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Review

Recent Progress in Rice–*Xanthomonas oryzae* Interactions

Yuting Qi [1,†], Qiong Rao [1,†], Chenglong Lu [2], Junyi Gong [2,*] and Yuxuan Hou [2,*]

[1] Zhejiang Key Laboratory of Biology and Ecological Regulation of Crop Pathogens and Insects, College of Advanced Agricultural Sciences, Zhejiang A&F University, Hangzhou 311300, China
[2] State Key Laboratory of Rice Biology and Breeding, China National Rice Research Institute, Hangzhou 311400, China
* Correspondence: gongjunyi@caas.cn (J.G.); houyuxuan@caas.cn (Y.H.)
† These authors contributed equally to this work.

Simple Summary: Rice serves as a staple food crop for billions of people, but bacterial diseases like bacterial blight and bacterial leaf streak, caused by *Xanthomonas oryzae*, can severely reduce rice yields and threaten food security. This review explores how *Xanthomonas oryzae* infects rice plants and how rice defends against *Xanthomonas oryzae*, focusing on the roles of bacterial type III secretion effectors and host resistance genes, as well as the holistic insights into interaction mechanisms between the rice host and *Xanthomonas oryzae*. Modern genetic technologies, such as gene editing and marker-assisted selection, are discussed for being employed to develop next-generation disease-resistant rice varieties. These advances are crucial for reducing rice losses and ensuring stable food production.

Abstract: Rice bacterial blight (BB) and bacterial leaf streak (BLS), caused by *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*), respectively, are among the most devastating bacterial diseases threatening global rice production. The interactions between rice and *Xanthomonas oryzae* are complex and dynamic, involving recognition, attack, defense, and adaptation mechanisms enacted by both the rice host and the pathogens. This review summarizes recent advances in understanding rice–*Xanthomonas oryzae* interactions, focusing on infection models, pathogenic mechanisms, and immune responses elicited by *Xanthomonas oryzae*. Special attention is devoted to the roles of transcription activator-like effectors (TALEs) and non-TALE effectors in pathogenicity, the functions of resistance (*R*) genes in defense, and the interconnected molecular networks of interactions derived from multi-omics approaches. Understanding these interactions is essential for developing effective disease-resistance strategies and creating elite disease-resistant rice varieties.

Keywords: rice; *Xanthomonas oryzae*; effector; resistance gene; multi-omics

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1. Introduction

Xanthomonas is a genus of Gram-negative bacteria that infects approximately 400 host species, including rice, citrus, tomato, and pepper [1]. *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*), two closely related pathovars, cause bacterial blight (BB) and bacterial leaf streak (BLS) in rice, respectively [2]. BB is one of the most destructive rice diseases, leading to yield losses of 10–30%, with some cases exceeding 50% [3,4]. Similarly, BLS results in yield reductions of 8–32% [5]. The interactions between rice and *Xoo*/*Xoc* are intricate and dynamic, with the pathogens attempting to bypass the host's defense mechanisms while the rice plant employs immune responses to resist

infection. This review provides a comprehensive overview of rice–*Xoo*/*Xoc* interactions and summarizes recent advancements regarding the immune responses induced by type III secreted effectors and the application of multi-omics technologies to elucidate the molecular mechanisms of these interactions.

2. *Xanthomonas oryzae* Infection Models

Xoo typically enters rice leaves through hydathodes at the edges and tips or through wounds. The bacteria multiply in the intercellular spaces of parenchyma cells and spread to the xylem, forming a beaded liquid on the leaf surface after a few days [6]. *Xoo* interacts with xylem parenchyma cells, moving vertically through the leaf via primary veins and laterally through commissural veins (Figure 1A). In contrast, *Xoc* penetrates the leaf mainly through stomata, multiplies in the sub-stomatal cavity, and remains confined to the apoplast of the mesophyll tissue without invading the xylem (Figure 1A) [2]. It exudes yellow beads or strands from natural openings, contributing to disease spread [6,7].

