Section 5. Advances in Research

Chapter 4. Molecular genetics of bacterial blight and bacterial leaf streak and its impact on future control strategies

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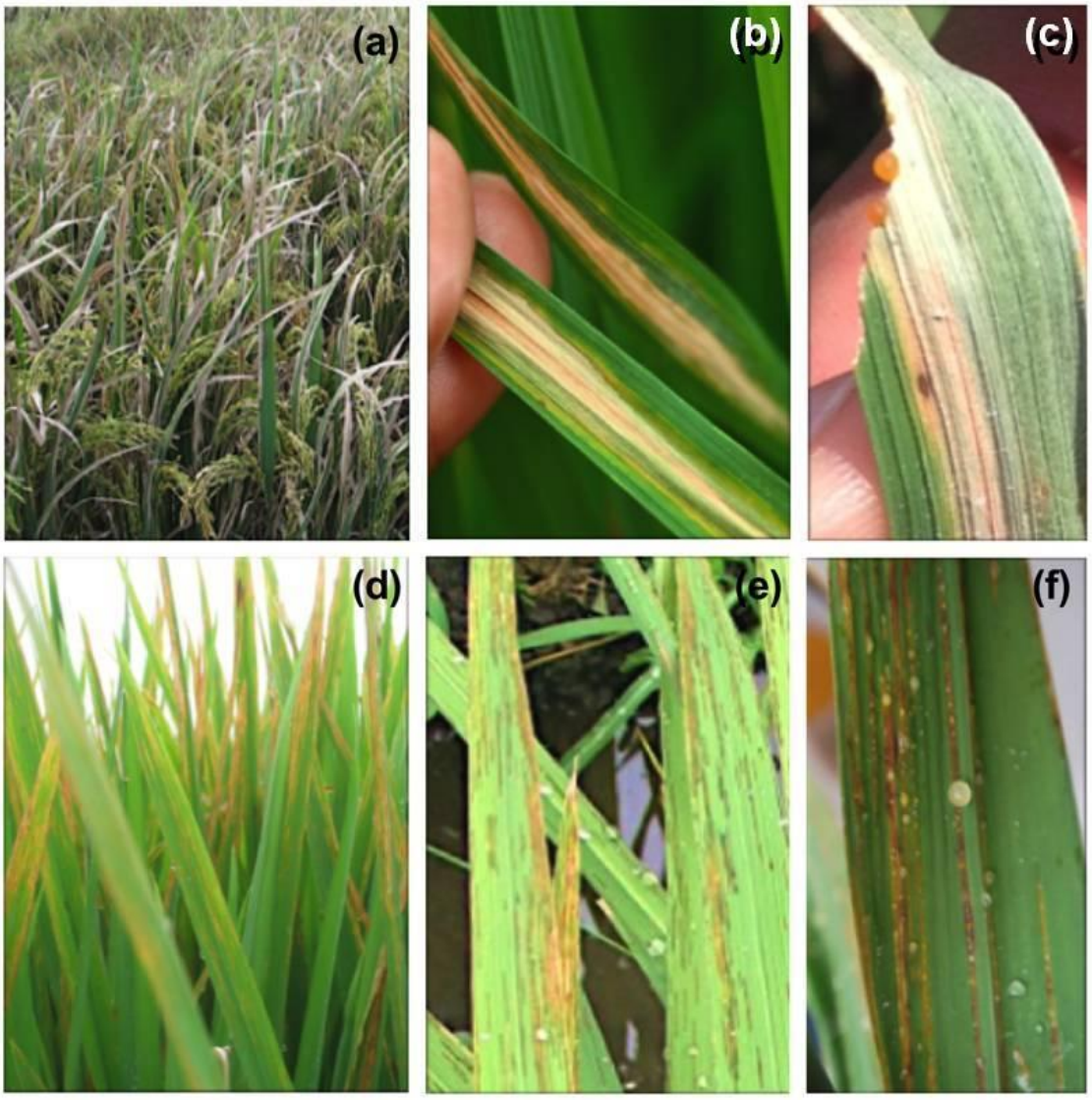
1. Introduction

Xanthomonads cause serious diseases in many economically important crops. Of the genus, *Xanthomonas oryzae* (*Xo*) is potentially the most destructive species due to the global importance of the staple grain it infects, rice (*Oryzae sativa*). Two pathovars within the species, *Xo* pathovar *oryzae* (*Xoo*) and *Xo* pathovar *oryzicola* (*Xoc*), cause two of the most significant bacterial diseases of rice, bacterial blight (BB) and bacterial leaf streak (BLS), respectively (**see Section 2, Chapter 2**). The diseases can be distinguished by the symptoms they cause on their host. Early symptoms of BB are water-soaked streaks that first appear on the margins and tips of rice blades. As infection progresses, the streaks elongate and expand along the veins culminating in tannish-gray to white lesions (MG Figures 1a–c). Rice seedling infection by *Xoo* may lead to a more severe form of BB known as Kresek disease. In the latter, bacteria enter rice seedlings through wounds caused by agronomic practices such as seedling transplanting, which directly expose the plant vasculature to bacterial infection. This often leads to severe wilting and high seedling mortality due to the direct access of the pathogen to the infection court and the higher susceptibility of the host at the young seedling stage. Similar to *Xoo*, *Xoc* infection causes narrow, dark-greenish, water-soaked translucent lesions of various lengths, but unlike *Xoo*, lesions induced by *Xoc* are vein delimited; in later stages, the lesions merge together to form streaks, often exuding bacterial ooze diagnostically referred to as bacterial beads from diseased tissue (MG Figures 1d–f).

In the field, incidence is variable and dependent on host genotype, pathogen inoculum pressure, agronomic practices, and environmental conditions. When disease occurs, typical rice yield reductions due to BB range from 20 to 50% (Ou 1985) but under heavy disease pressure, conducive environmental conditions, and lack of disease resistance in deployed varieties, yield losses due to BB epidemics may reach 70% (Mew and Misra 1994, Reddy et al 1979). BLS is not as destructive as BB, but is increasing in importance, especially in Africa where rice production and consumption are expanding due to the diversification of diets. In this scenario, BLS can limit maximum rice harvest by 20% (Ou 1985). To effectively and sustainably manage these two bacterial diseases, farmers incorporate both genetic resistance in deployed rice varieties and practice cultural disease management tactics. These include good water drainage, optimal plant spacing, timely fertilizer application, and routine field sanitation practices that are region specific (Leung et al 2003). Additional reported management practices include chemical pesticides (Chaudhary et al 2012, Devadath 1989), biological control agents, plant extracts (Vera Cruz et al 1984) and chitosan solutions (Gnanamanickam 2009). Chemical control tactics for BB and BLS, like for many bacterial diseases, are limited and are often expensive and unreliable (Chaudhary et al



MG Fig. 1. Characteristic BB (a, b, c) and BLS (d, e, f) disease symptoms and signs on rice. (a) A farmer's field with 100% BB incidence in Candaba, Pampanga, Philippines. (b) Elongated tannish-gray to white lesions along the leaf veins on an individual rice blade distinctive to BB infection. (c) Bacterial beads of yellow exudate a sign of *X. oryzae* pv. *oryzae* infections on the edge of a rice blade. (d) A rice field displaying typical BLS symptoms. (e) Vein delimited narrow, dark-green lesions of various lengths coalescing to form streaks typical of BLS infection. (f) Bacteria oozing out of symptomatic tissue a sign of *X. oryzae* pv. *oryzicola* infection. Photos courtesy of Casiana Vera Cruz, IRRI.

