Plant Communications
Review article

CellPress
Partner Journal

Genetic engineering, including genome editing, for enhancing broad-spectrum disease resistance in crops

Xinyu Han[1,8], Shumin Li[2,8], Qingdong Zeng[3,8], Peng Sun[1], Dousheng Wu[4], Jianguo Wu[5], Xiao Yu[6], Zhibing Lai[2], Ricky J. Milne[7], Zhensheng Kang[3], Kabin Xie[2,*] and Guotian Li[1,*]

[1]National Key Laboratory of Agricultural Microbiology, Hubei Hongshan Laboratory, Hubei Key Laboratory of Plant Pathology, The Center of Crop Nanobiotechnology, Huazhong Agricultural University, Wuhan 430070, China

[2]National Key Laboratory of Crop Genetic Improvement, Huazhong Agricultural University, Wuhan 430070, China

[3]State Key Laboratory for Crop Stress Resistance and High-Efficiency Production, College of Plant Protection, Northwest A&F University, Yangling 712100, Shaanxi, China

[4]Hunan Key Laboratory of Plant Functional Genomics and Developmental Regulation, College of Biology, Hunan University, Changsha 410082, China

[5]State Key Laboratory of Ecological Pest Control for Fujian and Taiwan Crops, Vector-borne Virus Research Center, Institute of Plant Virology, Fujian Agriculture and Forestry University, Fuzhou 350002, China

[6]National Key Laboratory of Agricultural Microbiology, Hubei Key Laboratory of Plant Pathology, Hubei Hongshan Laboratory, College of Plant Science and Technology, Huazhong Agricultural University, Wuhan 430070, China

[7]CSIRO Agriculture and Food, Canberra, ACT 2601, Australia

[8]These authors contributed equally to this article.

***Correspondence: Kabin Xie (kabinxie@mail.hzau.edu.cn), Guotian Li (leeguotian@163.com)**

https://doi.org/10.1016/j.xplc.2024.101195

ABSTRACT

Plant diseases, caused by a wide range of pathogens, severely reduce crop yield and quality, posing a significant threat to global food security. Developing broad-spectrum resistance (BSR) in crops is a key strategy for controlling crop diseases and ensuring sustainable crop production. Cloning disease-resistance (*R*) genes and understanding their underlying molecular mechanisms provide new genetic resources and strategies for crop breeding. Novel genetic engineering and genome editing tools have accelerated the study and engineering of BSR genes in crops, which is the primary focus of this review. We first summarize recent advances in understanding the plant immune system, followed by an examination of the molecular mechanisms underlying BSR in crops. Finally, we highlight diverse strategies employed to achieve BSR, including gene stacking to combine multiple *R* genes, multiplexed genome editing of susceptibility genes and promoter regions of executor *R* genes, editing *cis*-regulatory elements to fine-tune gene expression, RNA interference, saturation mutagenesis, and precise genomic insertions. The genetic studies and engineering of BSR are accelerating the breeding of disease-resistant cultivars, contributing to crop improvement and enhancing global food security.

Key words: genetic engineering, genome editing, broad-spectrum resistance, knock-in, *Oryza sativa*, *Triticum aestivum*

Han X., Li S., Zeng Q., Sun P., Wu D., Wu J., Yu X., Lai Z., Milne R.J., Kang Z., Xie K., and Li G. (2025). Genetic engineering, including genome editing, for enhancing broad-spectrum disease resistance in crops. Plant Comm. **6**, 101195.

INTRODUCTION

The global population is projected to increase from the current 8.0 billion to 9.7 billion by 2050, potentially peaking at nearly 10.4 billion in the mid-2080s (United Nations Population Division, 2022). As world population growth continues, it is estimated that total global crop yield must increase by 35%–56% between 2010 and 2050 to meet this rising demand (Springmann et al., 2018; van Dijk et al., 2021). However, crop yields are severely threatened by various biotic factors, including devastating diseases. Two globally distributed crop diseases, rice blast and wheat stripe rust, caused by the fungal pathogens *Magnaporthe oryzae* and *Puccinia striiformis* f. sp. *tritici*, respectively, lead to annual grain yield losses of 20%–30% for

rice and 10%–30% for wheat (Li et al., 2019; Stukenbrock and Gurr, 2023). Developing disease-resistant crops is crucial for achieving environmentally friendly control of these diseases. However, due to the dynamic evolution of pathogen populations and the consistent emergence of new pathogen strains, crop disease resistance (*R*) genes can become ineffective within a few years of deployment, resulting in significant crop losses over time (Zhao et al., 2024). Therefore, broad-spectrum resistance (BSR) genes, which can confer resistance to multiple strains of the same pathogen or various pathogen species, are critical for safeguarding global food security.

Disease resistance in plants is conferred by *R* genes, integral components of the plant immune system. The plant immune system consists of both membrane-localized and cytoplasmic receptors that perceive pathogen invasion. Upon pathogen recognition, the plant immune system can initiate robust immune responses through pattern-triggered, effector-triggered, or atypical immune pathways (Figure 1). Researchers have utilized a variety of technologies and tools to clone and study *R* genes mechanistically, thereby deepening our understanding of the plant immune system. Concurrently, breeders employ techniques such as gene pyramiding and genetic engineering, including genome editing, to develop durable and broad-spectrum disease resistance in crops. Recent advancements in genome editing technologies have significantly empowered both these processes.

In this review, we briefly describe the current understanding of the plant immune system and highlight recent advances in crop BSR studies. We then provide a comprehensive summary of various strategies to achieve BSR, ranging from traditional genetic engineering to newer genome editing technologies like gene knock-in, which facilitate precise genetic and epigenetic modifications. Finally, we offer insights into technological innovations, such as R protein design, and their potential applications for BSR in crops.

THE PLANT IMMUNE SYSTEM

Pattern-triggered immunity

During their long-term coevolution with pathogens, plants have developed a dual-layered innate immune system, which includes pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) (Jones et al., 2024). PTI, often referred to as basal immunity, is activated when conserved pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns are recognized by plasma membrane-localized pattern recognition receptors (PRRs), such as receptor-like kinases (RLKs) and receptor-like proteins (RLPs) (DeFalco and Zipfel, 2021; Ngou et al., 2021). This recognition triggers a phosphorylation relay involving receptor-like cytoplasmic protein kinases (RLCKs), leading to a series of defense responses. These responses include Ca^{2+} influx, reactive oxygen species (ROS) burst, activation of mitogen-activated protein kinases (MAPKs), deposition of callose, and transcriptional reprogramming of defense genes, effectively combating a broad spectrum of pathogens. For instance, during bacterial PTI in *Arabidopsis thaliana* (hereafter referred to as *Arabidopsis*), the bacterial flagellin epitope flg22 is recognized by the leucine-rich repeat (LRR) receptor kinase flagellin-sensing 2 (FLS2). This recognition stimulates the formation of a receptor complex with brassinosteroid insensitive 1 (BRI1)-associated receptor kinase 1 (BAK1), thereby activating botrytis-induced kinase 1 (BIK1), an RLCK. This complex initiates downstream defense signaling pathways and responses, including MAPK cascades and ROS bursts. In response to the PAMP chitin, the rice chitin elicitor receptor kinase OsCERK1, a lysin motif RLK, perceives but does not directly bind to chitin. Instead, chitin binding triggers interaction between the chitin elicitor binding protein (OsCEBiP) dimer and OsCERK1 to form a receptor complex. This interaction leads to the homodimerization and phosphorylation of OsCERK1, subsequently activating rice immune responses (Yang et al., 2022a). In addition to detecting "non-self" PAMPs, plants can also recognize "self" danger signals known as damage-associated molecular patterns (DAMPs), which induce danger-triggered immunity (DTI) (Zhou and Zhang, 2020). DTI is analogous to PTI, leading to the activation of similar plant immune responses. In *Arabidopsis*, plant elicitor peptides (Peps), a family of DAMPs, are recognized by two receptors, plant endogenous peptide 1 (PEP1) receptors 1 and 2 (PEPR1/2). Following this recognition, PEPR1 and its co-receptor BAK1 interact with BIK1 and PBS1-like 1 (PBL1) to directly phosphorylate BIK1, thereby initiating immune responses through synergistic ethylene (ET) and PEPR signaling pathways (Jing et al., 2023). *Arabidopsis* Pep1 (AtPep1) confers BSR to bacterial speck caused by the bacterial pathogen *Pseudomonas syringae* pv. *tomato* DC3000, gray mold caused by the fungal pathogen *Botrytis cinerea*, and *Arabidopsis* late blight caused by the oomycete *Phytophthora infestans* (Huffaker et al., 2006). In maize, *Zea mays* Pep 1 (ZmPep1), a homolog of AtPep1, enhances resistance to southern leaf blight and anthracnose (Huffaker et al., 2011).

Effector-triggered immunity

In ETI, nucleotide-binding LRR receptors (NLRs) bind directly or indirectly to pathogen-secreted effectors within plant cells, marking the initiation of robust immune responses. This response is often characterized by a hypersensitive response (HR), featuring localized cell death (Remick et al., 2023). Plant NLRs are classified into three types based on their N-terminal domains: coiled-coil (CC) NLRs, Toll/interleukin-1 receptor (TIR) NLRs, and resistance to powdery mildew 8 (RPW8)-NLRs (CNLs, TNLs, and RPW8-NBS-LRR [RNLs], respectively) (Jubic et al., 2019). In *Arabidopsis*, the RPW8 domain, which contains a putative N-terminal transmembrane domain and a CC motif, is encoded by two dominant *R* genes, *RPW8.1* and *RPW8.2,* conferring BSR to powdery mildew (Zhao et al., 2023). CNLs and TNLs, also known as sensor NLRs, recognize pathogen effectors and trigger ETI, while RNLs function as helper NLRs that operate downstream of TNLs in TNL-mediated immunity (Jacob et al., 2021). The discovery of resistosomes—structures formed by NLR proteins *in vitro* that trigger immune responses and cell death—has significantly advanced our understanding of plant immunity. For example, upon recognition of the effector AvrAC from the black rot bacterial pathogen *Xanthomonas campestris* pv. *campestris*, the *Arabidopsis* CNL ZAR1 is activated and forms a pentameric ring complex on the plant cell membrane, known as the ZAR1 resistosome (Wang et al., 2019). This resistosome functions as a Ca^{2+}-permeable channel, facilitating Ca^{2+} influx and leading to

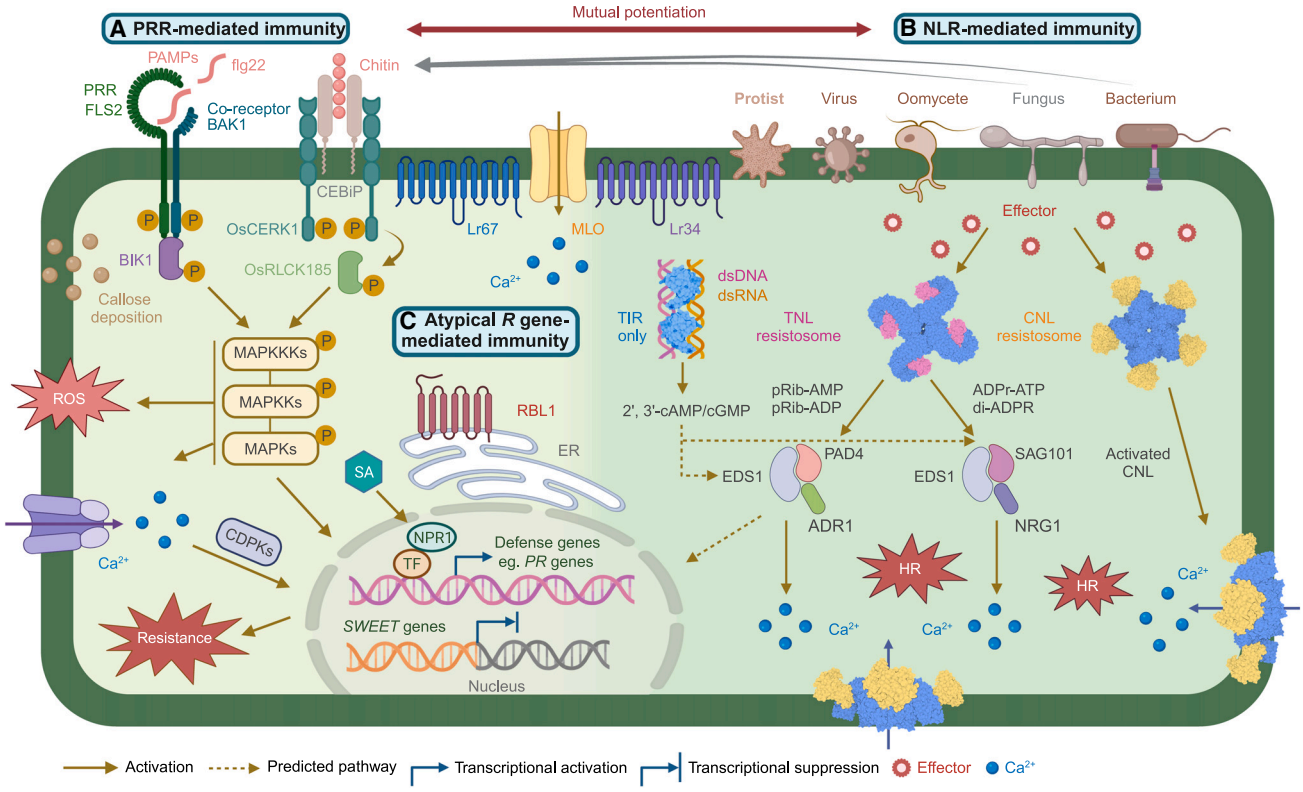

Figure 1. The plant immune system

(A) Recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) at the cell surface initiates pattern-triggered immunity (PTI). The bacterial flagellin epitope flg22 triggers the formation of a receptor complex containing the PRR FLAGELLIN-SENSING 2 (FLS2) and the coreceptor BRASSINOSTEROID INSENSITIVE 1 (BRI1)-ASSOCIATED RECEPTOR KINASE 1 (BAK1). This, in turn, *trans*-phosphorylates and activates the receptor-like cytoplasmic protein kinase (RLCK) BOTRYTIS-INDUCED KINASE 1 (BIK1) in *Arabidopsis*. Additionally, in rice, chitin induces oligomerization of the rice chitin receptor CEBiP and coreceptor OsCERK1, which phosphorylates and activates OsCERK1. This, in turn, phosphorylates and activates the RLCK member OsRLCK185. Phosphorylation of BIK1 and OsRLCK185 further induces downstream immune responses, including mitogen-activated protein kinase (MAPK) cascades and activation of downstream transcription factors, triggering the expression of a set of genes and initiating immune responses. CEBiP, chitin elicitor binding protein; OsCERK1, chitin elicitor receptor kinase 1; ROS, reactive oxygen species; CDPK, calcium-dependent protein kinase.