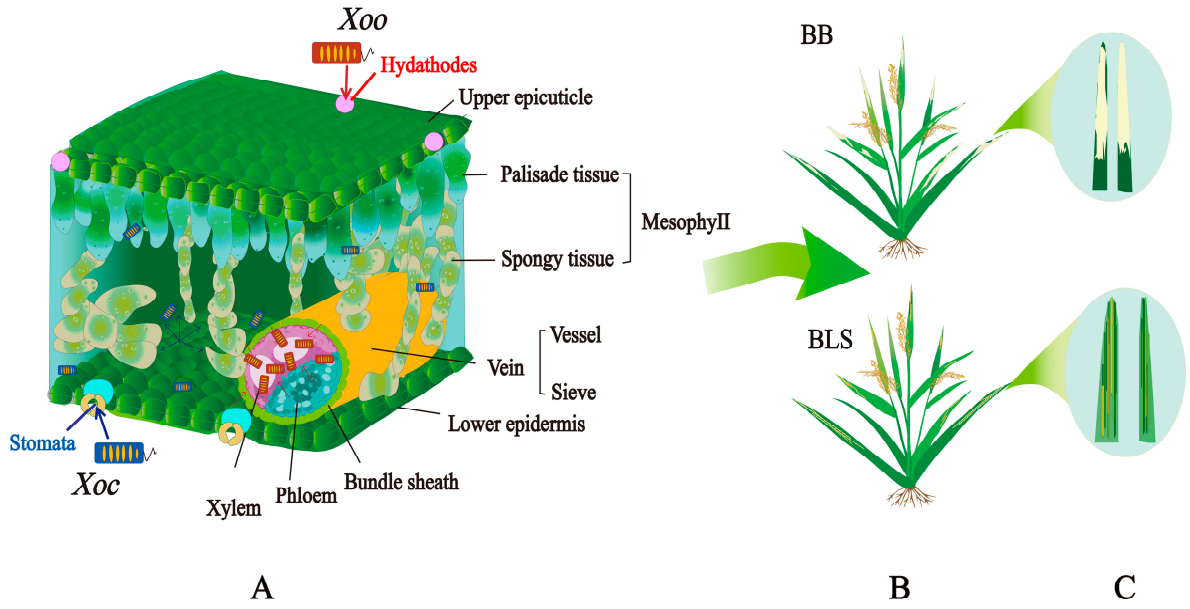

Figure 1. Infection modes of *Xoo* and *Xoc* in rice. (**A**) Schematic representation of the infection modes of *Xoo* and *Xoc* in rice leaf tissue. (**B**) Symptoms of BB and BLS caused by *Xoo* and *Xoc*, respectively. (**C**) The magnified images of BB and BLS symptoms.

Due to their different infection methods, BB and BLS are easily distinguishable in the early stages but may appear similar later. BB symptoms begin as small, green, water-soaked spots at the leaf edges that turn into gray lesions (Figure 1B,C). BLS starts with water-soaked lesions between veins that form into translucent yellow streaks (Figure 1B,C). As both diseases progress, their symptoms can overlap, leading to confusion. Both pathogens often coexist in rice fields, with individual leaves displaying symptoms of both diseases [6,8].

3. Type III Secreted Effectors of *Xanthomonas*—TALEs

During infection, *Xanthomonas* secretes effectors into host cells primarily via the type III secretion system (T3SS), which is crucial for pathogenesis [9,10]. Most secreted effectors, known as type III secreted effectors (T3SEs), include transcription activator-like effectors (TALEs). TALEs are notable for inducing the expression of host target genes in the nucleus [11]. TALE proteins exhibit specific structural features: (1) The NH2-terminal region is highly conserved and includes a T3SS signal (T3S) for translocating TALEs to the host cytoplasm; (2) The COOH-terminal region contains nuclear localization signals (NLSs) that

transport TALEs to the nucleus and a conserved acidic activation domain (AD) for gene transcription activation (Figure 2). Moreover, TALEs have tandem repeat regions (RR) and repeat variable di-residues (RVDs) at positions 12 and 13 that interact specifically with host DNA, binding to effector-binding elements (EBEs) in gene promoters to activate their expression (Figure 2).

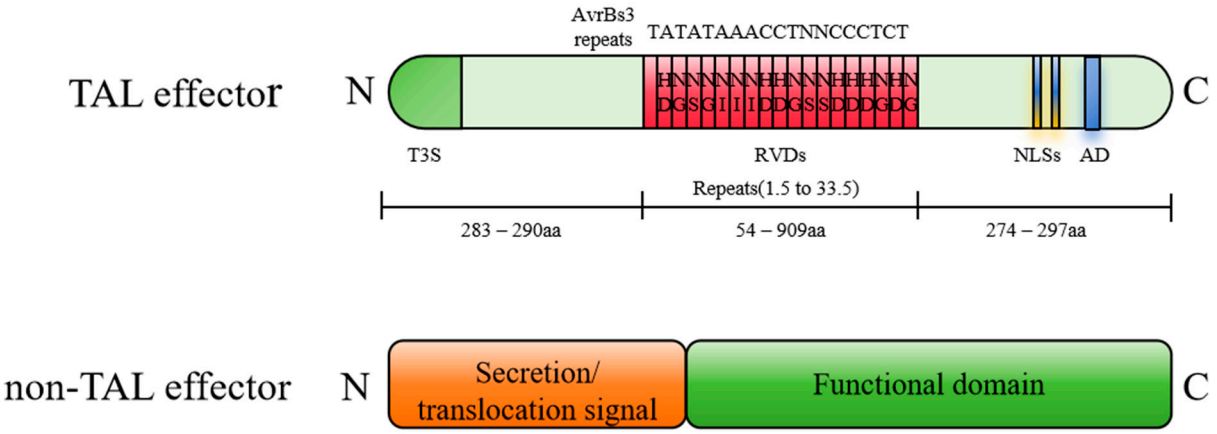

Figure 2. Structural features of TALEs and non-TALEs.