2012, Devadath 1989, Gnanamanickam et al 1999), especially in the tropics where heavy rainfall, temperatures, and high humidity limit efficacy.

In rice-producing areas where BB occurs, several sources of single-gene disease resistance (*R*-genes) are available and used to manage the disease. Deployment of rice cultivars with introgressed *R*-genes is the gold standard for disease control, having the strongest impact with minimal environmental effects and cost. More than 40 *R*-genes are described for BB management and, as of this time, less than 10 have been cloned (Shamim and Singh 2017, Triplett et al 2014, Valent and Leach 2019). Furthermore, a few *R*-genes such as *Xa4,* have been overcome by emerging pathogen populations in several parts of Asia (Vera Cruz et al 2000). During abiotic stresses such as high temperature and drought, several BB *R*-genes lose function (Dossa et al 2017, Webb et al 2010). The mechanism for this phenomenon is unknown, but it may involve transcriptome cross-talk between stress tolerance and defense responses (Cohen et al 2017). Two BB *R*-genes, *Xa7* and an unknown gene from African rice, retain function at high temperature (Dossa et al 2016, Webb et al 2010). Future studies will elucidate the mechanism of resistance conferred by these two genes at high temperatures. Meanwhile, only a few single *R*-genes that are effective against *Xoc* have been identified, including *Rxo1* (Zhao et al 2004), which was cloned from maize and characterized for effectiveness in rice (Han et al 2015, Shidore et al 2017, Triplett et al 2016b), and a newly discovered *R*-gene, *Xo1*, identified from the American heirloom variety of rice, Carolina Gold (Triplett et al 2016a).

2. Biology of *Xanthomonas oryzae*

Although *Xoc* and *Xoo* are highly related, over 85% DNA homology (Bogdanove et al 2011, Triplett et al 2011, Vera Cruz et al 1984), they each have distinct pathogenic lifestyles and can be differentiated on the basis of a set of phenotypic traits. Each pathovar has specialized to thrive in different plant tissues and invade rice through distinct infection courts. *Xoo* is a vascular pathogen that primarily enters rice via wounds or hydathodes (Ou 1985). Under high humidity, guttation droplets emerge at the leaf surface from the hydathode pores where they may encounter epiphytic *Xoo* cells. As humidity decreases, water droplets retreat into the plant epithem, which is directly connected to the xylem vessels, carrying bacterial cells into the host vasculature (Curtis 1943, Mew and Vera Cruz 1979). Once inside the host, *Xoo* multiplies and secretes pathogenicity and virulence factors that lead to the primary BB disease symptoms, white tan lesions along the leaf margins and veins.

Unlike *Xoo, Xoc* primarily infects the host through stomata, colonizing the host mesophyll and causing the vein-delimited streaks that give the disease its name (Ou 1985). In the advanced stages of disease and extensive tissue damage, *Xoc* may enter the host vasculature, likely because of spatial restrictions in the host tissue. Natural wounds caused by agronomic practices and environmental conditions typical to the monsoon seasons of the tropics, high wind and rain, also contribute significantly to *Xoo* and *Xoc* epidemics by providing direct access for bacteria. Recent microscopic studies focusing on plant physiology-*Xanthomonas* interactions at hydathodes suggest that xylem dwelling *Xanthomona*s have an innate tendency to react to specific signals arising from hydathodes and not stomata (i.e., chemical stimuli, microclimate, small

molecules) (Cerutti et al 2017). What these key signals are and the underlying genetic elements that link them to *Xoo* and *Xoc* tissue specialization remain to be resolved.

3. Distribution and taxonomic diversity

Xo pathovars are endemic to Asia and parts of West Africa; not surprisingly, their geographic distribution largely correlates with that of rice. *Xoo* was first isolated in Japan in 1884 (Ou 1973) and since has been reported in multiple tropical and temperate geographic locations (Adachi and Oku 2000, Niño-Liu et al 2006, Verdier et al 2012a). BB is favored by high temperature and high humidity, climatic factors typical of the tropics and subtropical regions of Asia, Africa, Northern Australia, Latin America, and the Caribbean, although reports of the presence of the disease in Latin America are limited and inconclusive (Mew et al 1993). The disease had a restricted geographic distribution until the early 1960s, when its distribution was propelled by the release and geographic movement of high yielding rice hybrids lacking BB resistance. Introduction of these hybrids into new locations is thought to have contributed to bacterial dissemination and increased inoculum level. Furthermore, shifts in cultural agronomic practices, such as increase in fertilizer use, also contributed to the geographic expansion of the disease (Verdier et al 2012a).

Thirty-four years after BB and its causative agent, *Xoo*, were first described, *Xoc* was isolated and described to cause a separate disease, i.e., BLS (Ou 1973). It was not until 1957, however, when it was reclassified as *Xoc,* that it was distinguished as a separate disease and causative agent from *Xoo* (Ou 1985). Relative to BB, BLS has a lower disease incidence, severity, and distribution worldwide (Gonzalez et al 2007), but unlike BB, sources of resistance for BLS are scarce. BLS was largely restricted to Southeast Asia, parts of northern Australia, and three major rice-growing countries in Africa (Senegal, Nigeria, and Madagascar) (Gonzalez et al 2007). However, in recent years and despite strong quarantine regulations, the disease has been increasing in frequency and geography in both Asia and Africa, with recent reports of BLS in Kenya, Mali, and Burkina Faso (Onaga et al 2018; Verdier et al 2012a; Wonni et al 2011, 2014). The geographic expansion of BLS is attributed to rice intensification, deployment of susceptible rice varieties into new regions, pathogen evolution, and changes in global climate patterns (Verdier et al 2012a). Although reported to occur in the Americas, neither *Xoo* or *Xoc* are considered endemic (Guevara and Maselli 1999, Lozano 1977), and are likely present due to transient introductions on seed.

In 1987, weakly virulent, endemic *Xo*-like strains referred to as US *Xo,* were isolated from rice leaves showing symptoms similar to BB in the southern United States (Jones et al 1989). Morphological and serological tests identified these strains as *Xo* but they were clearly distinct from pathovars *oryzae* or *oryzicola* (Jones et al 1989). Two of these strains (*Xo* X11-5A and X8-1A) have now been sequenced, and only 90 and 92% of the predicted ORF in the US *Xo* strains have predicted homologues in *Xoo* strain PXO99A and *Xoc* strain BLS256, respectively. Genetic and comparative genomic analyses classified the US *Xo* strains into a genetically distinct clade within *Xo* species (Ryba-White et al 1995, Triplett et al 2011). The origins and the biology of the US *Xo* strains remain to be elucidated, but their initial characterization has revealed more structural and functional diversity to the species. The US *Xo* strains have a functional Type III Secretion System (T3SS), but lack the characteristic transcription activator-like

(TAL) effectors present in many Xanthomonads (Triplett et al 2011). The lack of TAL effectors made the US *Xo* strains a valuable genetic tool to the scientific community, enabling the study of individual TAL effectors and their unique contribution to virulence and pathogenicity (Triplett et al 2016a, Verdier et al 2012b). The US *Xo* strains carry homologues of 20 non-TAL effectors, most of them *Xanthomonas* outer proteins (Xops). The role of these effectors in US *Xo* strains remains unknown, but it will be interesting to see how and if they contribute to the ecological fitness of these strains in the natural environment. Interestingly, both sequenced US *Xo* strains have a functional *bla* gene, which codes for ampicillin resistance, whereas *Xoo* and *Xoc* strains are ampicillin sensitive. How and why these strains acquired this gene are unknown but the finding suggests that US *Xo* strains have been subjected to unique environmental pressures that have contributed to their adaptation and divergence in these specific geographic locations.