(B) Once pathogen effectors are delivered into a plant cell, intracellular nucleotide-binding LRR receptors (NLRs), including CC domain-containing NLRs (CNLs) and Toll-interleukin 1-like receptor (TIR) NLRs (TNLs), directly or indirectly recognize these effectors and activate another layer of plant immunity known as effector-triggered immunity (ETI). For example, when activated by pathogen effectors, Sr35, a typical CNL, forms a resistosome at the plasma membrane and functions as a Ca^{2+}-permeable channel, facilitating Ca^{2+} influx into the plant cell and inducing cell death. Activated TNLs (e.g., RPP1) function as nicotinamide adenine dinucleotide glycohydrolase holoenzymes and produce secondary signaling messengers, including pRib-AMP/ADP and ADPr-ADP/di-ADPR, which activate two pathways: the enhanced disease susceptibility 1 (EDS1) pathway associated with senescence-associated gene 101 (SAG101) or phytoalexin-deficient 4 (PAD4). These pathways activate "helper" NLRs known as RPW8-NBS-LRRs (RNLs), forming activated disease resistance 1 (ADR1) and N requirement gene 1 (NRG1) resistosomes. These resistosomes function as Ca^{2+} channels that mediate transcriptional reprogramming of DR genes and trigger hypersensitive responses (HRs). TIR-only proteins act as 2′,3′-cyclic adenosine monophosphate (cAMP)/cyclic guanosine monophosphate (cGMP) synthetases by hydrolyzing dsRNA/dsDNA, promoting EDS1 signaling through an unknown mechanism. Salicylic acid (SA)-induced NPR1, a positive regulator of plant immunity, interacts with the TGA transcription factor (TF), which triggers the expression of pathogenesis-related (*PR*) genes in the nucleus, ultimately inducing the production of systemic acquired resistance (SAR). Sr35, stem rust resistance gene 35; RPP1, recognition of *Peronospora parasitica* 1; pRib-AMP, 2′-(5″-phosphoribosyl)-5′-adenosine monophosphate; pRib-ADP, 2′-(5″-phosphoribosyl)-5′-adenosine diphosphate; di-ADPR, ADP-ribosylated ADPR; ADPr-ATP, ADP-ribosylated ATP; ds, double-stranded.

(C) Atypical disease resistance (*R*) genes often provide durable, broad-spectrum disease resistance in crops. Examples include the dominant atypical *R* genes *Lr34* and *Lr67*, and the recessive *R* genes *mlo* and *rbl1*, which localize to distinct cellular organelles and contribute to diverse mechanisms that enhance disease resistance. The *MLO* gene, for instance, shows Ca^{2+} channel activity in the plasma membrane, which enhances resistance to powdery mildew in crops such as wheat, rice, and sorghum. RBL1 functions as a phospholipid synthase in the ER and is involved in pathogen effector translocation. When mutated, *RBL1* confers BSR to rice blast and bacterial blight.

cell death during HR (Bi et al., 2021). Unlike the indirect recognition of AvrAC by ZAR1, the CNL Sr35 in wheat, derived from the local variety *Triticum urartu*, directly recognizes the effector AvrSr35 from the stem rust fungus *Puccinia graminis* f. sp. *tritici* and assembles into a pentameric resistosome following allosteric activation. This activation occurs when the N-terminal CC domain of Sr35 interacts with its central nucleotide-binding oligomerization domain (Salcedo et al., 2017). The Sr35 resistosome also forms a Ca^{2+}-permeable channel in the plasma membrane, facilitating Ca^{2+} influx and

leading to localized cell death at the infection sites (Förderer et al., 2022). Similarly, the *Arabidopsis* CNL RPS2 recognizes the effector AvrRpt2 from *P. syringae*, inducing Ca^{2+} influx and triggering HR (Yuan et al., 2021). In rice, the CNL pair RGA4/RGA5 recognizes AvrPia and AvrCO39 from *M. oryzae* and mediates resistance to rice blast. PigmR, another CNL protein in rice, interacts with PigmR-INTERACTING and BLAST RESISTANCE PROTEIN 1 (PIBP1) through the CC domain. This interaction promotes the nuclear accumulation of PIBP1, which binds to the promoter of the defense-related (DR) genes *OsWAK14* and *OsPAL1*, thereby inducing robust blast resistance but reducing rice yield (Zhai et al., 2019). Conversely, *PigmS* in rice disrupts the homodimerization of *PigmR*, balancing resistance and yield (Deng et al., 2017). In maize, the typical CNL protein Rp1-D confers resistance to common rust (Liu et al., 2021b). Rp1-D21, generated by recombination of two NLRs encoded by genes *Rp1-dp2* and *Rp1-D*, triggers HR in *Nicotiana benthamiana* when expressed transiently alone or with its CC domain (Luan et al., 2021). *MLA1* encodes a CNL that is homologous to a protein with dual functionality, conferring resistance to powdery mildew in barley and stripe rust in wheat (Jordan et al., 2011).

Compared to CNLs, the N-terminal TIR domain of TNLs exhibits nicotinamide adenine dinucleotide (NAD) hydrolase activity (Ma et al., 2020; Jia et al., 2022). TIR domain proteins catalyze the ADP ribosylation of ATP and adenosine diphosphate ribose (ADPR) to activate two distinct immune signaling pathways: enhanced disease susceptibility 1 (EDS1) - phytoalexin deficient 4 (PAD4) in conjunction with helper NLR-activated disease resistance 1 (ADR1) and EDS1 - senescence-associated gene 101 (SAG101) alongside another helper NLR N requirement gene, 1 (NRG1). Upon activation, NRG1, similar to CNL resistosomes, oligomerizes into Ca^{2+}-permeable channels, leading to cell death (Huang et al., 2022). In *Arabidopsis*, the TNL RPP1 directly binds to the effector ATR1 of the downy mildew pathogen *Hyaloperonospora arabidopsidis*, forming a tetrameric resistosome. This assembly significantly enhances the nicotinamide adenine dinucleotide hydrolysis activity of RPP1. The nucleotide-binding oligomerization domain of RPP1 binds to ADP, triggering EDS1-dependent ETI (Martin et al., 2020; Duxbury et al., 2021). Additionally, TIR-only proteins, which lack the C-terminal effector-sensing domains, employ conserved signaling pathways similar to those of TNLs. For example, the transient expression of TIR-only proteins in *Nicotiana benthamiana* triggers nicotinamide adenine dinucleotide glycohydrolase-dependent cell death (Song et al., 2024). In *Arabidopsis*, the TIR-only protein RBA1 recognizes the effector HopBA1 from *Pseudomonas fluorescens* to induce EDS1-dependent ETI (Nishimura et al., 2017). Structural analyses of these R proteins and their biochemical mechanisms provide novel insights into the engineering of R proteins. However, the complete molecular events activated by these signaling molecules remain to be fully elucidated.

Atypical *R* genes

Atypical *R* genes are defined as immunity genes that do not encode traditional immune receptors but often exhibit durable BSR (Sun et al., 2024b). The first class of atypical *R* genes includes executor and executor-like *R* genes, which are direct targets of transcription activator-like (TAL) effectors. These effectors, a class of type III effectors predominantly secreted by *Xanthomonas*, trigger HR through TAL effector-dependent transcriptional activation of executor *R* genes (Boch and Bonas, 2010). For example, *Xa23*, an executor *R* gene cloned from wild rice (*Oryza rufipogon*), is activated by AvrXa23 of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), the causal agent of rice bacterial blight, conferring robust BSR to bacterial blight (Wang et al., 2015). Similar transcriptional activation-mediated resistance has been observed in other executor-like *R* genes. WeiTsing is specifically induced in the pericycle upon infection by the protist *Plasmodiophora brassicae* and mediates the formation of a pentameric ion channel that releases Ca^{2+} from the endoplasmic reticulum (ER) into the cytoplasm, activating a series of immune responses and conferring clubroot resistance in *Brassica napus* (Wang et al., 2023). The barley executor-like *R* gene *Rph3* is induced by Rph3-avirulent *Puccinia hordei* strains and confers resistance to leaf rust (Dinh et al., 2022). The pepper executor *R* gene *Bs3*, a flavin monooxygenase, is involved in the flavin adenine dinucleotide- and nicotinamide adenine dinucleotide phosphate-dependent oxidation reaction that confers resistance to bacterial spot disease (Romer et al., 2007). These atypical *R* gene-mediated signaling pathways are associated with both PTI and ETI, featuring reactions such as ROS burst, Ca^{2+} influx, and HR. However, some atypical *R* genes are involved in cellular processes that do not clearly align with PTI or ETI. For example, mycotoxin-degrading enzymes confer resistance to fungal pathogens. Notably, *Fhb7* in wheat encodes a glutathione S-transferase that catalyzes the breakdown of the mycotoxin (deoxynivalenol), resulting in resistance to *Fusarium* head blight (Wang et al., 2020a). Atypical *R* genes also encompass mutations in disease-susceptibility (*S*) genes or DNA elements. Arguably the most well-known atypical *R* gene, *MLO*, is a pleiotropic gene that affects both plant senescence and yield while functioning as a susceptibility factor to powdery mildew (Buschges et al., 1997). Initially cloned in barley, *mlo* orthologs have been identified in various crops, including wheat, rice, tomato, pea, cucumber, and grape, enhancing resistance to powdery mildew (Appiano et al., 2015; Kusch and Panstruga, 2017). Finally, TAL effectors from *Xoo* bind to effector binding elements (EBEs) in the promoter of some *S* genes, such as *SWEETs*, facilitating pathogen infection. When an EBE is mutated, TAL effectors cannot bind to these mutated EBEs, and the plant lines harboring these mutated EBEs exhibit BSR to bacterial blight (Nowack et al., 2022).

Unified plant immunity

Despite the distinct pathogen recognition mechanisms and immune signaling pathways of PTI and ETI, these systems synergistically enhance plant immunity. In *Arabidopsis*, Yuan et al. (2021) observed that ETI enhances the transcription and protein levels of RBOHD, while PTI specifically activates its phosphorylation. Additionally, Ngou et al. (2021) revealed that ETI can respond to PTI by robustly activating and prolonging the phosphorylation of key immune proteins, including BIK1, RBOHD, and MPK3. In rice, Zhai et al. (2022) demonstrated the critical role of the deubiquitinase PigmR-interacting and chitin-induced protein 1 (PICI1) in both PTI and ETI. Pathogen-secreted toxic effectors directly target and degrade PICI1, suppressing PTI. Conversely, PigmR competitively inhibits the interaction between pathogen effectors and PICI1, stabilizing PICI1 by reducing the ubiquitination

level of methionine synthase, which activates the ET pathway and thus stimulates robust ETI (Zhai et al., 2022). Furthermore, signals from PTI, DTI, and ETI interact with one another (Saijo et al., 2018; Ge et al., 2022). The LRR-RLK protein BAK TO LIFE 2 (BTL2) interacts with the DAMP receptors PEPR1/2 and male discoverer 1-interacting RLK2 (MIK2) upon the perception of Peps and serine-rich endogenous peptides, respectively. This interaction hyperactivates DTI when sensing BAK1 damage, initiating robust immune responses through the EDS1-PAD4-ADR1 signaling pathway, leading to cell death and compensating for compromised PTI (Yu et al., 2023). This unified view of plant immunity provides unique insights into BSR and facilitates the development of novel BSR engineering strategies.