The first TALE to be characterized was AvrBs3 from *Xanthomonas campestris* pv. *Vesicatoria*, which triggers Bs3-mediated resistance in peppers [12]. AvrBs3 homologs were subsequently found in *Xoo*, *Xoc*, *Xanthomonas campestris* pv. *campestris*, and other *Xanthomonas* species [13–16]. Some *Xanthomonas* genomes contain fewer than 6 TALEs, while others, like *Xoo* and *Xoc*, can have over 10, with a maximum of 28 [17]. It has been confirmed that PthXo1, PthXo2, PthXo3, and AvrXa7 are significant TALEs of *Xoo*, accounting for more than 80% of the virulence for rice, as quantified by lesion length, when compared to the full virulence associated with wild-type strains [10,18]. Truncated TALE genes, previously thought to be pseudogenes, have been identified in *Xoo*/*Xoc* strains and confirmed as truncated TALEs or interfering TALEs (iTALEs). Unlike typical TALEs, iTALEs have 45 or 129 bp deletions in the N-terminal region and lack C-terminal AD domains [19].

4. Type III Secreted Effectors of *Xanthomonas*—Non-TALEs

In addition to TALEs, T3SS includes non-TALE effectors. Non-TALEs are found in most *Xanthomonas* species and are primarily composed of a secretion translocation signal and a functional domain (Figure 2). Eighteen non-TALEs are universally present in *Xanthomonas*. Genome sequence analysis of *Xoo* and *Xoc* strains revealed that non-TALEs are highly conserved, although their numbers vary. Specifically, *Xoo* strains KACC10331, MAFF311018, and PXO99^{A} contain 19, 24, and 20 non-TALEs, respectively, while *Xoc* strain BLS256 has 26 [20–22].

Some effectors are unique to *Xanthomonas oryzae*, including XopU, XopW, XopY, and XopAB. Notably, XopT and XopAF are exclusively present in *Xoo* and *Xoc*, respectively, while XopO and XopAJ are unique to *Xoc* and *Xanthomonas citri* subsp. *viticola* [18,23,24]. AvrBs2, the first described non-TALE in *Xanthomonas campestris* pv. *vesicatoria*, is highly conserved [25,26]. Furthermore, XopN has shown similar pathogenicity to AvrBs2 in the GX01 strain of *Xoc*. In the PX099^{A} strain, a triple mutant (XopZ, XopN, XopV) exhibited shorter lesion lengths, but virulence was restored by reintroducing these effectors in the Kitaake variety [27].

5. TALEs-Induced Rice Immunity to *Xanthomonas oryzae*

The plant immune system serves as a barrier against pathogen infection and comprises pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) [28]. In PTI, plant cells employ pattern recognition receptors (PRRs) to recognize PAMPs and initiate basal immune responses. For example, FLAGELLIN SENSITIVE2 (OsFLS2) perceives bacterial flagellins, activating downstream defense signaling pathways [29]. In contrast, ETI involves resistance (R) proteins such as nucleotide-binding leucine-rich repeat (NLR)-type protein Xa1, which specifically recognizes TALEs and triggers stronger immune responses [30]. The presence of functional R proteins leads to ETI, whereas their absence results in effector-triggered susceptibility (ETS) [31]. The interplay between pathogen effectors and their corresponding R proteins reflects a molecular confrontation between the pathogen and the host plant. In *Xoo*/*Xoc*–rice interactions, TALEs with targeted *R* genes are key components determining rice resistance or susceptibility to *Xoo*/*Xoc*.

For ETI, rice *R* genes targeted by TALEs of *Xoo* have been identified and cloned. *Xa1* is the first cloned NLR-type *R* gene. *Xa1* can be recognized by multiple TALEs, such as PthXo1, Tal4, and Tal9d. It was reported that *Xa1*-mediated resistance triggered by TALEs can be suppressed by iTALEs [30,32]. *Xa2*/*Xa31*, *Xa14*, and *Xa45* have also been successfully identified and cloned as alleles of *Xa1*, exhibiting similar functional properties to *Xa1* (Table 1) [19,32,33]. Additionally, executor (*E*) resistance genes, including *Xa7*, *Xa10*, *Xa23*, and *Xa27*, are induced by altering the promoter structure, allowing recognition by their corresponding TALEs AvrXa7/PthXo3, AvrXa10, AvrXa23, and AvrXa27, thereby conferring resistance against *Xoo* (Table 1) [34–37]. Moreover, some TALEs, such as Tal7, Tal9A, and Tal1C, have been identified, but their molecular mechanisms of interacting proteins in rice remain unclear [38,39].

Table 1. Rice genes targeted by TALEs.