Historical classification of *Xo* strains has been through both phenotypic and genotypic methods, including fatty acid profiles, protein fingerprinting, restriction fragment length polymorphisms (RFLP) analysis (Leach et al 1992), multilocus sequence typing (MLST) (Maiden et al 1998), pathovar-specific monoclonal antibodies (Benedict et al 1989), and phage typing (Mew 1993). In addition, *Xoo* isolates were evaluated for virulence on a set of near-isogenic lines carrying one or multiple *R*-genes to determine race classification (Mew 1987, Ogawa et al 1991). In recent years, genomic approaches, including whole genome sequencing and comparative genomic studies, have provided: 1) accurate classification of the pathogen; 2) insight into the evolution, biology, and gene repertoires of *Xo*; 3) genetic markers for diagnostics; and 4) insight into how *Xo* interacts with rice. As of 10 June 2018, 135 *X. oryzae* genomes have been sequenced and are publicly available. Of these, 25 are complete genomes, 14 of *Xoo* and 11 of *Xoc* (MG Table 1). The remaining 110 are draft genomes.

Many of these draft genomes were sequenced prior to the advent of single-molecule real-time (SMRT) sequencing technology, commonly referred to as PacBio. This technology provides the robust, long-read sequencing to accurately sequence and assemble the tandem repeats characteristic of the TAL effectors common to *Xoo* and *Xoc* and to discern the diversity and genome distribution of TAL effectors within *Xoo* genomes (Booher et al 2015, Doucoure et al 2018, Quibod et al 2016, Wilkins et al 2015). The number of publicly available complete genomes of *Xo* will undoubtedly increase as long-read sequencing technologies, such as SMRT, improve and sequencing costs decrease, which will further our knowledge on the genomics of *Xo*.

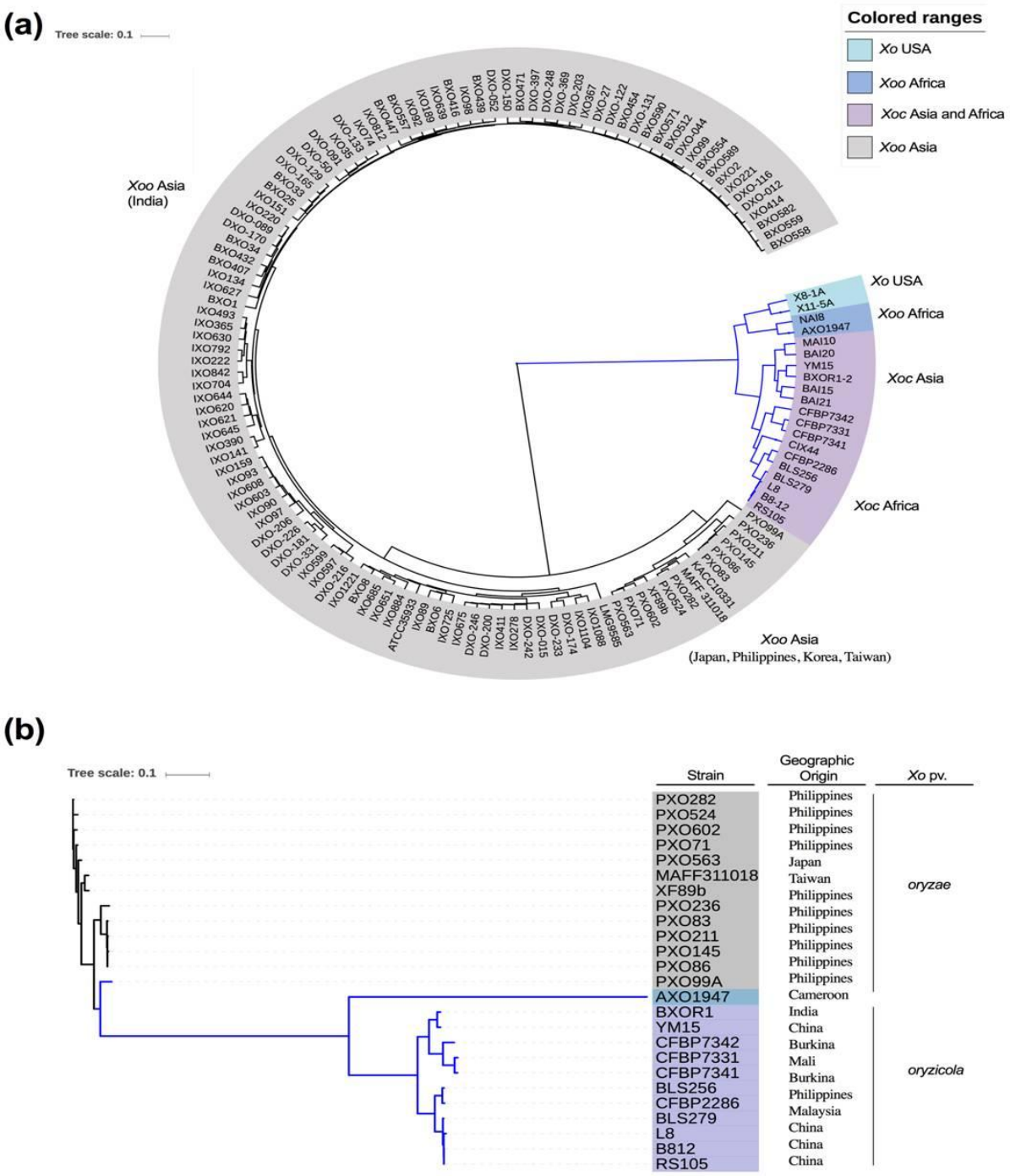
The ability to sequence and study the full genetic complement of an organism has provided insight into the evolutionary history and relationships among species as well as individual isolates within a species. Using an MLST analysis that compared sequences of nine housekeeping genes, the diversity and relationships among and between weakly virulent US *Xo* strains and highly virulent *Xoo* and *Xoc* strains were revealed (Triplett et al 2011). In a more recent phylogenetic analysis, draft genomes and the AutoMated PHylogenOmic infRrence (AMPHORA) pipeline (Wu and Eisen 2008) were used to characterize 100 *Xoo* isolates of Indian origin in reference to previously sequenced *Xo* strains (Midha et al 2017). The 31 genome-wide genetic markers identified in this analysis provided a strong phylogenetic signal, allowing for the differentiation between highly similar strains, i.e., those with average nucleotide identity (ANI) values of >99%.