Phytohormones

Phytohormones are small endogenous signaling molecules, some of which play crucial roles in plant defense responses, such as salicylic acid (SA), ET, and jasmonate (JA) (Fabregas and Fernie, 2021). SA is known to trigger systemic acquired resistance (SAR) in *Arabidopsis*, with NPR1 acting as a master regulator of SA-induced defense responses. A recent discovery shows that the mobile signal hydrogen peroxide (H_2O_2) sulfenylates the transcription factor CHE, which then binds to the promoter of the SA-biosynthesis gene *ICS1*, thereby promoting SAR (Cao et al., 2024). Loss of function mutations in *ICS* causes increased susceptibility to *Fusarium* head blight in wheat by reducing SA accumulation (Zhang et al., 2024c). JA, a lipid-derived phytohormone, positively regulates plant immunity against necrotrophic pathogens (Kumar et al., 2024). For example, *GausRVE2*, a Myb-like transcription factor, enhances resistance to *Verticillium* wilt in cotton by promoting the JA signaling pathway (Liu et al., 2023). In sweet potato, the overexpression of the B-box (BBX) transcription factor *IbBBX24* enhances resistance to *Fusarium* wilt by boosting JA signaling (Zhang et al., 2020). ET, a gaseous phytohormone, often acts synergistically with JA to enhance resistance to pathogen invasions. For instance, OsEIL1, a master regulator of the ET signaling pathway in rice, binds directly to the promoters of the nicotinamide adenine dinucleotide phosphate oxidase gene *OsRBOH* and the JA biosynthesis gene *OsOPR4*, activating their expression. This activation facilitates the accumulation of ROS and phytoalexins, thereby enhancing disease resistance to rice blast (Yang et al., 2017a). Overexpression of the transcription factor *NF-YC15* improves resistance to cassava bacterial blight via the ET-mediated immunity pathway (Zheng et al., 2024). The interaction among SA, JA, and ET forms a complex network that mediates resistance to various plant pathogens. Typically, SA and ET/JA-mediated responses antagonistically contribute to resistance against pathogens. In *Arabidopsis*, infection with the biotrophic pathogen *P. syringae* induces an SA-mediated immune response, which increases susceptibility to the necrotrophic pathogen *Alternaria brassicae* by inhibiting the JA/ET signaling pathway (Spoel et al., 2007). In rice, Meng et al. (2020) identified a nucleus-localized basic-helix-loop-helix transcription activator, OsbHLH6, which decreases rice blast disease resistance by activating JA signaling and suppressing the SA signaling pathway in the early stages of infection (before 24 h). However, at later infection stages (after 24 h), OsNPR1-induced export of OsbHLH6 from the nucleus to the cytosol substantially suppresses OsbHLH6-mediated activation of JA signaling but activates SA signaling, thereby conferring resistance to rice blast (Meng et al., 2020). Despite the well-established mutual inhibition between SA and JA, their relationship is not always antagonistic. OsEIL2, a positive regulator of the rice ET signaling pathway, regulates SA- and JA-mediated synergistic pathways. When induced by necrotrophs, OsEIL2 enhances resistance to *Rhizoctonia solani* through the accumulation of SA and JA. Conversely, during infections by the hemibiotroph *M. oryzae* and the biotroph *Xoo*, induced OsEIL2 reduces resistance to these pathogens by decreasing SA and JA levels (Zhao et al., 2024). Additionally, Wang et al. (2024a) demonstrated that introducing two healthy rhizosphere biomarkers, *Sphingomonas azotifigens* and *Rhizobium deserti*, into the rhizosphere confers resistance to wheat yellow mosaic virus (WYMV) by simultaneously activating SA and JA signaling pathways during infection. Furthermore, Li et al. (2023a) developed dual-inducible promoters by combining SA- and JA-responsive *cis*elements to drive the expression of antimicrobial peptides, enhancing BSR against powdery mildew in tobacco, early blight in tomato, and *Verticillium* wilt and *Fusarium* wilt in cotton.

Antimicrobial peptides and phytoalexins

Additionally, plants produce a diverse array of metabolites, including phytoalexins and antimicrobial peptides (AMPs), which play crucial roles in suppressing pathogen infections through their antimicrobial activities. In *Arabidopsis*, camalexin, an indolic compound derived from tryptophan metabolism, is pivotal in resistance to diseases such as gray mold (Zhou et al., 2020a). The regulation of camalexin-mediated disease resistance is synergistically influenced by ET and JA signaling pathways, facilitated by interactions between the ET response factor 1 (ERF1) and *WRKY33* transcription factor in *Arabidopsis* (Zhou et al., 2022a). In rice, resistance to rice blast is mediated by a hydroxycinnamoylputrescine biosynthesis gene cluster, which includes a decarboxylase gene (*OsODC*) and two putrescine hydroxycinnamoyl acyltransferase genes (*OsPHT3* and *OsPHT4*), leading to the accumulation of hydroxycinnamoylputrescine (Fang et al., 2021). Similarly, Shen et al. (2021) identified a hydroxycinnamoyl tyramine gene cluster that contains a pyridoxamine 5′-phosphate oxidase gene (*OsPDX3*), a pyridoxal phosphate-dependent tyrosine decarboxylase gene (*OsTyDC1*), and two duplicated hydroxycinnamoyl transferase genes (*OsTHT1* and *OsTHT2*). The end products of this cluster enhance resistance to both rice blast and bacterial blight (Shen et al., 2021). In maize, *ZmCCoAOMT2* encodes a caffeoyl-coenzyme A (CoA) *O*-methyltransferase that confers quantitative resistance to both southern leaf blight and gray leaf spot. This resistance is achieved through graded levels of metabolites synthesized in the phenylpropanoid and lipoxygenase pathways (Yang et al., 2017b). In oat, avenacins are antifungal metabolites biosynthesized by a gene cluster located in the subtelomeric region of the genome. These compounds are particularly effective against soil-borne diseases, such as take-all, providing significant protection (Li et al., 2021c). AMPs also play a crucial role in regulating several signaling pathways that enhance resistance to biotic stresses (Ghosh and Roychoudhury, 2024). Similar to phytoalexins, AMPs confer resistance against various plant pathogens. For example, the expression of defensin Mj-AMP1 from *Mirabilis jalapa* enhances resistance to early blight in tomato (Schaefer et al., 2005). Similarly, the overexpression of hevein-like proteins, antifungal peptides Pn-AMPs from seeds of morning glory, provides protection against crown and root rot in tobacco (Lee et al., 2003).

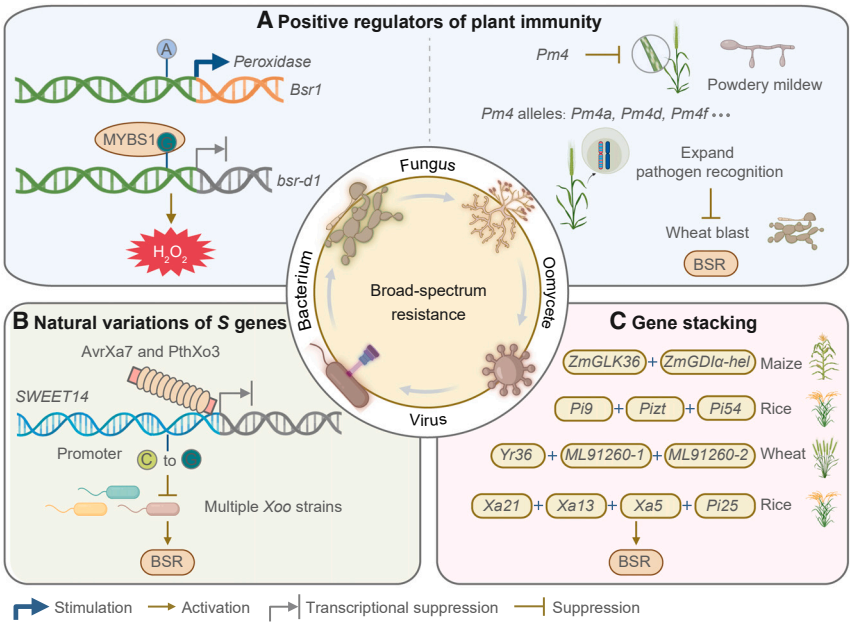

Figure 2. An overview of scenarios conferring BSR in crops

(A) A single *R* gene can confer broad-spectrum resistance (BSR) to multiple strains of the same pathogen or to multiple different pathogens in crops (left). In this example, the rice MYB transcription repressor (MYBS1) binds to the *bsr-d1* promoter and reduces the expression of *Bsr-d1*, which is induced by the rice blast fungus *M. oryzae*. This reduction in *Bsr-d1* expression decreases the transcription of peroxidase-encoding genes and attenuates hydrogen peroxide (H_2O_2) degradation, leading to H_2O_2 accumulation and conferring BSR to rice blast. Different alleles of *R* genes can sometimes confer BSR, offering insights into strategies for broadening the resistance spectrum of *R* genes (right). For example, in wheat, different alleles of the wheat powdery mildew *R* gene *Pm4* recognize various alleles of the *AVR-Rmg8* effector, and some *Pm4* alleles can confer resistance to wheat blast.

(B) Some plant pathogens secrete transcription activator-like (TAL) effectors into the host cell, where they bind to the effector-binding element (EBE) in the promoter of a susceptibility (*S*) gene, thereby inducing *S* gene expression and facilitating pathogen infection. A C-to-G substitution in the EBE of the rice *S* gene *SWEET14*, which encodes a sugar transporter hijacked by the pathogen *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), disrupts the induced expression of *SWEET14*, effectively starving the pathogen and enhancing BSR to isolates targeting this EBE.

(C) Gene stacking involves pyramiding multiple *R* genes into a single crop cultivar, which can be tailored to confer BSR against multiple diseases or to increase the durability of resistance by incorporating several *R* genes.

CURRENT UNDERSTANDING OF BSR MECHANISMS IN CROPS

The development of disease-resistant crops has been a major focus of both researchers and breeders (Deng et al., 2020). Understanding the molecular mechanisms underlying BSR opens new avenues for crop improvement. Most known plant resistance genes encode race-specific NLRs, which are generally susceptible to evasion by rapidly evolving pathogens. Therefore, genes that confer BSR are particularly valuable as they often provide durable resistance against multiple pathogens. Here, crop BSR genes are classified into three categories: positive regulators of plant immunity, negative regulators of immunity represented by deletions or variants of *S* genes and lesion-mimic mutant (LMM) genes, and stacks of multiple *R* genes (Figure 2). BSR genes have been identified across a variety of crops, providing resistance to a diverse array of pathogens. A summary of notable BSR genes is presented in Table 1.

Positive regulators of plant immunity conferring BSR

Some *R* genes have undergone evolutionary sequence variations that enhance BSR. In rice, the *Pike* locus, comprising two adjacent CNL genes, *Pike-1* and *Pike-2*, confers BSR to rice blast. The specificity of *Pike*-mediated resistance is determined by Pike-1, not Pike-2, as only the CC domain of Pike-1 can interact with AvrPik-D. A novel allele at the *Pik* locus, *Pikg,* features a single amino acid substitution (D229E) in the Pike-1 CC domain, enhancing BSR against various *M. oryzae* strains (Meng et al., 2021). In addition, Zhou et al. (2020b) identified 13 novel *Pi9* alleles with insertions or deletions (indels) in 361 blast-resistant rice varieties, with types 3/4/5/6/9/10/11 of *Pi9* alleles conferring BSR to rice blast. In wheat, the *Yr27* allele of the leaf rust *R* gene *Lr13* encodes a protein sharing 1043 of 1072 amino acids with the reference protein but differs by only 2.7%, enhancing resistance to stripe rust (Athiyannan et al., 2022). The recognition of various alleles of *AVR-Rmg8* by different alleles of the wheat powdery mildew *R* gene *Pm4* enhances resistance to both leaf and panicle blast (Sánchez-Martín et al., 2021). In barley, the *Mla* (*Mildew locus a*) locus displays substantial structural and copy number variability, with *Mla8* showing 97.4% identity to *Mla1.* Despite being a single-copy gene, *Mla8* exhibits polymorphisms exclusively in the LRR region and provides dual resistance to barley powdery mildew and wheat stripe rust (Bettgenhaeuser et al., 2021). These natural allelic BSR variants provide valuable resources for identifying additional BSR genes and developing new targets for genome editing and R protein engineering. In wheat, two durable BSR genes derived from naturally occurring membrane transporter variants have been particularly notable. The first gene, *Lr34*, encodes an ABC transporter variant that confers durable BSR against diseases such as rust and powdery mildew (Krattinger et al., 2019). Notably, stable transgenic expression of *Lr34* in various crops has conferred resistance to diseases adapted to those crops, including powdery mildew in barley, rice blast in rice, anthracnose and rust in sorghum, and leaf blight and rust in maize (Schnippenkoetter et al., 2017). Similarly, the second gene, *Lr67*, encodes a hexose transporter variant that confers resistance to the same wheat diseases as *Lr34* and exhibits cross-species functionality as a transgene (Milne et al., 2019). Specific mutations, G144R and V387L, underlie the resistant allele of *Lr67*, with the G144R mutation alone demonstrated to confer rust resistance when introduced into the barley ortholog of *Lr67* (*HvSTP13*). This finding suggests potential for