	Tale-Targeted (*R*/*S* Gene)	Encoding Products	Matched TALEs	References
Resistance	*Xa1* *Xo1* *Xa2/31* *Xa14* *Xa45*	NLR	Multiple TALEs, iTALEs/truncTALE	[19,30,33,40]
	Xa7	Executor	AvrXa7, PthXo3	[37,41]
	Xa10	Executor	AvrXa10	[35]
	Xa23	Executor	AvrXa23	[42]
	Xa27	executor	AvrXa27	[34]
	xa13	Sweet transporter	PthXo1	[43]
	xa25	Sweet transporter	PthXo2	[44]
	xa41	Sweet transporter	AvrXa7, PthXo3, Tal5, TalC	[45]
	xa5	TFIIA transcription factor	AvrXa5, PthXo7	[46–48]
Susceptibility	*OsSWEET11(Xa13/Os8N3)*	Sweet transporter	PthXo1	[49]
	OsSWEET14(Xa41/Os11N3)	Sweet transporter	AvrXa7, PthXo3, TalC, Tal5	[50–52]
	OsSWEET13(Xa25/Os12N3)	Sweet transporter	PthXo2	[44,53]
	OsSWEET12	Sweet transporter	ArtTAL12	[52]
	OsSWEET15	Sweet transporter	ArtTAL15	[52]
	OsTFIIAγ5	Gamma subunit of rice basal transcription factor	Multiple TALEs	[54]
	OsTFIIAγ1	Gamma subunit of rice basal transcription factor	PthXo7	[46]
	OsTFX1	bZIP transcription factor	PthXo6 $TalB_{MAl1}$	[46,55]
	OsERF#123	AP2/ERF transcription factor	$TalB_{MAl1}$	[55]
	OsSULTR3;6	Sulfate transporter	Tal2g	[56,57]

The genetics of resistance to *Xoc* are complex, and available resources on resistance are limited, resulting in significantly slower research progress compared to *Xoo*. *Rxo1*, the first cloned non-host resistance gene in maize, encodes a NLR protein and confers resistance to *Xoc* when introduced into rice [56,57]. *Xo1*, an allele of *Xa1*, recognizes diverse TALEs from both *Xoo* and *Xoc* (Table 1) [58]. However, the resistance mediated by *Xo1* can be suppressed by interfering TALEs (iTALEs). Additionally, *Xo1* only confers resistance to African *Xoc* strains and is ineffective against Asian *Xoc* strains [32,58,59]. Notably, the "truncTALE" Tal2h effector from *Xoc* strain BLS256 can suppress *Xo1*-mediated resistance [58,60].

For ETS, rice susceptibility (*S*) genes are genetically dominant, and their expression is induced upon pathogen infection. The induction of SWEET (Sugar Will Eventually Be Exported Transporter) genes facilitates pathogen nutrient acquisition and promotes disease development. For example, the TALE PthXo1 directly binds to EBE in the promoter of *OsSWEET11* (*Xa13*/*Os8N3*), inducing its expression and conferring susceptibility to *Xoo* [39, 43,49,61,62]. Similarly, the *OsSWEET14* (*Xa41*/*Os11N3*) promoter is targeted by multiple TALEs, including AvrXa7, PthXo3, TalC, and Tal5, leading to its activation [50–52,63]. Additionally, the susceptibility gene *SWEET13* (*Xa25*/*Os12N3*) can be activated by PthXo2 and PthXo2-like effectors, which bind to variable EBEs in its promoter (Table 1) [44,64]. In contrast, mutations in the EBEs of their recessive alleles, such as *xa13*, *xa41*, and *xa25*, prevent recognition by the aforementioned TALEs, disrupting pathogen colonization and conferring resistance to *Xoo* in rice (Table 1) [44,45,65]. *OsSWEET12* and *OsSWEET15* have also been identified as *S* genes during *Xoo* infection, as their expression can be induced by the artificial TAL effectors ArtTAL12 and ArtTAL15 [52].

Many non-SWEET *S* genes play critical roles during *Xoo*/*Xoc* infection. The gamma subunit of the basal transcription factor, TFIIAγ5 (also known as Xa5), binds directly to the TFB region of TALEs, forming a complex that facilitates the transcription of TALE-activated genes (Table 1) [54]. However, the mutant variant *xa5*, which encodes a naturally occurring V39E variant of TFIIAγ5, cannot interact with TALEs, reducing the expression of TALE-driven *S* or *E* genes to enhance rice resistance (Table 1) [66,67]. In the absence of *TFIIAγ5*, another *TFIIAγ* gene, *OsTFIIAγ1*, can be activated by PthXo7, explaining the reason that PthXo7-containing *Xoo* strains overcome *xa5*-mediated resistance (Table 1) [66]. Interestingly, *qBlsr5a* was identified as an allele of *xa5*, which confers resistance to *Xoc* [68]. Additionally, *OsTFX1*, encoding a basic leucine zipper (bZIP) transcription factor, is induced by PthXo6 and TalBMAI1 (Table 1) [46,55]. TalBMAI1 also activates *OsERF#123*, an AP2/ERF transcription factor gene that contributes to susceptibility to African *Xoo* strains (Table 1) [55]. In rice–*Xoc* interactions, the sulfate transporter gene O*sSULTR3;6* is targeted by Tal2g and serves as a major *S* gene for *Xoc* (Table 1) [69].

