | Tal2g | Xanthomonas oryzae pv. oryzicola (Xoc) | Cernadas et al., (2014) |

**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...
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 TALE 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 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 monoxygenases (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 AvrBs3(S 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 piperoc 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

### Table 2. R genes targeted by TALEs.

| R Genes     | Encoded products                        | Host species | TALEs          | Pathogen species | References                      |
|-------------|-----------------------------------------|--------------|----------------|------------------|---------------------------------|
| Executor    |                                        |              |                |                  |                                 |
| Bs3         | flavin-dependent monoxygenase (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    |                                        |              |                |                  |                                 |
| NbZnFP1     | C2H2-type zinc-finger protein           | tobacco      | AvrXa10        | Xoo              | Haq et al., (2022) |
### Table 3. R genes attenuating TALE-mediated gene induction.

| 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) | Schomack et al., (2004) |
| | | | | Hax3, Hax4 | X. campestris pv. armoraciae | Kay et al., (2005) |

| | Xa1, Xa2 (Xa1-2), Xa14, Xa31(t), Xa41(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) |

### 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 resistsomes, 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 Ta5 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. TFIIAγ5, 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 TFIIAγ5V39E, 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, PXO99A, for example, PthXo7 and PthXo10 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, OsTFIIAβ, 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 (β-γ) subcomplex, mimicking the function of the holo-OsTFIIA in gene transcription (Ma et al., 2018a). OsTFIIAβ-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 reduces 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 *BHL* and AvrBs4 or its derivatives from *Xcc* (Schornack et al., 2004). *BHL* 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. *amarioraceae*, 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 (Tripplett 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 (trunc-TALEs) (Read et al., 2016; Tripplett 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)
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 *Raltsonia* 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 (Schantry et al., 2016). The RipTAL Brg11 (formerly called RTL2) has been reported to target the tomato (*Solanum lycopersicum*) arginine decarboxylase 1/2 (*SIADC1/2*) genes (Table 4) (Wu et al., 2019). Coincidently, the EBE for Brg11 is part of the conserved ADC box, which represses transcription of *SIADC1/2*, and Brg11 induces truncated but active *SIADC1/2* 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 (Bt; formerly called Bat) proteins (de Lange et al., 2014; Carter et al., 2020). Bt proteins (Btts) 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, Bt119–Bt113 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 (MOsTALs) (de Lange et al., 2015). Like Btts, MOsTAL1 and MOsTAL2 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 *FokI* 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 *Tal* 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

| Class       | TALE-likes | Species                        | Target genes | Host species | References                        |
|-------------|-----------|--------------------------------|---------------|-------------|-----------------------------------|
| RipTAL      | Brg11     | *Ralstonia solanacearum*       | *SIADC1/2*    | tomato      | 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) |
| MOsTAL      | MOsTAL1, MOsTAL2 | 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).
TALEs lead to susceptibility and resistance

**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 homoyzgous 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...
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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 TaIC was mutated, rice plants did not show increased resistance to Xoo carrying TaIC, 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 AXXO1947 that contains TaIC 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; Tripplet et al., 2016). Although it was reported that Xa7- 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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