MG Table 1. Publicly available complete genome sequences of *X. oryzae* as of 10 June 2018.

Strain	Origin	Race	Reference
X. oryzae* pv. *oryzae			
KACC 10331	Korea	1	(Lee et al 2005)
MAFF 311018	Japan	1	(Ochiai et al 2005)
PXO99A	Philippines	6	(Booher et al 2015; Salzberg et al 2008)
PXO83	Philippines	2	(Grau et al 2016)
AXO1947	Cameroon		(Huguet-Tapia et al 2016)
PXO71	Philippines	4	(Quibod et al 2016)
PXO211	Philippines	8	(Quibod et al 2016)
PXO236	Philippines	5	(Quibod et al 2016)
PXO282	Philippines	1	(Quibod et al 2016)
PXO524	Philippines	9b	(Quibod et al 2016)
PXO563	Philippines	10	(Quibod et al 2016)
PXO602	Philippines	3c	(Quibod et al 2016)
PXO145	Philippines	7	(Quibod et al 2016)
PXO86	Philippines	2	(Booher et al 2015)
XF89b	Taiwan		**PRJNA284661**
X. oryzae* pv. *oryzicola			
BLS256	Philippines		(Bogdanove et al 2011)
CFBP7342 (BAI10)	Burkina		(Booher et al 2015)
YM15	China		**PRJNA248159**
B8-12	China		(Wilkins et al 2015)
BLS279	Philippines		(Wilkins et al 2015)
BXOR1	India		(Wilkins et al 2015)
CFBP7331 (MAI10)	Mali		(Wilkins et al 2015)
CFBP7341 (BAI5)	Burkina		(Wilkins et al 2015)
L8	China		(Wilkins et al 2015)
RS105	China		(Wilkins et al 2015)
CFBP2286	Malaysia		(Wilkins et al 2015)

Both studies contribute to the **most recent comprehensive *Xo* phylogenetic tree available** for the *Xo* species (MG Figure 2a; modified from NCBI, 10 June 2018). As more strains from different geographic origins are sequenced, this tree will undoubtedly change, and reveal more of the evolutionary history of this important bacterial pathogen.

The current tree supports two distinct phylogenetic linages that somewhat correlate to a geographic origin of strains and pathogen life style (pathovar) (MG Figure 2a). The Asian *Xoo* lineage is comprised of 116 strains that splits into two sister groups. One sister group (clade) includes all 101 strains of Indian origin. In addition, this clade includes the only sequenced *Xo* strain of South American origin in the NCBI database, LMG9585, isolated in Santa Cruz, Bolivia. The second clade includes 14 Asian *Xoo*



MG Fig. 2. Phylogenetic tree of the 134 publicly available *X. oryzae* genomes, modified from NCBI Genome Tree report. (a) Evolutionary relationship of all draft and complete genomes of *Xoo*, *Xoc,* and US *Xo* in the NCBI database as of 10 June 2018. Tree shows two major lineages, one groups all Asian *Xoo* isolates, including those isolated in Japan, Philippines, Korea, Taiwan, and India. The second branch is more heterogeneous and encompasses African *Xoo,* African and Asian *Xoc,* and US *Xo* isolates. (b) The evolutionary relationship among *Xoo* and *Xoc* isolates using complete genome sequences (left) including bacterial name, geographic origin, and pathovar designation (right). All modified from NCBI, 10 June 2018.

strains from different countries surrounding the East China and South China Seas (MG Table 1). The second and more diverse lineage in the *Xo* species encompasses African *Xoo,* African and Asian *Xoc* and US Xo strains. This lineage also splits into two sister groups, with the surprising revelation that one clade includes both US *Xo* and *Xoo* African stains (Gonzalez et al 2007; Midha et al 2017; Soto-Suarez et al 2010; Triplett et al 2011, 2014). This suggests that African *Xoo* strains are more genetically similar to the weakly virulent US *Xo* than to Asian *Xoo* strains (Triplett et al 2011). The second clade includes all publicly available *Xoc* isolates sequenced to date, showing that *Xoc* isolates split into clades that correlate to a strains geographic origin, African vs. Asian (MG Figure 2b).

4. Diagnostics

Plant disease diagnosis is one of the many fields that has greatly benefited from the genomic revolution. The ease and speed in which a bacterial isolate can be sequenced and its whole genome compared to previously sequenced organisms allows for the generation of sensitive, robust and accurate molecular diagnostic tools. Uniqprimer, a software pipeline, which was used in the design of species and pathovar-specific primers for *Xoo, Xoc*, the US *Xo*, and other genera (Ash et al 2014; Lang et al 2014. 2017; Langlois et al 2017; Triplett et al 2015), has recently been deployed as a user-friendly internet tool in Rice Galaxy (Juanillas et al 2018). The tool allows for rapid comparative genome analysis for the design of primer sets for PCR assays that aid in the detection and diagnosis of any bacterial taxa in plant tissue, including seed (Vera Cruz et al 2017).

The most effective assay for the detection and differentiation of *Xo* isolates is the Multiplex PCR designed by Lang and co-workers (MG Table 2, modified from Lang et al 2010, Vera Cruz et al 2017). The Multiplex protocol is composed of four primers pairs, three of which differentiate between *Xo*, *Xoo* and *Xoc*. The fourth primer pair is an

MG Table 2. Multiplex PCR Primers for *X. oryzae* pathovars detection and differentiation. Modified from Lang et al (2010) and described in detail in Vera Cruz et al (2017).

***Xo* specificity**	**Primer pairs**	**Sequence (5'-3')**	**PCR product size (bp)**
X. oryzae	*Xo*3756F	CATCGTTAGGACTGCCAGAAG	
	*Xo*3756R	GTGAGAACCACCGCCATCT	331
X. oryzae pv.	*Xoo*80F	GCCGCTAGGAATGAGCAAT	
Oryzae	*Xoo*80R	GCGTCCTCGTCTAAGCGATA	162
X. oryzae pv.	*Xoc*3866F	ATCTCCCAGCATGTTGATCG	
Oryzicola	*Xoc*3866R	GCGTTCAATCTCCTCCATGT	691
16S rDNA	S-Univ-0008-a-S-19	GAGTTTGATCCTGGCTCAG	
	S-Univ-1528-a-A-17	AAGGAGGTGATCCAGCC	1538

internal control that amplified a region of the universal bacterial 16S rDNA (Vera Cruz C 2017). These tools are important to detect the presence or absence of pathogenic agents in symptomatic and asymptomatic plant tissue. This is of high importance for *Xoo* and *Xoc* due to their designation as select agents by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 of the United States Department of Agriculture (USDA). Additionally, they are listed as quarantine pests by the European and Mediterranean Plant Protection Organization. The tight regulation and strict exclusion protocols prescribed for *Xo* are designed to protect the local agriculture and natural landscapes by excluding these destructive bacterial pathogens from the Americas and Europe.