6. Non-TALE-Induced Rice Immunity to *Xanthomonas oryzae*

The targets and molecular mechanisms for most non-TALEs in plant cells remain largely unknown, and a few non-TALEs in *Xoo* have been characterized (Table 2). It was reported that the interaction between non-TALE XopN and OsVOZ2 promotes rice susceptible to *Xoo*, while the interaction between XopN and OsXNP is speculated to induce calcium deposition and hydrogen peroxide accumulation against *Xoo* (Table 2) [27,70,71]. Additionally, XopR of *Xoo* interacts with OsBIK1, suppressing PAMP-triggered stomatal closure in *Arabidopsis* (Table 2) [72]. Other non-TALEs, such as XopY (Xoo1488), XopAA (Xop2875), and XopK, interact with OsRLCK185, OsBAK1, and OsSERK1, respectively. OsRLCK185 is involved in chitin-induced immune responses. Xoo1488 suppresses chitin-induced MAPK activation by inhibiting the phosphorylation of OsRLCK185 [73]. OsBAK1 is a key component of both microbe-associated molecular patterns (MAMPs) and brassinosteroid (BR) receptors, suggesting that the virulence activity of Xoo2875 is likely mediated

by the inhibition of OsBAK1 [74]. XopK directly ubiquitinates the receptor kinase OsSERK2, leading to its degradation and thereby suppressing the immune response triggered by PAMP [75]. XopP interacts with the rice E3 ubiquitin ligase OsPUB44 to inhibit rice resistance to *Xoo* (Table 2) [76]. Furthermore, XopL interacts with ferredoxin proteins (NbFd) in non-host plants, promoting reactive oxygen species (ROS) burst and inducing cell death (Table 2) [77]. XopZ was found to interact with ORP1C in *Xoo* strain PXO99^{A}, but ROS burst and PTI marker gene expression data suggest that ORP1C is not involved in the PTI pathway in rice (Table 2) [78]. These findings highlight the potential for cooperation among multiple non-TALEs and their diverse physiological functions in the host, particularly in modulating innate immune responses.

Table 2. Rice genes interacted with non-TALEs.

Rice Genes (Interaction Genes)	Encoding Products	Matched TALEs	References
OsVOZ2, OsXNP	Vascular plant one zinc finger protein 2, putative thiamine synthase	XopN	[27,70,71]
OsBIK1	Receptor-like kinases	XopR	[72]
OsRLCK185	Receptor-like kinase	XopY	[74]
OsBAK1	Receptor-like kinase	XopAA	[74]
OsSERK1	Somatic embryogenic receptor kinase 2	XopK	[75]
OsPUB44	Ubiquitin E3 ligase	XopP	[76]
NbFd	Ferredoxin protein	XopL	[77]
OsORP1C	Oxysterol-binding related protein	XopZ	[78]

7. Whole Picture of Rice–*Xanthomonas oryzae* Interaction Mechanisms from Multi-Omics View

Although many bacterial virulence factors and rice resistance genes have been identified or cloned in rice–*Xanthomonas oryzae* interactions as described above, the molecular mechanisms behind these interactions remain fragmented, with most studies focusing on individual components rather than systemic networks. Over the past two decades, genome-derived multi-omics studies have gradually evolved and expanded. Numerous plant functional genomics studies, which integrate the generation of transgenic and mutant plants with parallel analyses of mRNA expression, protein levels, and metabolic profiles, have been applied to uncover the complex molecular basis underlying rice immunity against *Xanthomonas oryzae* [79–82]. The systems-level understandings derived from integrated multi-omics reveal interconnected molecular networks and lay the groundwork for the breeding of *Xoo*/*Xoc*-resistant rice varieties, as well as broad-spectrum disease-resistant cultivars. Furthermore, they offer valuable data to develop novel organic pesticides.

Genome re-sequencing of diverse rice varieties can be conducted to comprehensively reveal genomic variations and interactions, facilitating the discovery of novel genes associated with disease resistance. Genome-wide association study (GWAS) analysis can validate the known resistance genes and identify novel sites to expand the current resistance gene pool. A total of 77 and 7 loci associated with *Xoo* and *Xoc* resistance, respectively, were identified with the GWAS analysis of 895 accessions from the 3000 Rice Genomes Project (3K RGP) (Table 3). Among the loci, seven for *Xoo* resistance were co-localized with known *Xoo* resistance genes, and one locus for *Xoc* resistance overlapped with a previously reported *Xoc* resistance QTL. The remaining novel loci encompass several defense-related genes potentially involved in *Xoo* and *Xoc* resistance [83]. Through another GWAS involving 340 accessions from the 3K RGP, a total of 11 QTLs associated with *Xoo* resistance were

identified (Table 3). Eight of these resistance loci were mapped to relatively small genomic intervals, consistent with previously reported QTLs or resistance genes. Linear regression analysis revealed a significant correlation between bacterial blight lesion length and the number of favorable resistance alleles [84]. Furthermore, whole genome sequences can provide insights into phylogenetic relationships and help predict genes associated with strain-specific virulence factors and behaviors. A GWAS of 172 global indica rice germplasm infected by representative strains from six *Xoo* races (China and the Philippines) highlighted the importance of chromosomes 11 and 12 in the evolution of rice disease resistance (Table 3). The hotspot region on chromosome 11 contained 89.6% of significant SNPs associated with resistance to race P1, while the chromosome 12 hotspot encompassed 85.3% of SNPs linked to race P9a resistance [85].