Gene	Host	Product	Pathogen	Reference
DMR6	*Arabidopsis*	2-oxoglutarate and Fe(II) oxygenase	*C. higginsianum*, *H. arabidopsidis*, *H. parasitica*, *P. capsici*, *P. syringae* pv. *tomato* DC3000	Wang et al., 2024
EFR	*Arabidopsis*	elongation factor TU or elf18 receptor	*D. dadantii*, *P. atrosepticum*, *P. carotovorum*, *P. syringae* pv. *tomato DC3000*	Lacombe et al., 2010
FLS2	*Arabidopsis*	flagellin receptor	*P. syringae* pv. *phaseolicola*, *P. syringae* pv. *tomato* DC3000	Robatzek et al., 2006
PEN1	*Arabidopsis*	syntaxin	*B. graminis* f. sp. *hordei*, *E. pisi*	Johansson et al., 2014
PEN2	*Arabidopsis*	glycosyl hydrolase	*B. graminis* f. sp. *hordei*, *E. cichoracearum*, *E. pisi*	Parween et al., 2021
PEN3	*Arabidopsis*	ATP binding cassette transporter	*E. cichoracearum*, *P. syringae* pv. *tomato* DC3000	Parween et al., 2021
NPR1	*Arabidopsis*	BTB/POZ-ankyrin repeat protein	*P. syringae, P. parasitica*	Zavaliev et al., 2020
RPW8.1	*Arabidopsis*	NH2-terminal transmembrane domain and CC protein	*E. cichoracearum*, *P. syringae*	Yang et al., 2024
Mla	barley	*mildew locus a*	*B. graminis* f. sp. *hordei*, *P. striiformis* f. sp. *tritici*	Bettgenhaeuser et al., 2021
MLO	barley	calcium channel	*B. graminis* f. sp. *hordei* stains	Buschges et al., 1997
Rph3	barley	putative transmembrane protein	*P. hordei* strains	Dinh et al., 2022
GhMPK7	cotton	MAPK	*C. nicotianae*, potato virus Y	Shi et al., 2010
GhnsLTPsA10	cotton	non-specific lipid transfer protein	*V. dahliae*, *F. oxysporum* f. sp. *vasinfectum*	Chen et al., 2021
GhRVD1	cotton	intracellular immune receptor	*V. dahliae* strains	Zhang et al., 2023
RppK	maize	CC-NB-LRR protein	*P. polysora* strains	Chen et al., 2022a
ZmAuxRP1	maize	auxin-regulated protein 1	*F. graminearum*, *F. verticillioides*	Ye et al., 2019
ZmCCoAOMT2	maize	caffeoyl-CoA-*O*-methyltransferase	*C. heterostrophus*, *C. zeina*	Yang et al., 2017b
ZmGLK36	maize	A G2-like transcription factor	maize rough dwarf virus, rice black-streaked dwarf virus	Xu et al., 2023
ZmMM1	maize	transcription factor	*C. heterostrophus*, *C. zeina, S. turcica*	Wang et al., 2021
ELR	potato	ELR protein	*Phytophthora* species	Du et al., 2015
StDND1	potato	cyclic nucleotide-gated cation channel	*P. infestans* strains	Sun et al., 2022
BSR1	rice	receptor-like cytoplasmic kinase	*B. glumae*, *C. miyabeanus*, *M. oryzae*, rice stripe virus, *X. oryzae* pv. *oryzae*	Wu et al., 2022
Bsr-d1	rice	transcription factor	*M. oryzae* strains	Li et al., 2017
Bsr-k1	rice	TPR-domain RNA-binding protein	*M. oryzae*, *X. oryzae* pv. *oryzae*	Zhou et al., 2018
HDT701	rice	histone H4 deacetylase	*M. oryzae*, *X. oryzae* pv. *oryzae*	Ding et al., 2012
IPA1	rice	transcription factor	*M. oryzae*, *X. oryzae* pv. *oryzae*	Wang et al., 2018a
LML1	rice	eukaryotic release factor	*M. oryzae*, *X. oryzae* pv. *oryzae*	Qin et al., 2018
LMM5.1/5.4	rice	translation elongation factor 1A-like protein	*M. oryzae*, *X. oryzae* pv. *oryzae*	Zhao et al., 2017
OsNPR1	rice	BTB/POZ-ankyrin repeat protein	*M. oryzae*, *X. oryzae* pv. *oryzae*	Feng et al., 2011
OsWRKY45	rice	transcription factor		Shimono et al., 2012

Table 1. Selected BSR genes in plants.

(Continued on next page)

Gene	Host	Product	Pathogen	Reference
			M. oryzae, *X. oryzae* pv. *oryzae*, *X. oryzae* pv. *oryzicola*	
RBL1	rice	CDP-DAG synthase	*M. oryzae, U. virens*, *X. oryzae* pv. *oryzae*	Sha et al., 2023
ROD1	rice	C2 domain Ca^{2+} sensor	*M. oryzae, R. solani*, *X. oryzae* pv. *oryzae*	Gao et al., 2021
SPL11	rice	U-box/ARM E3 ubiquitin ligase	*M. oryzae*, *X. oryzae* pv. *oryzae*	Fan et al., 2018
SPL28	rice	clathrin associated	*M. oryzae*, *X. oryzae* pv. *oryzae*	Qiao et al., 2010
SPL33	rice	translation elongation factor	*M. oryzae*, *X. oryzae* pv. *oryzae*	Wang et al., 2017
Xa5	rice	small (γ) subunit of the basal transcription factor	*X. oryzae* pv. *oryzicola*, *X. oryzae* pv. *oryzae*	Jiang et al., 2006
Xa13	rice	sugar transporter	*R. solani*, *X. oryzae* pv. *oryzae*	Gao et al., 2018
Xa21	rice	receptor kinase-like protein	*X. oryzae* pv. *oryzae* strains	Ercoli et al., 2022
GmMEKK1	soybean	MAPK	*P. manschurica*, soybean mosaic virus	Xu et al., 2018
GmMPK4	soybean	MAPK	*P. manschurica*, soybean mosaic virus	Liu et al., 2011
eIF4E1/eIF 4E2	tomato	translation initiation factor	tomato spotted wilt virus, alfalfa mosaic virus, cucumber mosaic virus, and TMV	Mazier et al., 2011
SlDMR6-1	tomato	2-oxoglutarate and Fe(II) oxygenase	*P. syringae* pv. *tomato* DC3000, *P. capsica, X. gardneri*, *X. perforans*	Thomazella et al., 2021
SlPUB24	tomato	U-box E3 ubiquitin ligase	*X. euvesicatoria* pv. *euvesicatoria*, *X. vesicatoria*, *X. euvesicatoria* pv. *perforans*, *X. cynarae* pv. *gardneri*	Liu et al., 2021
SlRIPK	tomato	receptor-like cytosolic kinase	*R. solanacearum*, *P. carotovorum*, *B. cinerea*, *F. oxysporum*	Wang et al., 2022
Sw-5b	tomato	intracellular immune receptor	tomato spotted wilt virus, groundnut ring spot virus, tomato chlorotic spot virus	Zhu et al., 2017
Fhb7	wheat	glutathione S-transferase	*Fusarium* species	Wang et al., 2020a
Lr34	wheat	ABC transporter	*B. graminis* f. sp. *tritici*, *P. triticina*, *P. graminis* f. sp. *tritici*, *P. striiformis* f. sp. *tritici*	Krattinger et al., 2019
Lr67	wheat	hexose transporter	*B. graminis* f. sp. *tritici*, *P. triticina*, *P. graminis* f. sp. *tritici*, *P. striiformis* f. sp. *tritici*	Milne et al., 2019
Pm21	wheat	typical CC-NBS LRR protein	*B. graminis* f. sp. *tritici* strains	He et al., 2018
Pm24/Rwt4	wheat	tandem kinase	*B. graminis* f. sp. *tritici*, *Pyricularia oryzae* (syn. *M. oryzae*)	Lu et al., 2020; Arora et al., 2023
Pm4	wheat	putative chimeric kinase-MCTP protein	*B. graminis* f. sp. *tritici*. *Pyricularia oryzae* (syn. *M. oryzae*)	Sánchez-Martín et al., 2021
Stb16q	wheat	plasma membrane cysteine-rich RLK	*Z. tritici* strains	Saintenac et al., 2021
Yr15	wheat	tandem kinase-pseudokinase	*P. striiformis* f. sp.*tritici* strains	Klymiuk et al., 2018
Yr27/Lr13	wheat	intracellular immune receptor	*P. triticina*, *P. striiformis* f. sp. *tritici*	Athiyannan et al., 2022

Table 1. ***Continued***

modifying orthologous genes for disease resistance across diverse crops via base or prime editing, given the conservation of the G144 residue and the STP13 family across species (Gupta et al., 2021; Skoppek et al., 2022). The wheat stripe rust BSR gene *Yr36* encodes a protein with a serine/threonine kinase and a putative steroidogenic acute regulatory protein-related lipid transfer lipid-binding domain. Yr36 confers resistance to multiple stripe rust races by phosphorylating thylakoid ascorbate peroxidases, resulting in ROS accumulation (Gou et al., 2015). In barley and wheat, overexpression of the dominant *R* gene, *barley stripe resistance 1* (*BSR1*), encoding a typical CNL protein, confers resistance to barley stripe mosaic

virus (Wu et al., 2022). In rice, the MYB transcription repressor (MYBS1) binds to the *bsr-d1* promoter, preventing the induction of *bsr-d1* by *M. oryzae*. This leads to reduced expression of *bsr-d1* and the accumulation of its encoded peroxidase, thereby attenuating the degradation of H_2O_2 and enhancing BSR to rice blast (Li et al., 2017). Similarly, *IPA1* encodes a transcription factor that bolsters blast resistance through binding to the promoter of the immune regulatory gene *WRKY45* upon *M. oryzae*-induced phosphorylation of IPA1 (Wang et al., 2018a). In maize, *RppK*, a typical *R* gene, confers resistance to southern corn rust caused by *Puccinia polysora*. Introgression of *RppK* into multiple maize lines has shown robust BSR against all tested *P. polysora* races (Chen et al., 2022a). In potato, the R protein RLP ELR (elicitin response) from the wild potato *Solanum microdontum* enhances BSR to potato late blight by recognizing elicitins as oomycete PAMPs (Du et al., 2015). Although the primary functions of these *R* genes require further investigation, their conservation in various crops highlights the potential for developing new sources of multipathogen resistance.

Loss of susceptibility and LMM genes conferring BSR

Loss-of-function mutations in *S* genes, often considered negative regulators of plant immunity, frequently confer BSR in crops (van Schie and Takken, 2014). In rice, TAL effectors secreted by *Xoo* bind to EBEs in the promoters of *SWEET* sucrose transporter genes, inducing their expression and hijacking these transporters to siphon nutrients, which results in disease susceptibility. Counteracting *Xoo*-mediated *SWEET* induction is a strategy to achieve disease resistance. Natural variations in the EBEs of the *SWEET13* and *SWEET14* genes have been identified. A 2-bp deletion and a substitution in the EBE of *OsSWEET13* effectively inhibit infection by the *Xoo* PXO339 strain carrying the TAL effector PthXo2. Similarly, a single-nucleotide substitution in the EBE of *OsSWEET14* prevents invasion by the *Xoo* strain PXO86 that carries AvrXa7 (Zaka et al., 2018). A single substitution in the promoter of *OsSWEET11* prevents recognition by the *Xoo* strain PXO99, which carries PthXo1, leading to enhanced BSR in rice (Römer et al., 2010). For multipathogen resistance in rice, *ROD1* encodes a Ca^{2+} sensor protein, a disease-susceptibility factor, where a natural variant of *ROD1* caused by a single-nucleotide deletion exhibits robust BSR to rice blast, bacterial blight, and sheath blight. In maize, loss of function of *ZmROD1* shows enhanced resistance to maize sheath blight, demonstrating that *ROD1* is a candidate gene for trans-crop applications (Gao et al., 2021a). In soybean, GmMPK4 acts as a negative immune regulator. GmMPK4-silenced lines show increased resistance to downy mildew and soybean mosaic virus due to the accumulation of SA and H_2O_2 (Rui and Wang, 2024). In addition to the loss of susceptibility factors, LMM genes also confer BSR in various crops. In maize, Zhang et al. identified a teosinte-derived allele of a resistance gene, *ZmMM1*, which encodes a transcription repressor with an MYB-DNA binding domain. ZmMM1 confers BSR to northern leaf blight, gray leaf spot, and southern corn rust by binding to the promoter region of the long non-coding RNA gene *ZmMT3*, thereby suppressing its transcription and promoting ROS accumulation (Wang et al., 2021). A dominant *disease lesion mimic* mutant, *Les8,* shows enhanced resistance to both *Curvularia* leaf spot and southern leaf blight through the accumulation of JA and lignin (Li et al., 2023). The LMM gene *LLS1*/*LES30*, encoding pheophorbide *a* oxidase involved in chlorophyll degradation, confers BSR to *Curvularia* leaf spot, common rust, southern leaf blight, and anthracnose in maize (Li et al., 2022a). Similarly, Liu et al. (2017) cloned the LMM gene *OsCUL3a*, encoding a negative regulator of plant immunity. Early termination of the OsCUL3a protein in the LMM mutant *oscul3a* confers BSR to rice blast and bacterial blight (Liu et al., 2017). These *S* genes and LMM genes that negatively regulate plant immunity represent important targets for genetic engineering, including genome editing, to improve plant disease resistance. They provide new genetic resources for breeding disease-resistant crop varieties (Lapin and Van den Ackerveken, 2013).