5. Disease management and pathogen evolution

As different evolutionary forces allow the pathogens to overcome deployed resistance genes, comparative genomics studies will provide the tools to identify the varying alleles responsible for the population shifts that lead to disease epidemics. This knowledge can help accelerate development of strategies to detect and manage disease outbreaks. The ecological and epidemiological outcome of plant-pathogen interactions provides the basis for a coevolutionary arms race where host and pathogen respond to selective biotic and abiotic pressures (Jones and Dangl 2006). Increased virulence of a bacterial strain exerts a strong selective pressure on the host. In response, the host increases or alters its defense response to counter the breach of its defenses. The host now exerts a selective pressure on the pathogen population to evolve and overcome the newly adapted immune response. In a natural setting, this arms race spans long time periods and large spaces, but in an agronomic setting, this phenomenon is accelerated largely by human manipulation and monoculture. This is exemplified in the recent analysis of 1,719 *Xoo* strains from the International Rice Research Institute strain collection (Quibod et al 2016). Here, evidence is presented for the *Xoo* population shift observed in the Philippines in the early 1970s, where *Xoo* Race 1 (*Xa4* incompatible) was displaced by Race 2 (*Xa4* compatible) due to widespread deployment of rice varieties with the *R*-gene *Xa4* (Mew et al 1992, Quibod et al 2016). Additional selective pressures, such as newly implemented management practices, can disrupt race composition, as observed by the displacement of all *Xoo* races, except Races 1 and 3, by Race 9 starting in the early 1990s as observed by Vera Cruz et al (2000) and Ponciano et al (2003).

Effective and durable disease resistance is dependent on a thorough understanding of the bacterial population structure of a pathogen. Long-term success largely depends on the virulence and pathogenicity factors harbored within and across the pathogen population and the emergence of more aggressive races of the pathogen. In *Xo*, this largely depends on the repertoires of pathogen effectors, such as the TAL effectors that dominate the effector complements of *Xoo* and *Xoc* (see below for a discussion of TAL effectors). Prior to the sequencing revolution, effector complements had to be determined via phenotypic tests and race classification.

Today, TAL effector repertoires are identified from complete genome sequences, and from these susceptibility profiles can be associated with rice varieties. To this end, recent comparative genomic studies explored the complete genomes of 10 ecologically distinct *Xoo* (Quibod et al 2016) and 10 geographically diverse *Xoc* strains (Wilkins et al

2015). From these, a total of 431 TAL effectors were identified (Quibod et al 2016; Wilkins et al 2015). From *Xoo*, 181 *Xoo* TAL effectors were classified into 30 TAL effector families based on RVD sequence composition. This clustering suggests that members within one TAL effector family (TEF) converge on similar gene targets in the rice genome. Of the complete repertoire of *Xoo* TAL effectors (called a TALome), 11 have been functionally characterized: *pthXo1*, *pthXo6*, *tal9A*, *avrXa23, avrXa27*, *tal3b*, *pthXo2/avrXa25*, *avrXa10*, *avrXa7*, *pthXo7,* and *tal3a* (Quibod et al 2016). These TAL effectors cover 11 of the 30 proposed TAL effector families, leaving more than half of the TEF uncharacterized. This raises the questions: *what is the role of these uncharacterized effectors in Xo virulence and what are their host targets?*

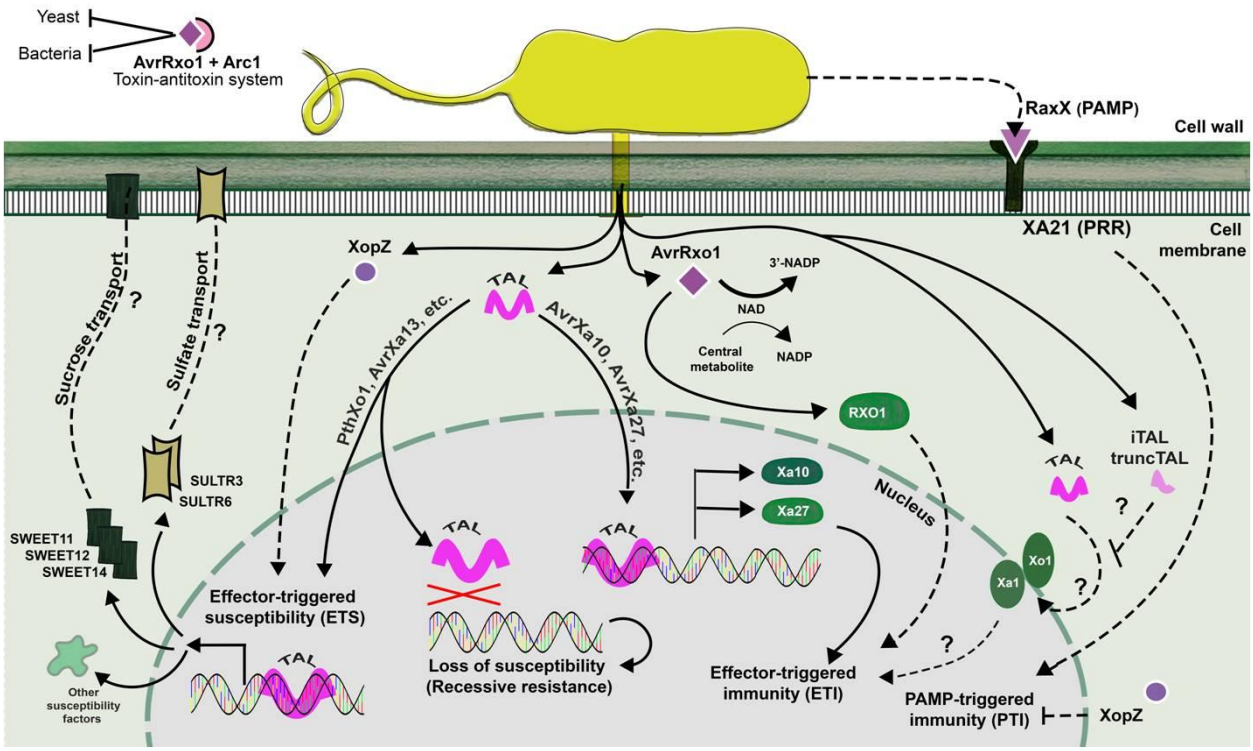
The TALome of *Xoc* is comprised of 250 TAL effectors identified from complete genome sequences of 10 *Xoc* strains (Wilkins et al 2015). Each strain harbored from 17 to 27 TAL effectors. In this study, TAL effector predictive software was coupled with transcriptomic data to find that one TAL effector could potentially target and activate more than one gene. Li et al (2018) recently showed that TAL effector PthXo3 from *Xoo* strain JXOV binds and activates multiple genes in rice, in support of the hypothesis that one TAL effector targets multiple susceptibility genes, each contributing to pathogen virulence quantitatively.