Table 3. Holistic analysis of rice–*Xoo*/*Xoc* interactions throuth multi-omics.

Omics	Rice Varieties	*Xanthomonas oryzae*	Main Conclusion	References
Genomics	895 accessions from the 3K RGP	*Xoo* *Xoc*	7 and 77 loci linked to resistance for *Xoo* and *Xoc*, respectively, were identified	[83]
Genomics	340 accessions from the 3K RGP	*Xoo*	11 loci linked to resistance against *Xoo* were identified	[84]
Genomics	172 *indica* rice	*Xoo*	Chromosomes 11 and 12 were important for the evolution of rice resistance for *Xoo*	[85]
Proteomics	IR24	*Xoo*	Carbohydrate-metabolizing enzymes play a key roles in rice–*Xoo* interactions	[86]
Proteomics	Shanyou63	*Xoc*	DSF may play an important role in *Xoc* virulence and growth	[87]
Proteomics	H471 and HHZ	*Xoo*	Phytoalexin and SA signaling pathways were activated faster in the incompatible interaction than in the compatible interaction	[88]
Transcriptomics	ZH11	*Xoc*	Early PTI: conserved DEGs drive basal defense; Late ETI/ETS: TALE targets and specialized DR genes prevail	[89]
Transcriptomics	IR24	*Xoo*	The Δ*xanA* and Δ*imp* mutants dysregulated photosynthesis, redox balance, and secondary metabolism	[86]
Transcriptomics	IR24	*Xoo*	Rice plants tend to shift their focus from defensive responses to growth and reproduction at high temperatures	[90]
Metabolomics	IRBB27, *Oryza minuta*-CG154, IR24	*Xoo*	Key metabolites such as flavonoids, terpenes, and phenolic compounds showed significantly higher levels in resistant varieties	[91]
Metabolomics	CBB23	*Xoo*	Metabolites such as alkaloids and amino acid were involved in rice defense against *Xoo*	[92]

Proteomic analyses of resistant and susceptible rice cultivars during pathogen infection have revealed key proteins associated with defense mechanisms [93]. Time-course proteomic profiling of susceptible rice (RLX) leaves at 3, 6, and 12 h post-inoculation identified critical virulence-related proteins in *Xoo*, including carbohydrate metabolism

enzymes (hexose phosphate mutase, inositol monophosphatase), arginase, and septum site-determining protein (Table 3) [86]. Comparative proteomics between wild-type *Xoc* and its *rpfF* mutant (encoding diffusible signal factor synthase) demonstrated DSF's regulatory role in virulence through nitrogen transfer, protein folding, ROS scavenging, and flagellum formation (Table 3) [87]. In another study comparing incompatible (H471-PXO99A) and compatible (HHZ-PXO99A) interactions, 374 host and 117 pathogen differentially abundant proteins (DAPs) were identified, predominantly involved in secondary metabolism and virulence, respectively. Further, it was demonstrated that phytoalexin and salicylic acid (SA) signaling pathways were activated faster in the incompatible interaction than in the compatible interaction (Table 3) [88].

Transcriptomic profiling serves as a powerful tool for the systematic identification of defense response (DR) genes involved in rice–*Xoo* interactions. RNA-sequencing analysis of susceptible rice inoculated with two *Xoc* strains (hypervirulent HGA4 and hypovirulent RS105) revealed distinct temporal patterns of differentially expressed genes (DEGs) at 12 h (PTI phase) and at 3 days post-inoculation (ETI/ETS phase) (Table 3) [89]. The early PTI stage was characterized by conserved DEGs mediating broad-spectrum basal defense, while the late stage showed the predominant regulation of TALE and DR genes. Parallel investigations in *Xoo*–rice interactions demonstrated that mutants of host-induced virulence factors (Δ*xanA* and Δ*imp*) similarly disrupted photosynthetic efficiency, redox homeostasis, and secondary metabolite biosynthesis pathways (Table 3) [86]. Furthermore, temperature-dependent transcriptomic analysis demonstrated that WRKY and ERF transcription factor families mediate a temperature-sensitive defense-growth trade-off in rice. Under low-temperature condition, plants sustained the robust activation of defense pathways against *Xoo* infection. Conversely, elevating temperature induced a physiological shift where resources were preferentially allocated to growth and reproductive processes, resulting in attenuated pathogen responses (Table 3) [90].

When plants are infected by pathogens, they synthesize specialized metabolites. These metabolites generally fall into three categories: primary metabolites, secondary metabolites, and plant hormones [94]. Among these, secondary metabolites such as terpenoids, phenolics, nitrogen-containing compounds, sulfur-containing compounds, and others play a critical role in plant interactions with biotic and abiotic environments and act as modulators of plant defense [95–97]. By analyzing and comparing the metabolic characteristics of three rice varieties—resistant (IRBB27), susceptible (IR24), and wild-type (CG154)—in response to bacterial leaf blight, various defense-related metabolites were identified, including amino acids, flavonoids, alkaloids, terpenes, nucleotide derivatives, organic acids, inorganic compounds, fatty acids, and lipid derivatives. Among these, key metabolites such as flavonoids, terpenes, and phenolic compounds showed significantly higher levels in resistant varieties [91]. Rice variety CBB23, which carries the *Xa23* resistance gene, was inoculated with *Xoo* strains AH28 and PXO99^{A}. Metabolomics analysis showed that a large amount of alkaloid and terpenoid metabolite content decreased significantly after inoculation with AH28 compared to inoculation with PXO99^{A}, while the content of amino acids and their derivatives significantly increased [92].