Gene stacking of *R* genes for BSR using a traditional breeding strategy

Gene stacking is an effective strategy for integrating multiple desirable traits into crops (Crété et al., 2020), particularly for enhancing disease resistance. This approach often involves combining multiple *R* genes, typically encoding NLR and executor R proteins, to confer BSR against various crop diseases. Zheng et al. (2020) developed wheat lines with enhanced BSR and improved grain quality by stacking the stripe rust *R* gene *Yr26* and the powdery mildew *R* gene *ML91260* into elite wheat cultivars (Zheng et al., 2020). Additionally, the combination of *Yr30* with a quantitative trait locus on chromosome arm 4BL (YrFDC12) demonstrated enhanced resistance to stripe rust (Zhou et al., 2022b). In maize, the *ZmGLK36* and *ZmGDIα-hel* genes were combined in lines highly susceptible to maize rough dwarf disease, significantly improving resistance (Li et al., 2024d). In rice, extensive use of pyramiding different *Pi* genes has proven effective in conferring BSR to rice blast. Monogenic near-isogenic lines (NILs) NIL^{Pi9}, NIL^{Pizt}, and NIL^{Pi54}, which carry the *Pi9*, *Pizt*, and *Pi54* genes, respectively, were developed through marker-assisted backcrossing. The polygenic pyramid lines *Pi9*/*Pi54* and *Pizt*/*Pi54* showed BSR to rice blast (Xiao et al., 2016). Similarly, gene combinations such as *Pigm*/*Pi1*, *Pigm*/*Pi54*, *Pigm*/*Pi33*, and *Pijx*/*Piz-t* have also conferred BSR to rice blast (Wu et al., 2019; Xiao et al., 2023). The hybrid rice line 9A/R8012, produced by multi-generation hybridization and backcrossing with several superior hybrid rice lines harboring multiple *R* genes, including *Xa21*, *Xa13*, *Xa5*, and *Pi25*, exhibited robust resistance to both rice blast and bacterial blight (Chukwu et al., 2019). Lines pyramided with multiple genes, such as those combining *Xa7* and *Xa21*, *Xa21*, *Xa4* and *Xa23*, and *Xa5*, *Xa13* and *Xa21*, have shown BSR to bacterial blight. However, not all combinations of *R* genes result in additive disease resistance. For example, *Xa27*-mediated resistance was significantly compromised by the addition of the *R* gene *Xa5* (Gu et al., 2009). Similarly, when the *Xa5*, *Xa23*, *Xa10*, and *Xa27* genes were combined, the resultant lines showed reduced resistance to bacterial blight to some extent (Tian et al., 2014). While the pathogen population and pleiotropy must be considered carefully in gene stacking, this strategy remains the most effective for achieving BSR in breeding.

TRADITIONAL GENETIC ENGINEERING FACILITATES BSR

Transgenic approaches to combine *R* gene-mediated BSR in crops

Transgenic approaches have significantly expedited the acquisition of desired traits in plants, particularly in enhancing disease resistance. For instance, to combat wheat stem rust, a gateway

recombinase cloning strategy was employed to construct a gene cassette containing five *R* genes: the race-specific resistance genes *Sr22*, *Sr35*, *Sr45*, *Sr50* and the multipathogen resistance gene *Sr55*. This cassette was transformed into wheat at a single locus, enabling rapid gene stacking and conferring BSR against both stem rust and leaf rust (Luo et al., 2021). Similarly, four wheat *R* genes (*Sr22*, *Sr33*, *Sr35*, and *Sr45*) were introduced into barley, providing BSR against stem rust (Hatta et al., 2021). Additionally, *Sr26* and *Sr61*, derived from tall wheat-grass (*Thinopyrum ponticum*), encode unrelated NLR proteins. Their combined expression confers resistance to multiple races of stem rust (Zhang et al., 2021). In maize, Zhu et al. (2018) employed a similar strategy to pyramid nine genes (*Chi*, *Glu*, *Ace-AMP1*, *Tlp*, *Rs-AFP2*, *ZmPROPEP1*, *Pti4*, *Iap*, and *p35*), resulting in a maize line with enhanced resistance to maize sheath blight and southern leaf blight. Overexpression of the polyamine oxidase (*PAO*) gene in soybean leads to increased production of H_2O_2, enhancing resistance to multiple *Phytophthora* isolates without affecting other key agronomic traits (Yang et al., 2022b). In rice, six genes (*EPSPS*, *OsLecRK1*, *Bph14*, *Cry1C*, *Xa23*, and *Pi9*) were introduced into an elite rice cultivar using a multi-gene transformation method, enhancing resistance to multiple diseases (rice blast and bacterial blight), pests (brown planthopper), and herbicides (glyphosate) (Li et al., 2024c). Transgenic approaches are crucial for rapidly transferring multiple genes into a single locus, resulting in much simpler heritability than gene stacking via conventional breeding.

Antimicrobial peptides and phytoalexins can facilitate BSR in crops

The production of proteinaceous and chemical compounds with antimicrobial activities is an important approach for achieving BSR in crops (Li et al., 2021a). During infection, pathogens secrete small effector proteins to manipulate plant immunity and facilitate successful colonization. Successful effector translocation often requires host components, including various phospholipid species, which are also integral to defense mechanisms involving AMPs. Specific proteins that bind to phosphatidylinositol 3-phosphate (PI3P) can direct AMPs to the surfaces of *Phytophthora* pathogens, thereby inhibiting their infection. For example, transgenic tobacco, soybean, and potato plants expressing two AMPs from the Chinese medicinal herb Gastrodia elata, GAFP1 or GAFP3, fused with a PI3P-specific binding domain, have shown enhanced BSR against *Phytophthora* pathogens (Zhou et al., 2021; Helliwell et al., 2022; Yang et al., 2023). This strategy utilizes the same AMPs to disrupt the infection processes of multiple pathogens, thereby achieving BSR. Like AMPs, phytoalexins exhibit biological activity against various pathogens and play an important role in disease resistance. In rice, overexpression of the selenium-binding protein homolog (*SBP*) gene increased resistance to rice blast and bacterial blight through the accumulation of momilactone A (Sawada et al., 2004). Additionally, overexpression of *CYP71Z18* significantly enhanced blast resistance in rice by catalyzing the accumulation of the antimicrobial diterpenoid phytoalexin dolabralexin (Shen et al., 2019). Stilbene, another type of phytoalexin, inhibits fungal growth. Overexpression of the grapevine stilbene synthase gene *Vst1* in common spring wheat has enhanced resistance to powdery mildew (Liang et al., 2000). Advanced techniques from medical biology for identifying useful AMPs and phytoalexins can be adapted for crop applications. For instance, a machine learning approach was employed to screen 2349 AMPs derived from the human gut microbiome, leading to the identification of 11 AMPs with high antimicrobial potency (Ma et al., 2022). Such AI-assisted methods could potentially expedite BSR studies by identifying novel AMPs. Furthermore, the application of AMP sprays, such as peceleganan, has been utilized to treat skin wound infections and has reached the clinical trial stage (Wei et al., 2023; 2024b). Similarly, the topical application of AMPs or phytoalexins could serve as a viable complementary method to genetic strategies for enhancing BSR in crops.

Epigenetic modifications conferring BSR in crops

In plant immune regulation, epigenetic modifications, such as histone methylation, acetylation, ubiquitination, and DNA methylation and demethylation, play crucial roles in *R* gene-mediated immunity (Xie and Duan, 2023). These processes are emerging as promising strategies to enhance BSR (Ramirez-Prado et al., 2018). In rice, JMJ704, a histone H3 lysine 4 trimethylation (H3K4me2/3) demethylase, acts as a positive regulator of immunity against bacterial blight. JMJ704 enhances resistance by suppressing the expression of negative immune regulators, such as *NRR* and *OsWRKY62*, through the removal of H3K4me2/3, maintaining their transcriptional inactivation (Hou et al., 2015). Similarly, histone acetylation is pivotal in plant immunity; in rice, the HD2 subfamily histone deacetylase HDT701 functions as a negative regulator by modulating histone H4 acetylation of *DR* genes against bacterial blight (Ding et al., 2012). In wheat, the histone deacetylase TaHDA6 interacts with TaHOS15 and is recruited to the promoter of *R* genes, including *TaPR1*, *TaPR2*, *TaPR5*, and *TaWRKY45*, fine-tuning resistance to powdery mildew (Zhi et al., 2020). Histone ubiquitination also influences plant immunity by modulating JA, SA, and ET hormone signaling pathways (Gao et al., 2022). For instance, HUB1, an E3 ligase for histone 2B monoubiquitination, is a crucial regulator of plant defense against necrotrophic pathogens. In tomato, SlHUB1 and SlHUB2 positively regulate plant defense responses to *B. cinerea* by modulating hormone-mediated signaling pathways (Zhang et al., 2015). Moreover, maintaining DNA methylation homeostasis is essential for *R* gene expression and enhancing crop disease resistance. For example, DNA methylation in the promoter of the *R* gene *Pib* regulates its induction upon *M. oryzae* infection, thereby enhancing resistance to rice blast (Li et al., 2011). Additionally, *PigmS*, a gene harboring two tandem miniature transposons in its promoter (MITE1 and MITE2), shows increased expression through the methylation of MITE1 and MITE2, thereby interfering with *PigmR* homodimerization and mitigating *PigmR*-mediated resistance to rice blast in the panicle, balancing yield and immunity (Deng et al., 2017). Epigenetic factors serve as key regulators in the transcriptional reprogramming of plant immune responses, suggesting that epigenetics-based strategies can be broadly employed to enhance plant disease resistance.

RNAi-mediated BSR

RNA interference (RNAi) has emerged as an effective approach for achieving BSR in crops (Tang et al., 2021). This method involves gene silencing mediated by double-stranded RNA (dsRNA) that specifically targets the mRNAs of homologous genes. Dicer-like proteins process these dsRNA molecules into

small interfering RNAs (siRNAs) of 21–23 bp. These siRNAs then associate with Argonaute proteins and other enzymes to form the RNA-induced silencing complex, which binds to complementary mRNA and cleaves it, thereby suppressing gene expression. In plants, RNAi generates various small RNAs (sRNAs), including microRNAs (miRNAs) and siRNAs, which facilitate mRNA degradation (Rosa et al., 2018). Specifically, miR164-no apical meristem/Arabidopsis transcription activation factor/cup-shaped cotyledon (NAC) transcription factors are known to negatively regulate disease resistance against stripe rust in wheat, rice blast in rice, and *Verticillium* wilt in cotton caused by the fungal pathogen *Verticillium dahliae* (Feng et al., 2014; Wang et al., 2018b; Hu et al., 2020). For example, Osa-miR164a targets *OsNAC60*, reducing its expression and thereby enhancing BSR to rice blast and bacterial blight. miR160a enhances disease resistance partially by suppressing *ARF8,* and *ARF8* protein binds directly to the promoter and suppresses the expression of *WRKY45*, which acts as a positive regulator of rice immunity (Feng et al., 2022). Interestingly, the insect salivary microRNA miR-7-5P, secreted into host plants during feeding, facilitates communication between insects and plants. Silencing miR-7-5P in the insect *Nilaparvata lugens* enhances plant resistance by upregulating the plant immune-associated basic leucine zipper transcription factor 43 (OsbZIP43) (Zhang et al., 2024). In tomato and soybean, the miR164a/OsNAC60 regulatory module enhances resistance to late blight in tomato and root rot in soybean (Wang et al., 2018b). Beyond fungal and oomycete pathogens, RNAi also proves effective against plant viruses. Viral genes must be introduced into the host and utilize its molecular machinery to replicate; thus, RNAi can silence these viral genes without requiring sRNAs to penetrate the virus itself. In rice, a hairpin RNA structure incorporating sequences from rice ragged stunt virus and rice grassy stunt virus was introduced into *Indica* rice through double transfer DNA transformation. The resulting marker-free rice lines demonstrated enhanced resistance to both viruses without impacting yield (Xie et al., 2024). Similarly, Li et al. (2024b) engineered hairpins that target sequences from four viruses—rice black-streaked dwarf virus (RBSDV), southern RBSDV, rice stripe virus (RSV), and rice ragged stunt virus. This innovative approach produced the ZJU-4K rice line, which exhibits BSR to all four viruses, showcasing the potential for rapid development of elite crop varieties resistant to viral pathogens (Li et al., 2024b).

Host-induced gene silencing (HIGS) is a cross-kingdom RNAi strategy that suppresses pathogen genes through the expression of pathogen-derived dsRNAs in host plants. This method significantly enhances plant resistance to pathogens. sRNAs can be transferred between plants and pathogens, resulting in the silencing of target genes, a process known as cross-kingdom RNAi. In the *Arabidopsis-B. cinerea* pathosystem, plants transfer sRNAs into *B*. *cinerea*, silencing fungal virulence genes and thereby reducing fungal infection to achieve BSR (Cai et al., 2018). In rice, the simultaneous targeting of two chitin synthase genes of *Ustilaginoidea virens*, *UvChs2* and *UvChs5*, which are responsible for the synthesis of key components of fungal cell walls and are involved in *U. virens* infection—enhances resistance to rice false smut (Li et al., 2021b). In the stripe rust fungus of wheat, *PsFUZ7*, a MAPK-encoding gene, regulates fungal infection. Stable RNAi of *PsFUZ7* in wheat confers robust resistance to stripe rust (Zhu et al., 2017b). For another wheat disease, *Fusarium* head blight, host-induced silencing of three virulence genes (*FgSGE1*, *FgSTE12*, and *FgPP1*) of *Fusarium graminearum* enhances resistance. These genes respectively encode a regulator of deoxynivalenol biosynthesis, a key transcription factor for penetration structure formation, and an essential phosphatase (Wang et al., 2020b). In maize, *Aspergillus flavus*, a fungal pathogen that produces mycotoxins including aflatoxins, is targeted by HIGS. Omolehin et al. (2021) transformed maize with a hairpin construct targeting the alkaline protease (*alk*) gene involved in aflatoxin biosynthesis in *A. flavus*, thereby conferring resistance to aflatoxin production. During cotton-*V*. *dahliae* interactions, VdEXG, a cell wall-degrading enzyme, is upregulated and plays a pivotal role in fungal carbon source utilization, cell wall penetration, and pathogenesis (Su et al., 2020). Utilizing the HIGS strategy, Su et al. (2024) developed transgenic cotton varieties with enhanced resistance to *Verticillium* wilt by specifically silencing *VdEXG*. In pepper, targeting the *Phytophthora capsici* RXLR effector genes *RXLR1* or *RXLR4* enhances resistance to *Phytophthora* blight disease (Cheng et al., 2022). RNAi gene silencing techniques are powerful tools for engineering disease-resistant crops and have the potential to significantly enhance crop resistance to multiple diseases caused by fungi, oomycetes, and viruses (Lopez-Gomollon and Baulcombe, 2022). These advancements have profound implications for agricultural production.