6. Genetics of avirulence and virulence of *Xo*-rice interactions

Plant pathogenic bacteria infect their host using a variety of virulence factors that are tightly regulated in response to environmental stimuli. Critical to *Xo* virulence are *the Xanthomonas* outer proteins (Xops) and the Transcription Activator-Like effectors (TAL) (Triplett et al 2014) (MG Figures 3 and 4). Both *Xoo* and *Xoc* strains house a large and diverse repertoire of these effector genes. Some have major effects on the host and, thus, contribute to the “all or nothing” phenotype observed in pathogenicity studies: long lesion lengths or plant cell death (Bai et al 2000, White and Yang 2009). Other effectors which differently and specifically contribute to pathogen virulence, also contribute to bacterial fitness (Bai et al 2000, Ponciano et al 2003).

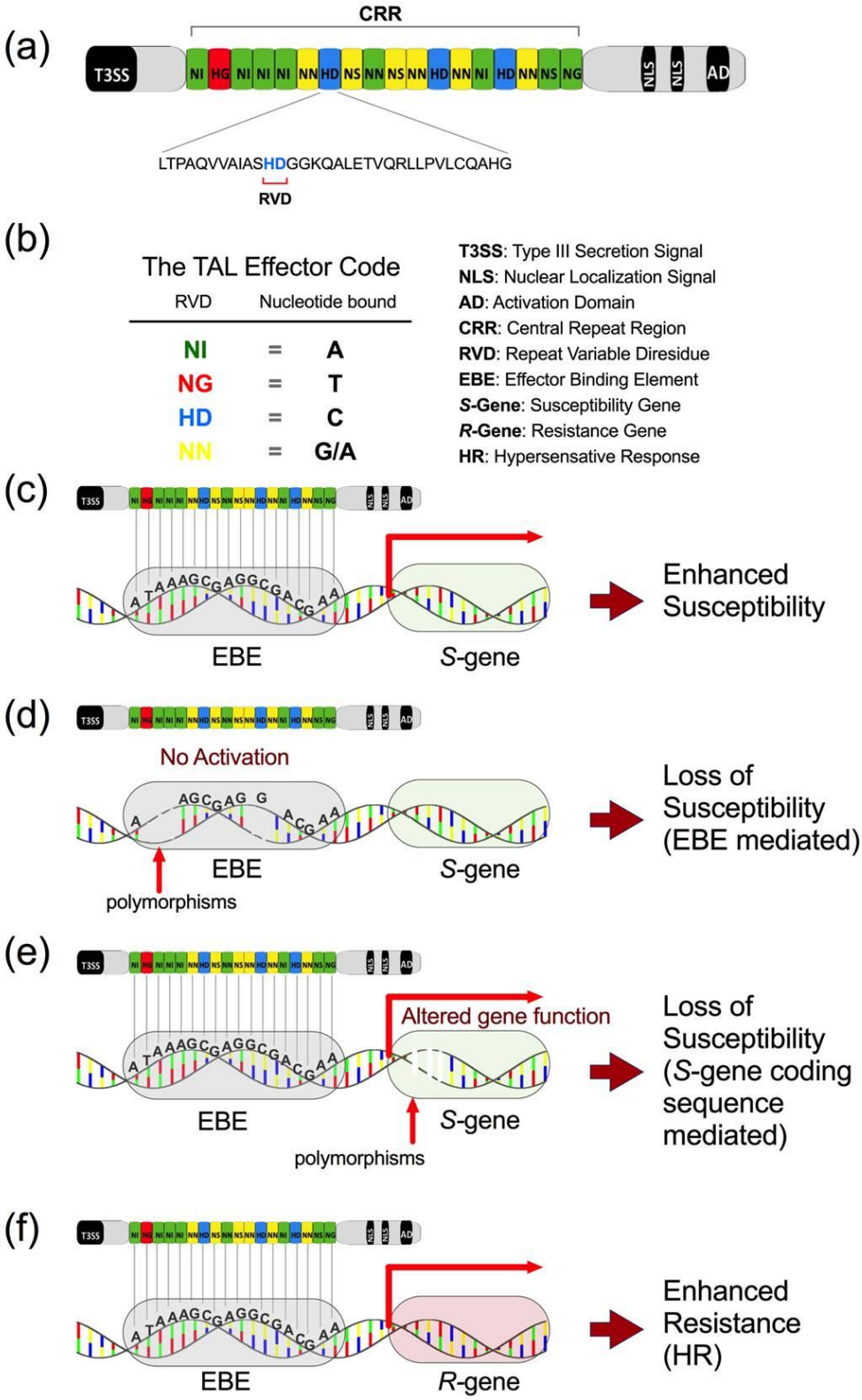
In many plant pathogenic bacteria, Xop effectors or their homologues significantly contribute to virulence (Furutani et al 2009, Song and Yang 2010). In *Xo*, however, *Xop* genes contribute little or none to pathogen virulence. Of the 18 Xop effectors identified in *Xoo* strain PXO99A, only one, *XopZ*, significantly contributed to virulence (Song and Yang 2010). Detailed characterization of this effector confirmed its role in suppression of pattern-triggered immunity (PTI), the first tier of defense of the plant immune system (Jones and Dangl 2006) (MG Figure 3). PTI is triggered by conserved microbe-associated molecular patterns (MAMPs), such as the bacterial flagellum, which are detected by pattern recognition receptor (PRRs). This first round of defense can be overcome by the bacterial T3S effectors, which suppress PTI and lead to effector-triggered susceptibility, which is how many of the TAL effectors function (MG Figure 3). Plants, in turn, adapt and evolve to recognize effector proteins via *R*-genes to trigger effector-triggered immunity.

During *Xo*-rice interactions, TAL effectors act as activators of host genes, utilizing four functional protein domains; a T3SS, a nuclear localization signal (NLS), a central repeat region (CRR) and activation domain (AD) (MG Figure 4a). The N-terminal T3SS



MG Fig. 3. Resistance and susceptibility mechanisms of *Xo*-rice interactions. Basal resistance or pattern triggered immunity (PTI) can be activated by interaction of bacterial pathogen associated molecular patterns (PAMPs) with membrane spanning PRRs. One example of this is *Xa21*, a PRR that recognizes the sulphated RaxX protein that is conserved in *X. oryzae* isolates. TAL effectors produced by *X. oryzae* pv. *oryzae*, such as PthXo1 and AvrXa13, induce effector-triggered susceptibility (ETS) by activating transcription of susceptibility (S) genes that encode membrane localized sugar transporters, such as *SWEET11*, *SWEET12*, and *SWEET13*. Alternatively, *Xoc* derived TAL effectors activate transcription of *SULTR3* and *SULTR6*, the sulfate transporter genes. Some *X. oryzae* TAL effectors, like AvrXa27 and AvrXa10, activate plant executor genes *Xa27* and *Xa10* triggering effector triggered immunity (ETI), or cell death. ETI can also be activated in rice by AvrRxo1 through interaction with the transgenically expressed NLR protein RXO1.

signal directs translocation of the effector from the bacterial cell to the plant host cytoplasm via the T3SS (Buttner and Bonas 2003). Once in the host cytoplasm, the C-terminal NLS direct the effectors into the host nucleus. DNA binding is dictated by the CRR and a C-terminal AD activates host gene transcription. The CRR is made up of a variable number of 34 amino-acid residue repeats with each repeat binding to a single nucleotide (MG Figures 4a and b). Nucleotide specificity is achieved via the repeat variable diresidue (RVD), hypervariable residues at positions 12 and 13. RVD to base pair specificity has been well characterized and has allowed for the prediction of TAL effector targets sites on the genomes of plant hosts (Boch et al 2009, Moscou and Bogdanove 2009) (MG Figure 4b). In addition to the C-terminal AD, a transcription factor-binding domain is also required for activation of the host genes (Yuan et al 2016). While the activation mechanism is not yet understood, it was recently found that TAL effectors are able to directly interact with host basal transcription factor IIA α and γ subunits (Ma et al 2018).