Generally, metabolomics provides a comprehensive analysis of all small molecules within an organism, positioned at the phenotypic endpoint of the omics cascade. It captures the results of an informative sequence starting from the genome and extending through the transcriptome and proteome, offering critical insights into the biochemical basis of plant–pathogen interactions.

8. Concluding Remarks and Future Perspectives

Significant progress has been made in understanding the interaction between rice and *Xoo*, particularly in identifying and cloning pathogenic effectors and the corresponding rice *R* genes. However, there exists a notable gap in knowledge concerning the effectors of *Xoc* and their targeted *R* genes. Therefore, it is imperative to explore new effectors and their interactions with rice for *Xoc* infection.

To date, a total of 44 *R* loci conferring resistance to BB have been identified, with 15 of these *R* genes having been successfully cloned [98]. Among the 15 *R* genes, *Xa4*, *xa5*, *Xa7*, *xa13*, *Xa21*, and *Xa23* have demonstrated strong and broad-spectrum resistance and been widely used in disease-resistant breeding. However, in recent years, due to the evolution of *Xoo*, many previously resistant rice varieties have lost their effectiveness, highlighting the urgent need to identify new resistance genes and develop new disease-resistant rice varieties adapted to the emerging *Xoo* strain [99].

To address this challenge, gene editing strategies and molecular marker-assisted selection (MAS) have been employed to create broad-spectrum disease-resistant rice varieties (Figure 3). The disruption of the binding elements for PthXo3, AvrXa7, and PthXo2 within the promoter regions of the *OsSWEET14* and *OsSWEET13* genes through TALEN technology has demonstrated significant resistance to BB [44,100]. The application of CRISPR/Cas9 technology to target and mutate EBEs of *OsSWEET11* and *OsSWEET14* in the rice cultivar Kitaake has successfully generated novel rice cultivars. These cultivars, exhibiting mutations in PthXo2-EBE, along with mutations in PthXo1-EBE and PthXo3-EBE, have been shown to confer a broad spectrum of resistance to *Xoo* infection [53]. Prime Editor (PE) technology addresses the limitations of low homology-directed repair (HDR) efficiency and significantly enhances gene editing precision. Gupta et al. successfully employed the PE5max system to introduce EBE from *OsSWEET14* into the promoter of the dysfunctional *R* gene x*a23*, creating a functional *R* gene, $Xa23^{SW14}$. This modification led to dominant resistance, effectively protecting rice against all *Xoo* strains carrying pthXo3/avrXa7. Additionally, they converted *TFIIA*γ*5* to *xa5*, which offers protection against all Asian *Xoo* strains except those carrying pthXo1 [101]. Further, the double-mutant lines obtained by converting *TFIIA*γ*5* to *xa5* and *xa23* to *Xa23* using the duplex PE system exhibited robust broad-spectrum resistance against multiple *Xoo* strains [102]. These studies demonstrate the potential of PE technology for precise genetic modifications to enhance disease resistance in crops.

Similarly, several modified disease resistance genes targeting *Xoc* have been identified in rice. EBEs of *OsSWEET11*, *OsSWEET14*, and *OsSULTR3;6* in the rice cultivars Guihong 1 and Zhonghua 11 were precisely edited using CRISPR/Cas9 technology. This resulted in the development of the GT0105 (derived from Guihong 1) and ZT0918 (derived from Zhonghua 11) rice varieties, which exhibited significantly enhanced resistance to both *Xoo* and *Xoc* strains while maintaining agronomic traits comparable to their wild-type counterparts [103,104]. These findings demonstrate that precise editing of EBEs and *S* genes in the rice genome can effectively reduce disease incidence without compromising plant performance.

MAS breeding is increasingly used to enhance crop resistance (Figure 3). The success of MAS relies on the availability of strong genes and effective molecular markers. Scientists have developed markers like PR-Bs3, Xa27Fun, Xa23Fun, and MX7 based on *E* gene promoter characteristics, leading to the creation of rice varieties with improved resistance [105,106]. Resistance in *E* genes largely depends on the EBEs in their promoters. It was reported that adding six EBEs to the *Xa27* promoter allowed the susceptible rice cultivar Kitaake to gain broad-spectrum resistance to both *Xoo* and *Xoc* [107]. Similarly, using a promoter with five EBEs to drive *Xa10* expression also provideed broad-spectrum resistance to *Xoo* [108].