GENOME EDITING FOR BSR

Over the past few decades, the development of genome editing tools, such as zinc-finger nucleases (ZFNs), transcription-activator-like effector nucleases (TALENs), and CRISPR-Cas systems, has significantly advanced BSR engineering in crops (Karmakar et al., 2022). Among these, the CRISPR-Cas system has emerged as one of the most advanced and precise methods for genetic manipulation due to its simplicity, high efficiency, and versatility (Gao, 2021). Various CRISPR-Cas tools have been developed for a range of genetic modifications, including targeted gene knockout, gene insertion and replacement, base editing, epigenome editing, and CRISPR-mediated transcriptional regulation (Figure 3). Additionally, a novel genome editing tool based on a transposon-associated RNA-guided endonuclease known as TnpB, considered the ancestor of Cas12, has been engineered for genome editing (Karvelis et al., 2021). Recent applications of TnpB-mediated genome editing have successfully knocked out target genes in *Arabidopsis*, rice, and several medicinal plants, demonstrating its efficacy (Zhang et al., 2024a; Li et al., 2024f; Karmakar et al., 2024; Lv et al., 2024). Given its smaller size (approximately 400 amino acids) compared to Cas nucleases, as well as its comparable editing efficiency to SaCas9, programmability, and extensive diversity, TnpB holds significant potential for improving BSR in crops. In contrast to conventional crop breeding approaches, which largely rely on the discovery and screening of natural genetic variations and the pyramiding of elite traits through cross-breeding, genome editing propels innovation in plant breeding. This technology facilitates the exploration and application of crop disease resistance, pushing beyond current limitations and advancing to the next generation of crop improvement strategies (Li et al., 2024a).

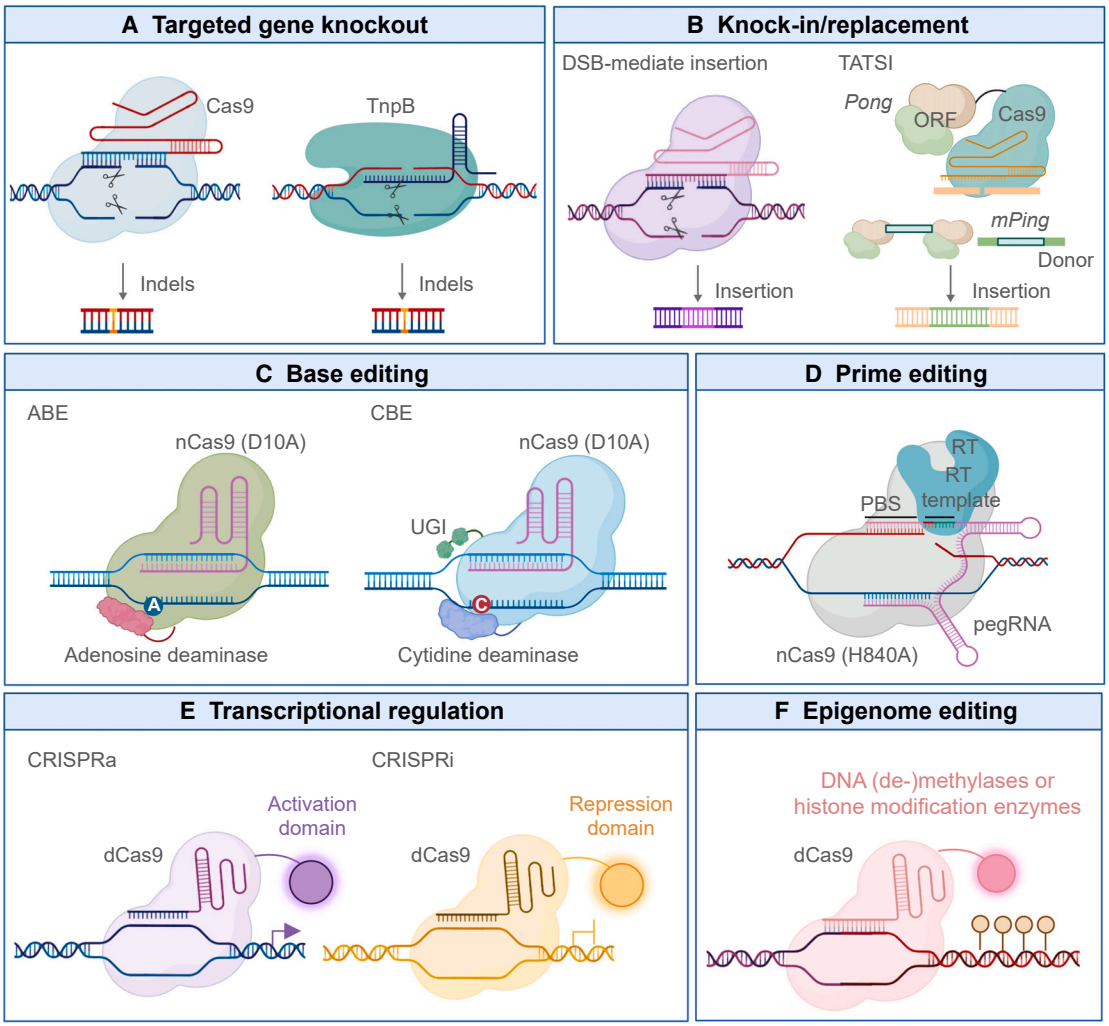

Figure 3. Diverse genome editing technologies facilitate BSR engineering

(A) CRISPR-Cas-mediated targeted gene knockout. Loss-of-function mutations are generated by introducing insertions or deletions (indels) into the target gene. A small TnpB protein, consisting of 400 amino acids, was used to develop hypercompact genome editors, which achieve high editing efficiency. This approach can modify a considerable number of *S* genes, generating novel *R* alleles.

(B) Targeted DNA segment insertion and allele replacement are achieved through DNA double-strand break (DSB)-mediated DNA repair in the presence of donor templates. For example, targeted insertion or replacement of resistant alleles can be accomplished by excision and insertion of the non-autonomous rice transposable element *mPing* by *Pong* ORF1 and ORF2. TATSI, transposase-assisted target site integration.

(C) The adenine base editors (ABE) and cytosine base editors (CBE) consist of a catalytically impaired Cas9 (nCas9 [D10A]) and either an adenosine deaminase or cytidine deaminase enzyme. Using base editing, a G > A mutation (M441I) was introduced into the endogenous *pi-d2* gene, restoring its resistance to rice blast. UGI, uracil DNA glycosylase inhibitor.

(D) Prime editing utilizes a Cas9 nickase (nCas9 [H840A]) fused to an engineered reverse transcriptase (RT) along with a prime editing guide RNA. The prime editing-mediated recombination of opportune targets (PrimeRoot) enables precise insertion of large DNA fragments. Using PrimeRoot, the *R* gene *PigmR*, driven by the *OsAct1* promoter, was precisely integrated into the rice genome, conferring resistance to rice blast. PBS, primer binding site.

(E) CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi) systems use a catalytically dead Cas9 (dCas9) along with a transcriptional activation or repression domain, respectively. CRISPRa and CRISPRi can be employed to regulate gene expression, achieving BSR in crops.

(F) Epigenome editors consist of dCas9 and one or more enzymes that modify DNA methylation, demethylation, or histone modifications. The reversibility of epigenetic markers enables the manipulation of chromatin and epigenetic signatures, making it an appealing strategy for BSR breeding.

Genome editing strategies for improving BSR in crops are summarized in Figure 4.

Targeted insertions and substitutions for BSR

In genome editing, targeted DNA insertion or replacement leverages endogenous DNA double-strand break (DSB) repair mechanisms: non-homologous end joining (NHEJ) and homology-directed repair (HDR). NHEJ, which can be engineered to cut and ligate DNA fragments at the DSB site (Chang et al., 2017), often results in non-directional integrations and introduces insertions or deletions (indels) at the ends of the inserted donor fragments, making this method less precise (Suzuki et al., 2016). Conversely, HDR-mediated genome editing allows for the precise incorporation or replacement of desired sequences at specific loci in crop genomes. However, using HDR in plants is

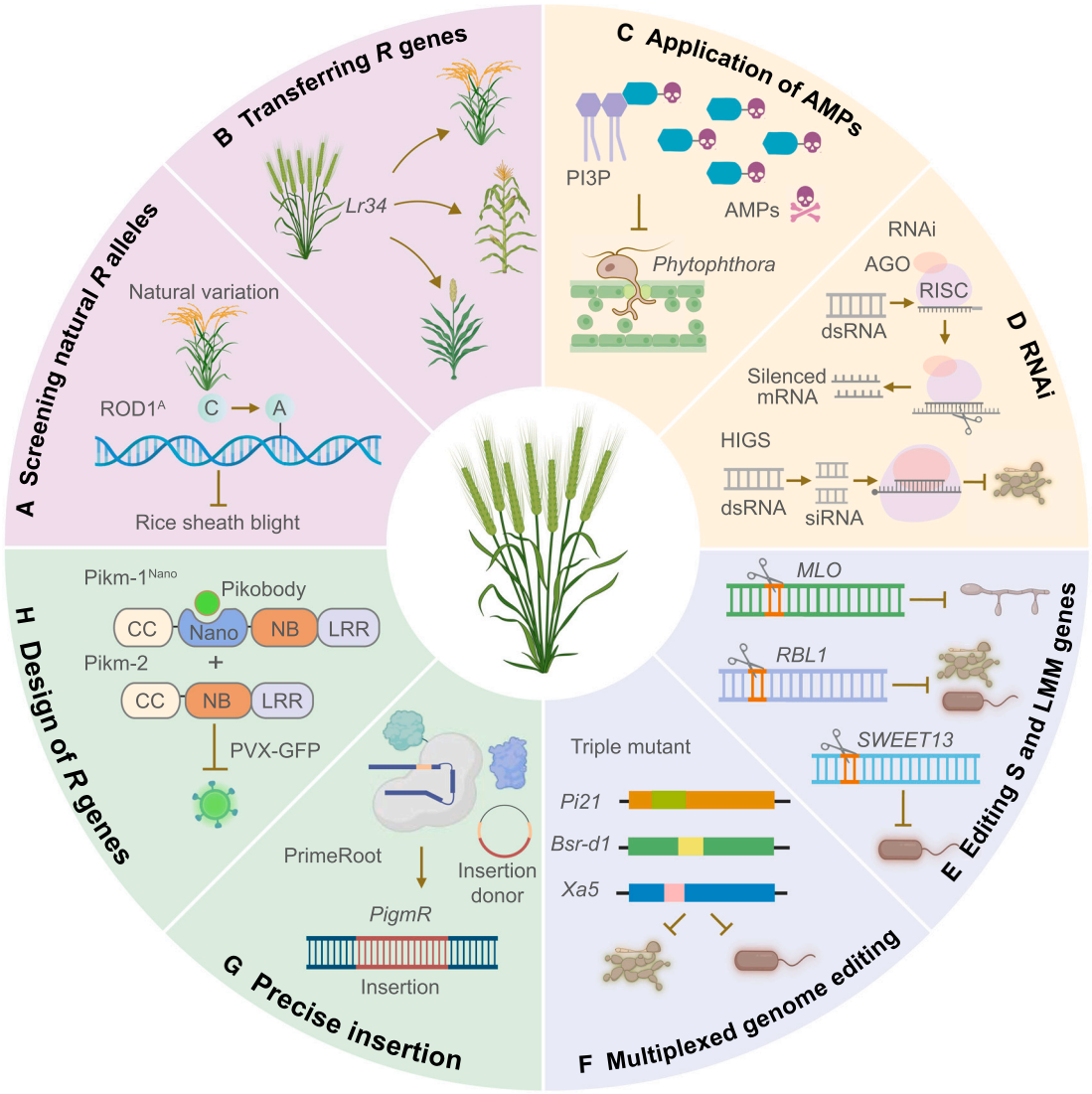

Figure 4. Strategies for BSR in crops

(A) Screening for *R* gene alleles is a common method for identifying naturally occurring mutations associated with BSR, providing targets for genetic engineering. For example, *ROD1* (SNP1^{A}), a SNP in the coding region of *ROD1*, enhances resistance to sheath blight in rice.