MG Fig. 4. Schematic representation of a TAL effector and mechanism of action with rice. (a) A TAL effector model featuring the type 3 secreted signal (T3SS), nuclear localization signal (NLS) and the activation domain (AD). (b) The TAL effector code and acronym definition. (c) TAL effectors bind to their cognate effector binding element (EBE) in the promoter region of the target *S*-gene leading to enhanced susceptibility. Polymorphisms in the (d) EBE or (e) coding sequence region disable activation or function of the *S*-gene by the cognate TAL effector contributing to resistance through loss of susceptibility. (f) TAL effectors bind to their cognate effector binding element (EBE) in the promoter region of the target *R*-gene leading to enhanced resistance through activation of executor *R*-genes leading to HR.

TAL effectors can act as both susceptibility-inducing effectors in compatible interactions and avirulence factors in incompatible interactions (MG Figures 3 and 4) (Doyle et al 2013, Zhang et al 2015). As primary virulence factors for *Xo,* they activate expression of susceptibility (S) genes, to promote bacterial growth, tissue colonization, and disease symptomology. In disease-inducing interaction, the RVDs bind sequences in the target host gene promoter located upstream of an *S*-gene, termed the effector-binding element (EBE) (MG Figures 3 and 4c). The most notorious TAL effector *S*-gene targets are the Clade III *SWEET* sucrose transporter genes (Streubel et al 2013). These include *OsSWEET11* induced by the major-effects virulence effector PthXo1 (Yang et al 2006), *OsSWEET 13* induced by PthXo2 (Zhou et al 2015), and *OsSWEET14* induced by multiple TAL effectors including AvrXa7 (Antony et al 2010), PthXo3 (Yang and White 2004), TalC (Yu et al 2011) and TalF (Doucouré et al 2018, Streubel et al 2013).

SWEET genes are hypothesized to provide nutrients to the bacteria by effluxing host sucrose to the xylem, the preferred living site of *Xoo*, although additional roles are plausible (Chen et al 2010, Hutin et al 2015). Additional *S*-genes targeted by small-effects TAL effectors include the transcription factors *OsTFIIAγ1* and *OsTFX1*, induced by PthXo7 and PthXo6, respectively (Ma et al 2018, Römer et al 2010, Sugio et al 2007, Yuan et al 2016). These *S*-genes, however, contribute moderately to *Xoo* virulence compared to the *SWEETs.* Interestingly, the only *S*-gene targets identified for *Xoc,* the mesophyll pathogen, are the sulfate transporter genes, *SULTR3* and *SULTR6,* which are induced by Tal2b of BLS256 (Cernadas et al 2014) (MG Figure 3).

Many TAL effector *S*-gene interactions may be abolished, either through host adaptation or genome engineering, leading to a recessive resistance, commonly referred to as loss of susceptibility (MG Figures 3 and 4d and e) (Li et al 2012, Yuan et al 2009). This resistance mechanism is the result of either polymorphisms in the EBE of rice *S*-gene or polymorphisms in the coding sequence of the *S*-gene itself, reviewed in Hutin et al (2015). Polymorphisms in the EBE impact TAL effector-DNA binding and thus disable activation of virulence-enhancing genes, whereas polymorphisms in the coding sequence of the *S*-gene itself can disrupt gene function.

TAL effectors may also act as avirulence factors, triggering host resistance genes (MG Figures 3 and 4f) (Tian et al 2014). These so-called executor genes do not belong to a uniform family, but act in a dominant, transcription-dependent manner that triggers host cell death. Within this category, there are AvrXa27, AvrXa10, and AvrXa23 that activate the major *R*-genes *Xa27* (Gu et al 2005), *Xa10* (Tian et al 2014), and *Xa23* (Wang et al 2015), respectively, reviewed in Zhang et al (2015).

TAL effectors may also trigger host resistance through a dominant transcriptional independent mechanism, where host factors perceive TAL effectors through a yet undescribed mechanism (Kay et al 2005, Schornack et al 2004, Triplett et al 2016a) (MG Figure 3). *Xo1*, identified in the American heirloom rice variety Carolina Gold and *Xa1* from IRBB1 and Kogyoku are the only two major *R*-genes that encode NLR proteins. *Xo1* is triggered by a range of full-length TAL effectors including PthXo1, AvrXa7, AvrXa10, TalC, TalF, Tal1C, Tal2a, Tal8, and Tal2g (Triplett et al 2016a). Interestingly, a severely truncated PthXo1 TAL effector lacking the AD, the NLS and

only three repeats of the CRR was enough to induce plant cell death in Carolina Gold (Triplett et al 2016a). *Xo1*, like the Bs4 resistance NLR in the tomato-*Xanthomonas euvesicatoria* pathosystem is hypothesized to be dependent on cytoplasmic recognition of the highly conserved CRR (Schornack et al 2004).

Both *Xoo* and *Xoc* strains have modified their TAL effector gene complements to include interfering TALEs (iTALEs) (Ji et al 2016) or truncated TALEs (truncTALEs) (Read et al 2016). Synonymous in their function, but discovered independently by two different groups, iTALEs and truncTALEs, rather than activating resistance, disrupt detection of host resistance triggering TAL effectors and lead to induction of host susceptibility (Ji et al 2016, Read et al 2016). Unfortunately for disease management goals, both iTALEs and truncTALEs break the resistance provided by both *Xo1* and *Xa1*.

Knowing the TAL effector code has allowed scientists to predict TAL effector gene targets, and thus, identify putative TAL effector-induced susceptibility or resistance genes in multiple *Xanthomonas* hosts (Cox et al 2017, Doyle et al 2012, Pérez-Quintero et al 2013, Wilkins et al 2015). Several software packages have been developed that utilize the TAL effector code to predict targets in the rice genome. The *Target Finder* tool from the TAL-NT 2.0 suite predicts TAL effector targets by scoring RVD sequences against plant genomes using RVD-nucleotide association frequencies from known TAL effector-target pairs, a strategy later improved by *Talvez* and *Storyteller* (Doyle et al 2012, Pérez-Quintero et al 2013). The *TALgetter* software package uses a statistical model based on transcriptome data for target prediction (Grau et al 2013).

Combining whole genome sequencing, host-plant transcriptomics, and TAL effector target prediction, Wilkins et al (2015) generated a testable number of candidate TAL effector targets for highly conserved *Xoc* TAL effectors, one of which has already been experimentally confirmed (Cai et al 2017). Unfortunately, the TAL effector target predictors are not perfect. Blanvillain-Baufumée et al (2017) revealed the limitations of current TAL effector target predictions by showing that, while TalC does activate its predicted target, the host susceptibility gene *OsSWEET14*, it also activates an additional, unknown susceptibility gene. Similarly, the *Xoo* effector PthXo2 triggers the gene *OsSWEET13*, which was not among the predicted targets (Zhou et al 2015).