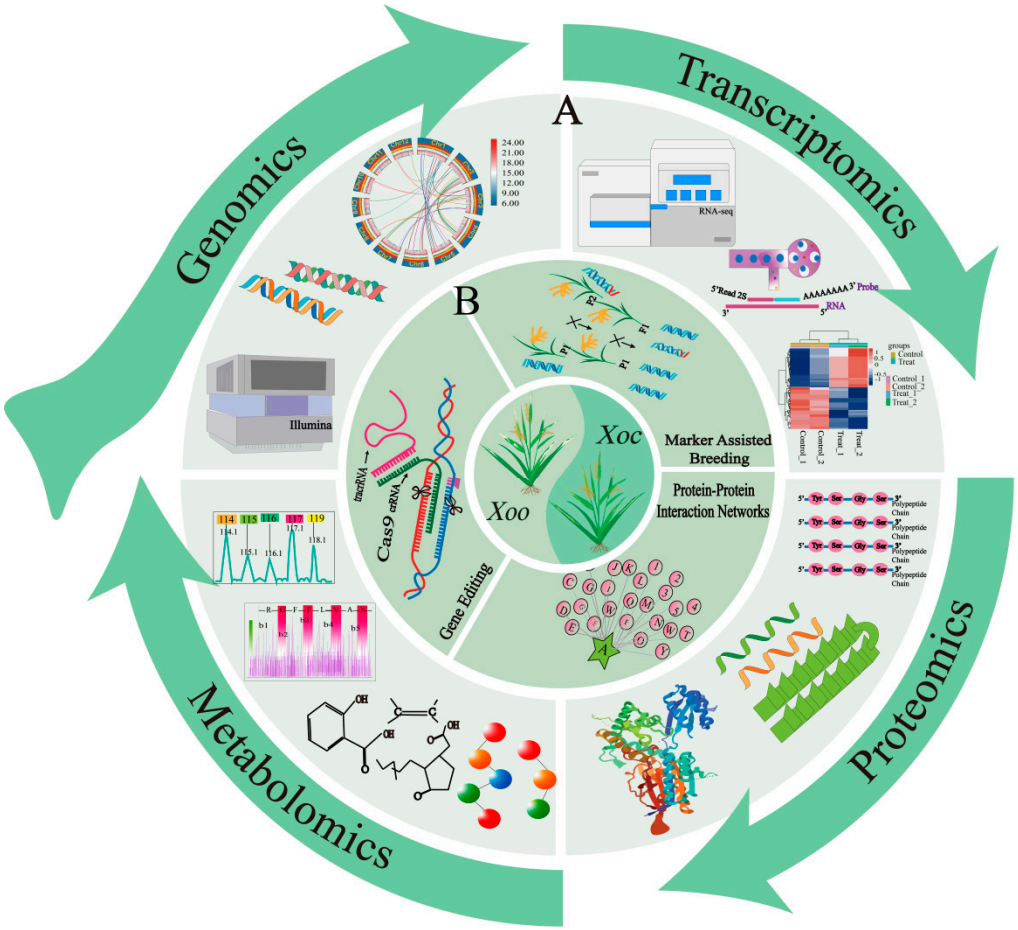

Figure 3. Multi-omics research and modern biotechnology strategies in rice–*Xoo*/*Xoc* interactions. (**A**) Application of four omics approaches (genomics, transcriptomics, proteomics, and metabolomics) in rice–*Xoo*/*Xoc* interactions. (**B**) Utilization of modern molecular biotechnology for resistance breeding against *Xoo*/*Xoc*.

The elucidation of the molecular mechanisms underlying rice disease resistance, especially through the application of multi-omics approaches, remains insufficiently explored. The study of plant–pathogen protein interactions (PPI) is crucial for understanding plant diseases and developing effective control strategies (Figure 3). Researchers have constructed plant–pathogen interactomes through predictions and experimental methods. For instance, a study identified 3074 potential PPIs between *Ralstonia solanacearum* and *Arabidopsis thaliana*, highlighting the importance of pathogen-targeted proteins in the *Arabidopsis* PPI network [100]. A computational framework based on structural information has also been proposed to predict PPIs, which is more effective than sequence-based methods [109]. Experimental studies are revealing PPIs as well. Two pathogens and approximately 8000 *Arabidopsis* proteins were used to create an immune system protein interaction network, finding critical links between effectors and immune receptors [110]. Additionally, researchers developed a network of virulence effector protein interactions involving both *ascomycete* pathogens and *Arabidopsis* host proteins, identifying converging host proteins [110,111]. An ABA–T3SE interactome network was also established to study how T3SEs influence abscisic acid responses [112].

However, studies on pathogen–rice interaction networks, particularly those involving *Xanthomonas oryzae*, remain limited. Developing comprehensive interaction networks between pathogens and rice could help clarify the relationships between effector proteins

and rice genes, paving the way for the identification of novel resistance (*R*) genes and a deeper understanding of the associated mechanisms.

In summary, the rice–*Xoo*/*Xoc* pathosystem is a powerful model for advancing disease control research. By combining genomics, proteomics, transcriptomics, and metabolomics, this system provides a multi-omics framework to dissect rice resistance genes and their regulatory networks (Figure 3). A thorough understanding of the interactions between rice and *Xanthomonas oryzae* is crucial for designing more effective and sustainable strategies to combat bacterial diseases in rice.

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