(B) Transferring *R* genes across different crops can serve as a source of BSR. For instance, *Lr34* from wheat has been shown to enhance resistance to powdery mildew in barley, rice blast in rice, anthracnose and rust in sorghum, and leaf blight and rust in maize through trans-crop applications.

(C) AMPs can suppress pathogen invasion and confer BSR. *Phytophthora*-derived phosphatidylinositol 3-phosphate (PI3P) has been used to guide AMPs to the surface of *Phytophthora* pathogens during infection, enhancing disease resistance.

(D) Silencing virulence genes via RNAi is an effective strategy for conferring BSR in crops, particularly for the control of viruses. Host-induced gene silencing (HIGS) has been successfully used to confer BSR to fungal and oomycete pathogens. dsRNA, double-stranded RNA; siRNA, small interfering RNA; AGO, Argonaute; RISC, RNA-induced silencing complex.

(E) Editing *S* genes, LMM genes and or negative regulators of plant immunity, which are exploited by pathogens, is a reliable technique for achieving BSR. For example, knockout of wheat *MLO* and rice *SWEET* genes confers BSR.

(F) Multiplexed genome editing enables the simultaneous editing of multiple *S* genes, enhancing BSR in crops.

(G) Precise insertion or replacement techniques are used to insert or replace *R* gene alleles in crops. For example, *PigmR* has been successfully applied using PrimeRoot technology.

(H) *R* gene design strategies can also mediate BSR in crops. For example, the NLR immune receptor Pikm, when fused with nanobodies that recognize fluorescent proteins, confers enhanced resistance to Potato virus X (PVX) that expresses the corresponding fluorescent proteins. Nano, nanobody.

challenging due to its significantly lower efficiency compared to NHEJ in DSB repair. Recent advancements include a study in rice where introducing a 10-EBE array, responsive to TAL effectors from various *Xoo* and *X. oryzae* pv. *oryzicola* strains, into the commercial cultivar Nangeng 46 through genome editing conferred durable BSR to 50 *Xoo* strains and 30 *Xanthomonas oryzae* pv. *oryzicola* strains (Wang et al., 2024c). Additionally, Li et al. (2016) achieved gene replacements in rice by applying NHEJ-mediated site-specific replacement and insertion to confer glyphosate resistance through the modification of

the endogenous gene *EPSPS*. In tobacco, the *R* gene *N′* mediates resistance only against the tobacco mosaic virus (TMV) crucifer-infecting strain (TMV-Cg) but not the TMV-U1 strain. Employing the CRISPR-Cas9 system, two resistance-related regions of the *N′* gene were replaced with homologous fragments of the *N′alata* gene, which shares high sequence identity with *N′*, thus conferring resistance to the TMV-U1 strain (Li et al., 2023b). Furthermore, Liu et al. (2024) developed a novel genome engineering tool, the transposase-assisted target-site integration (TATSI) system, by fusing the rice Pong transposase protein with Cas nucleases. TATSI was successfully applied for sequence-specific targeted insertion of enhancer elements, an open reading frame, and a gene expression cassette in the genomes of *Arabidopsis* and soybean, demonstrating its versatility and precision (Liu et al., 2024).

In addition to DSB-based gene insertion and replacement, base editors and their derived tools, which do not introduce DSBs, have been used to introduce single-nucleotide variants, contributing significantly to BSR in crops such as rice, wheat, maize, and tomato. *Pi-d2*, an agriculturally important *R* gene in rice, confers resistance to *M. oryzae,* the causative agent of rice blast. A single amino acid substitution (I441M) at position 441 in Pi-d2 results in the loss of resistance to *M. oryzae* (Chen et al., 2006). To counter this, an optimized base editor known as rBE5, which combines a mutant version of the human activation-induced cytidine deaminase cytosine deaminase with nCa9 (Cas9 nickase), was employed to introduce a G > A substitution (M441I) into the endogenous *Pi-d2* gene, thereby restoring its resistance to rice blast (Ren et al., 2018). In citrus, the effector PthA4, which is transported from the pathogen to plant cells, binds to the EBE in the promoter of the *S* gene *LOB1*, activating its expression and contributing to the development of citrus canker. Jia et al. (2024) employed Cas12a/CBE co-editing technology to generate transgene-free, canker-resistant citrus plants by mutating the EBE in the *LOB1* promoter. Prime editing, a precise and highly versatile editing technology that avoids DSBs, can induce all 12 types of DNA substitutions, as well as indels, at targeted sites. Prime editing technologies have advanced rapidly and are being applied in crops with increasing success. For example, an optimized prime editor engineered by modifying the Moloney murine leukemia virus reverse transcriptase—by removing its ribonuclease H domain and incorporating a viral nucleocapsid protein with nucleic acid chaperone activity—has greatly improved prime editing efficiency across a variety of target sites in rice and wheat (Zong et al., 2022). Despite its broad utility, prime editing is often limited by its inability to insert large DNA fragments. A new genome editing tool, PrimeRoot, which combines prime editing with site-specific recombinases, has been developed to precisely insert large DNA fragments of up to 11.1 kb into the rice genome. Using PrimeRoot, the rice BSR gene *PigmR*, driven by the *OsAct1* (rice *Actin1*) promoter, was accurately integrated into the rice genome, conferring enhanced resistance to rice blast (Sun et al., 2024a).

Saturation mutagenesis for new *R* genes alleles

Although natural *R* gene alleles are limited, they have provided valuable resources for disease resistance in crops (Deng et al., 2024). In contrast, saturation mutagenesis produces diverse variant libraries, offering a resource for identifying new *R* gene alleles. In saturation mutagenesis, random or targeted mutations are introduced into the protein-coding sequences or regulatory regions of genes, creating a library of mutant alleles. These alleles are then screened for those exhibiting desirable traits, such as enhanced resistance. Saturation mutagenesis is a straightforward technique for functional studies of genes and the generation of elite alleles. In rice, an elite allele named *RBL1*$^{\Delta 12}$ was generated through CRISPR–Cas9-based saturation mutagenesis, which harbors a 12-bp deletion in *RBL1 and* confers BSR to rice blast, rice false smut, and bacterial blight without a yield penalty (Sha et al., 2023). Additionally, the trade-off between immunity and yield—often caused by known BSR genes—can now be circumvented (Figure 5). Engineered dual-base editors have also been applied for the directed evolution of *OsACC*, achieving near-saturation mutagenesis and rapidly generating herbicide-resistant rice lines (Li et al., 2020). Recently, Chen et al. (2024) developed a novel platform, helicase-assisted continuous editing, which fuses helicase with deaminase to induce hypermutation in the downstream genomic sequence. This platform has the potential to serve as a powerful tool for targeted saturation mutagenesis to generate numerous candidate BSR genes (Chen et al., 2024). In addition to these advancements, saturation mutagenesis can also be used to knock down or knock up phytoalexin biosynthetic pathway genes, thereby maximizing their production and contributing to BSR. Overall, the current genome editing toolkit represents a powerful set of resources for the directed evolution of crops with enhanced BSR.

Editing *S* genes and negative regulators of resistance for BSR

SWEET sugar transporters are a family of plant susceptibility factors commonly targeted by bacterial pathogens. Loss of *SWEET* function or preventing the hijacking of *SWEET* gene expression can confer disease resistance. For example, targeted mutagenesis of the *OsSWEET14* promoter confers resistance to rice bacterial blight through transcription-activator-like effector nuclease-based disruption (Zeng et al., 2020). Similarly, targeted mutation of *OsSWEET13* also results in resistance to rice bacterial blight (Zhou et al., 2015). In another case, mutating *OsAP47*, an aspartic proteinase, enhances resistance against RBSDV and southern RBSDV (Wang et al., 2022c). Knockout of *DMR6* orthologs using CRISPR-Cas9 confers resistance to a range of diseases including downy mildew in barley, bacterial leaf streak in rice, banana *Xanthomonas* wilt in banana, and bacterial spot and powdery mildew in tomato (Thomazella et al., 2021). Similarly, the same tool was used to knock out *TaPsIPK1*, a negative immune regulator in wheat, enhancing BSR to stripe rust without compromising yield (Wang et al., 2022a). The *TaHRC* gene encodes a histidine-rich calcium-binding protein that serves as a disease susceptibility factor for wheat *Fusarium* head blight. Ding et al. (2023) discovered the rice homolog, *OsHRC*, and mutation of *OsHRC* confers resistance to rice blast. The goal of multiplexed genome editing is to simultaneously target multiple loci or genes, enabling the rapid generation of genetic variants with enhanced BSR (Zhu et al., 2020). By editing multiple *S* genes, multiplexed genome editing can enhance disease resistance in crops to various pathogens. In rice, mutations in the promoters of three *SWEET* genes (*SWEET11*, *SWEET13*, and *SWEET14*) using CRISPR-Cas9 enhance resistance to bacterial blight (Oliva et al., 2019). The

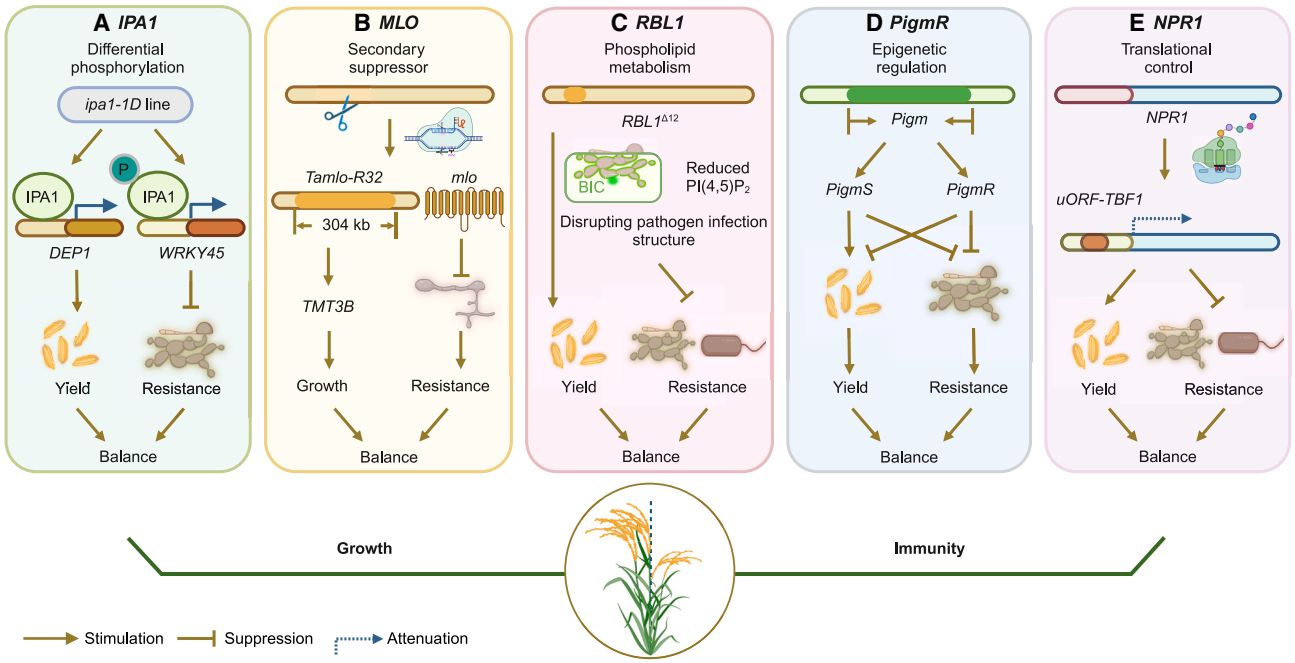

Figure 5. Strategies to balance growth-immunity trade-offs in crops

(A) Phosphorylation of IPA1 is critical for balancing immunity and yield in rice. In the *ipa1-1D* mutant, IPA1 binds to the promoter of *DEP1* to promote its expression, thereby regulating rice yield. Phosphorylated IPA1, induced by *M. oryzae* infection, preferentially binds to the promoter of *WRKY45*, a positive transcription factor of plant immunity, and enhances its expression, thereby improving disease resistance.

(B) *Tamlo-R32*, generated by editing the *MLO* genes, alters chromatin structure, increasing the expression of the upstream gene *TaTMT3*, which encodes tonoplast monosaccharide transporter 3. This modification mitigates the growth penalties caused by *MLO* mutations, achieving a balance between immunity and yield.

(C) Phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), a disease susceptibility factor in rice, is enriched in cellular structures involved in fungal effector translocation. A specific novel allele, $RBL1^{\Delta 12}$, involved in $PI(4,5)P_2$ biosynthesis, is generated via CRISPR-Cas9 and confers BSR without yield penalty by disrupting pathogen infection-specific structures through the reduction of $PI(4,5)P_2$. BIC, biotrophic interfacial complex.

(D) PigmR NLR forms homodimers that confer BSR but cause yield losses. In contrast, PigmS competitively suppresses the homodimerization of PigmR to inhibit resistance. Additionally, *PigmS* is epigenetically regulated and is highly expressed in rice pollen, counteracting the yield penalty associated with *PigmR*.