TAL effector sequences have given insight into divergence of *Xo* lineages and effector diversification. The *QueTAL* and *AnnoTALE* software suites were developed to compare complete TAL effector sequences phylogenetically and functionally (Grau et al 2016, Pérez-Quintero et al 2015). This strategy was used to show that all known *Xoo* populations in the Philippines descended from three genetic lineages and that TAL effector repetoire diversification was a driver of *Xoo* adaptation (Quibod et al 2016). *In silica* analysis has also given insight into how TAL effectors evolve (Erkes et al 2017). In *Xoo,* TAL effectors evolve through mutations in the CRR or recombinations between separate TAL effectors. Interestingly, in *Xoc*, TAL effectors are reassorted in the genome through an integron-like mechanism where multiple TAL effectors are stockpiled and separated by short spacers. Elucidation of effector evolution provides insights into host susceptibility and will contribute to future strategies for controlling *Xo*.

7. Other Type III secreted effectors

Prior to the identification of *Xo1* (Triplett et al 2016a) and the recenlty described broad-spectrum disease resitance QTL by Bossa-Castro et al (2018; discused below), the only resistance available for geographically diverse *Xoc* was the maize-derived NLR protein Rxo1 when expressed as a transgene in rice (Zhao et al 2004). Rxo1 recognizes the conserved T3S effector AvrRxo1. Unlike the previosuly described *Xo* effectors, AvrRxo1 is a structural homologue of an ancient family of toxin-antitoxin systems common in bacteria and functional against both prokaryotes and eukaryotes (Triplett et al 2016b). AvrRxo1 is found in all sequenced Asian *Xoc* strains and lacking in most African *Xoc* strains from Mali, Burnkina Faso (Wonni et al 2014), and Senegal (Verdier et al *in prep.*). The ecological role of AvrRxo1 in intra- and inter-species competition remains unknown. The design of disease management strategies could benefit from an understanding of how AvrRxo1 contribues to bacterial fitness in competition with other organisms in the phytobiome.

8. Applications of the knowledge of effectors for disease control

Artificial TAL effectors (ArtTALs), also referred to as designer TAL effectors, are becoming increasingly prevalent in assessing the role of gene activation during plant-*Xanthomonas* interactions. Using ArtTALs, Streubel et al (2013) determined that only five closely related *OsSWEET* genes, referred to as clade-III *OsSWEET* genes, enhanced host susceptibility in *Xoo*-rice interactions. This tool has been adapted for pathosystems beyond rice-*Xoo*. ArtTALs were utilized to show that bHLH transcription factors were contributing to a water-soaking phenotype during tomato-*Xanthomonas gardneri* interactions (Schwartz et al 2017). During citrus-*Xanthomonas citri* interactions, the pathogen activates expression of the host gene *CsLOB1 using* the TAL effector PthA4; ArtTALs were utilized to show that the triggering of *CsLOB1* alone contributed to host susceptibility, revealing a new family of potential host susceptibility genes (Hu et al 2016). ArtTALs have also been used to explore how TAL effectors function. ArtTALs were used with artificial promoters in two independent studies to show that TAL effectors drive transcription bidirectionally, a revelation that may allow the more precise discovery and prediction of TAL effector targets (Streubel et al 2017, Wang et al 2017).

Modified TAL effectors have become a widely-used tool in biotechnology. TAL effector nucleases (TALENs) have been widely adopted and optimized for genome editing in several systems (Joung and Sander 2013). While CRISPR/cas9 has become a popular option for genome editing, TALENs provide more versatility in target site selection, owing to the lack of required protospacer adjacent motif (Jinek et al 2012). TALENs have been utilized for precise genome editing in rice to remove EBEs in host promoters; e.g., three EBEs were removed from the rice susceptibility gene *OsSWEET14* (Blanvillain-Baufume et al 2017). Notably demonstrating the versatility of TALEN technology, TALEN-derived chimeric antigen receptor T cells have been used to treat acute lumphocytic leukemia in two infants (Qasim et al 2017). Modified TAL effectors have also been used to silence genes in Arabidopsis, through the fusion of a transcription repression domain to a TAL effector (Mahfouz et al 2012) or through steric interference with host transcription machinary (Lin et al 2016). Additional work has been conducted to optimize binding between TAL effectors and DNA. The modification of TAL effectors is thus a versatile strategy with applications in many fields of biotechnology.

Identifying loci associated with resistance and suceptibility to BB and BLS in rice is imperative in the quest for durable and broad-spectrum disease resistance. Historically, novel alleles were identified through bi-parental populations in which two parents with contrasting phenotypes were mated to identify the genetic loci contributing to the trait of interest. Although insightful, the narrow genetic diversity resulting from the combination of only two parents limited gene discovery. To overcome this constraint, the Multi-Parent Advanced Generation Inter-Cross (MAGIC) Populations were generated at the International Rice Research Institute and include the indica MAGIC, MAGIC PLUS, japonica MAGIC, and the Global MAGIC populations (Bandillo et al 2013, Huang et al 2015). MAGIC populations capture the genetic diversity of multiple parents, recombined over several generations, to ultimately generate a population with large phenotypic and genetic diversity and fine mapping resolution.

The indica MAGIC was recently used to screen for resistance and susceptibility loci to 20 *Xo* isolates that represented geographic, genetic and pathovar diversity within *Xo* (Bossa-Castro et al 2018). Using interval mapping and genome-wide association studies, a total of 37 stain-specific QTLs were identified. Of these,14 were associated with resistance to more than one *Xo* strain and 11 of the loci were effective agsinst both *Xoo* and *Xoc* isolates (Bossa-Castro et al 2018). In a similar approach, the senstivity of the indica MAGIC population was investigated to detect resistance and susceptibility loci to one minor-effect *Xoo* TAL effector, Tal7b (Huerta et al, *in prep*). Nine QTLs were found that specifically directed resistance to Tal7b. In both studies, previously-mentioned TAL effector predictive softwares (Pérez-Quintero et al 2013) were used to identify TAL effector targets that converge onto the identified loci, generating a list of novel candidate susceptibility and resistance genes putatively exploited by *Xo*. Combined, these studies show the power of MAGIC populations in identifying novel sources of resistance to diverse *Xo*, in general, and to individual TAL effectors encoded by *Xo.*

9. Future perspectives

The characterization and identification of new sources of resistance in rice is of particular importance in the context of food security and the demand for this grain. Intensified rice production in rice-producing areas has resulted in higher disease pressures and yield losses due to both BLS and BB. Our understanding of how the pathogens *Xoo* and *Xoc* interact with rice to induce disease and the identification of new and distinct sources of resistance to control the diseases they cause have been greatly enhanced by improved genetic sequencing and bioinformatic tools such as the MAGIC populations, long-read sequencing technologies, TAL effector target-prediction software, and genome-editing technologies. Together, these tools are quickly revolutionizing gene discovery, functional characterization of resistance and susceptibility loci, and application of this knowledge for the development of improved crops for the benefit of society.

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