(E) Constitutive activation of NPR1, an activator of SA-mediated plant immunity, significantly inhibits plant growth. The translation of TBF1, a key immune regulator, is rapidly and transiently induced to enhance resistance upon pathogen infection in *Arabidopsis*. The upstream open reading frame (uORF) of *TBF1-NPR1* mediates this translational control mechanism, conferring BSR to rice blast, bacterial blight, and bacterial leaf streak without compromising plant fitness.

pi21-bsr-d1-xa5 triple mutant shows significantly enhanced resistance to both rice blast and bacterial blight without growth penalties (Tao et al., 2021). Similarly, mutations in *Bsr-d1*, *Pi21*, and *ERF922* enhance resistance to rice blast and bacterial blight (Zhou et al., 2022b). *MLO* was originally identified as an *S* gene for powdery mildew resistance in barley and is conserved across monocots and dicots (Bai et al., 2008). In wheat, Wang et al. (2014) knocked out all three *TaMLO* genes simultaneously, conferring BSR to powdery mildew. A novel *mlo* wheat line, *Tamlo-R32*, shows disease resistance to powdery mildew without compromising yield due to induced chromatin structure remodeling (Li et al., 2022c). Likewise, targeted mutation of *SlMLO* through CRISPR-Cas9 enhances disease resistance to powdery mildew in tomato (Nekrasov et al., 2017). NPR3, a homolog of NPR1, negatively regulates SA-mediated defense responses. Mutation of *NPR3* confers resistance to potato zebra chip disease by activating SA signaling (Ramasamy et al., 2024). In tomato, knockout of *SlBBX20*, a BBX transcription factor, confers resistance to gray mold disease by modulating JA signaling (Luo et al., 2023). In barley, simultaneous knockout of *HvMORC1* and *HvMORC6a* confers BSR to powdery mildew and *Fusarium* head blight (Galli et al., 2022).

Transcriptional and translational control of *R* genes for BSR

The ability to regulate gene expression and protein translation to generate quantitative phenotypic changes is crucial for developing novel and desirable traits in crops, including enhanced BSR (Xue et al., 2023). Gene expression is governed by diverse regulatory elements, including promoters, 5′ upstream open reading frames (uORFs), and 5′ and 3′ untranslated regions (UTRs). In the context of crop disease resistance, these regulatory elements play a significant role in modulating resistance levels. For example, in wheat, a transposon insertion in the 3′ UTR of the *R* gene *Pm41b* reduces its expression and resistance to powdery mildew (Li et al., 2022b). In rice, 3′ UTR polymorphisms in two *S* genes, *RNG1* and *RNG3*, are associated with changes in their expression levels and blast resistance (Xu et al., 2023a). *Cis*-regulatory element variants generally induce

subtle phenotypic changes by modulating the expression levels of target genes, making the editing of these elements a promising strategy for improving agronomic traits. For example, CRISPR-Cas9-mediated mutagenesis of the *SlCLV3* promoter in tomato generates novel *cis*-element alleles, leading to a wide range of quantitative variations in gene expression (Rodríguez-Leal et al., 2017). The CRISPR-Cas12a promoter editing (CAPE) system has been applied in rice to produce quantitative trait variation continuums for grain starch content, size, and semidwarfism by targeting *OsGBSS1*, *OsGS3*, and *OsD18*, respectively. This approach could be adapted for BSR engineering in crops (Zhou et al., 2023). In addition to editing cis-regulatory elements, introducing transcriptional regulatory proteins is another effective method for manipulating gene expression. CRISPR-dCas-mediated transcriptional interference (CRISPRi) and activation (CRISPRa) are used to suppress or enhance gene expression, respectively (Heidersbach et al., 2023). While altering gene expression by fusing dead Cas9 (dCas9) with transcriptional or epigenetic regulators has been widely explored in mammalian systems and model plants, its application for achieving BSR in crops is still emerging. Recently, CRISPRi has been applied to pathogens for pathogenesis studies. Zhang et al. (2023b) developed a novel CRISPRi toolkit that employs a single guide RNA to achieve a 100-fold reduction in target gene expression. Using tRNA-gRNA strategies, they simultaneously silenced *MoATG3*, *MoATG7*, and *UvPal1* in rice blast and false smut fungi, respectively, facilitating functional genomics studies of these two devastating fungal pathogens. This approach provides new targets for crop BSR engineering (Zhang et al., 2023b). Another promising approach to achieving BSR is pathogen-induced CRISPRa, which upregulates genes involved in plant immunity. For example, diacylglycerol kinase 5, which is involved in phosphatidic acid biosynthesis, contributes to resistance against both bacterial and fungal pathogens (Gong et al., 2024). In a recent study, Yao et al. (2024) introduced an *in-locus* activation technique to achieve efficient multiplexed gene upregulation in rice through CRISPR-Cas-mediated insertion of short transcriptional enhancers into target gene promoters (Yao et al., 2024). The ability of CRISPRi and CRISPRa to simultaneously control the expression of multiple genes makes them powerful tools for achieving BSR in crops. These techniques allow precise reprogramming of *R* and *S* genes, which could strike a balance between disease resistance and other important traits in crops. Given the potential of these methods, they are likely to become key components of crop improvement strategies aimed at enhancing disease resistance.

In addition to altering gene expression levels using the methods described above, 5′ uORFs are important alternative targets for genome editing due to their role in the regulation of protein translation (Si et al., 2020). For example, in rice, $uORF_{TBF1}$-mediated translational control of NPR1, a master regulator of SA-mediated immunity, is used to precisely regulate its protein translation, resulting in enhanced BSR to rice blast, bacterial blight, and bacterial leaf streak without affecting other agronomic traits (Xu et al., 2017). Similarly, by editing the uORF to suppress the translation efficiency of *OsGS2* in rice, BSR has been achieved with minimal fitness costs (Tian et al., 2024). Base editing and prime editing technologies have also been used to generate novel uORFs or extend existing ones, enabling the fine-tuned regulation of protein translation to produce differential phenotypes. For instance, a series of rice plants with graded phenotypes was generated by editing the 5′ UTR of *OsDLT*, a gene involved in the brassinosteroid signaling pathway (Xue et al., 2023).

Precise control of gene expression is the goal of CRISPR-Cas-based transcriptional and translational tools. AI-guided genome editing has become an increasingly effective strategy for generating desired traits by fine-tuning the expression levels of target genes. When combined with techniques such as assay for transposase-accessible chromatin with high throughput sequencing (ATAC-seq), chromatin immunoprecipitation sequencing (ChIP-seq), and other data providing candidate sites for promoter editing, these strategies can be used to manipulate *R* gene expression and enhance resistance without a growth trade-off in crops (Liu et al., 2021a; Hendelman et al., 2021; Zhou et al., 2023).

CONCLUDING REMARKS AND PROSPECTS

Genetic resistance to crop diseases, particularly BSR, is essential for global food security. Here, we reviewed the plant immune system, common BSR genes and their mechanisms, and genetic engineering approaches, including genome editing, for enhancing BSR. A mechanistic understanding of the plant immune system, including the mutual potentiation of PTI and ETI, along with insights into the biochemical and structural nature of R proteins, significantly advances our knowledge for BSR engineering. Some *R* genes have evolved to provide enhanced BSR, offering valuable insights for engineering new immune receptors with enhanced BSR. For instance, some orphan receptors have been modified to mimic the effector-binding region of Sr35, enabling them to recognize the non-corresponding effector Avr35 (Förderer et al., 2022). These findings suggest that novel elite *R* gene alleles can be identified and integrated into crops to rapidly improve BSR.

Moreover, the study of paired *R* genes presents an innovative strategy for R protein design, which can be widely applied to enhance BSR (Liu et al., 2021d; Zhang et al., 2024b). For example, fusing the NLR Pikm with a nanobody that recognizes fluorescent proteins provides resistance to potato virus X, which expresses the corresponding fluorescent proteins (Kourelis et al., 2023). In addition, newly developed AI-enabled protein design algorithms, such as Rfdiffusion, are facilitating the design of R proteins with enhanced functionality (Watson et al., 2023).

Genome editing will continue to play an increasingly important role in future BSR development. Technological advancements will make genome editing more versatile, enabling diverse strategies for improving disease resistance. Large-scale genome-edited crop populations will provide numerous genetic variants for novel *R* gene alleles. The recent development of the PrimeRoot genome editing tool, which allows the insertion of large fragments into crop genomes, offers a promising avenue for rapidly stacking *R* genes for BSR in different crops (Sun et al., 2024a). Furthermore, AI-enabled technologies will accelerate precise genome editing for BSR, advancing molecular breeding efforts.

Multiplexed genome editing to target multiple *S* genes for BSR will also play an important role in the future of BSR engineering across various crops.

In addition to the aforementioned engineering approaches, natural and mutagenized crop populations will continue to be important sources of BSR genes. These populations have already been developed for several major crops. For instance, a whole-genome-sequenced wheat population consisting of 827 wheat lines from Watkins landraces and 3366 whole-genome-sequenced chickpea varieties has provided 1582 previously unutilized genes, representing an untapped source of new BSR genes (Varshney et al., 2021; Cheng et al., 2024). In rice, a set of 18 142 rice lines, derived from 16 parent accessions of diverse geographic origins, was used to map 1207 quantitative trait loci for 16 agronomic traits using genome-wide association studies, offering a large genetic resource for BSR in crop improvement (Wei et al., 2024a). In maize, a high-density genomic variation map based on 744 maize genomes identified over 70 million SNPs, providing another valuable resource of genetic diversity for the identification of novel BSR alleles (Chen et al., 2022b). The sequencing of multiple wheat genomes has enabled multi-genome comparisons and characterization of the wheat NLR repertoire, facilitating the identification of *Sm1*, a gene associated with insect resistance (Walkowiak et al., 2020). These genetic resources are expected to play a pivotal role in the rapid identification and cloning of crop BSR genes in the future.

As genome editing tools continue to advance and demonstrate success in the genetic improvement of crops, regulatory barriers to transgenic and genome-edited crops are gradually easing (Vora et al., 2023). Attitudes toward the regulation of such crops are becoming more open, facilitating the broader application of genetic engineering and genome editing to enhance BSR in various crops. In summary, the rapid advancement of genetic engineering technologies, including genome editing, combined with positive changes in regulatory policies toward transgenic and genome-edited crops, is accelerating the commercialization of genetically modified crops with substantial implications for global food security.

GLOSSARY

ABE: adenine base editor. Composed of *Escherichia coli* transfer RNA adenosine deaminase and nCas9 (D10A); mediates the conversion of A•T to G•C in genomic DNA.

AMP: antimicrobial peptide. Endogenous polypeptides produced by multicellular organisms; play a crucial role in the innate immunity of the host.

BSR: broad-spectrum resistance. Plant disease resistance to most races or strains of the same pathogen species or resistance to multiple pathogen species.

CBE: cytosine base editor. Composed of cytidine deaminase fused with nCas9 (D10A) and uracil glycosylase inhibitor; converts C•G to T•A in genomic DNA.

CRISPR-Cas: Clustered regularly interspaced palindromic repeats/CRISPR-associated proteins. Targets DNA or RNA in microbes as part of the adaptive immune system and has been engineered into the canonical genome editing tool for RNA-guided genetic manipulation.

DTI: danger-triggered immunity. A process whereby plant plasma membrane receptor kinases recognize plant-derived DAMPs and subsequently initiate host immune responses.

EBE: effector binding element. A DNA sequence that TAL effectors recognize and bind. The presence of an *EBE* in the promoter of a gene makes the gene inducible by TALE effectors.

Effector: A protein produced by pathogens that is secreted into host cells and can disrupt the plant immune response or alter plant gene expression to facilitate infection.

ETI: effector-triggered immunity. The process by which pathogen effectors are sensed by NLR receptors to activate a strong immune response.

LMM: lesion-mimic mutant. A mutant that typically exhibits autoimmunity and HR-like cell death in the absence of biotic or abiotic stress.

NLR: nucleotide-binding LRR receptor. An immune receptor that recognizes pathogen effectors within the cell.

PAMP: pathogen-associated molecular pattern. A highly conserved molecular structure present in microorganisms, such as chitin and flagellin.

PE: prime editor. Composed of a Cas9 nickase (Cas9 H840A) fused to a reverse transcriptase, which utilizes a prime editing guide RNA to target and encode specific edits. PEs can introduce all 12 types of base substitutions and small DNA indels in a precise and targeted manner.

PrimeRoot editor: prime editing-mediated recombination of opportune targets (PrimeRoot). A tool derived from prime editors that combines a PE and site-specific recombinases. It is capable of precisely inserting large DNA fragments into plants without DSB intermediates.

PRR: pattern recognition receptor. Located on the plasma membrane, PRRs can directly recognize specific molecular structures on the surface of pathogens.

PTI: pattern-triggered immunity. A type of plant immune system mediated by cell surface-localized PRRs. PTI is triggered by the recognition of conserved molecular structures present in pathogens.

Resistosome: a large oligomeric complex formed via the direct or indirect recognition of pathogen effectors by plant NLRs. Resistosomes play a crucial role in plant innate immunity and are divided into CNL and TNL types, which mediate plant immune responses.

RLK: receptor-like kinase. A specific type of transmembrane receptor kinase comprising an extracellular LRR domain, a transmembrane domain, and an intracellular kinase domain. RLKs play a pivotal role in immune signaling.

RLP: receptor-like protein. A type of transmembrane receptor that functions in plant immune processes, lacking a cytoplasmic kinase domain.

S gene: A plant susceptibility gene that facilitates pathogen infection and contributes to host susceptibility.

TAL effector: transcriptional activator-like effector. A protein secreted by the bacterial genus *Xanthomonas* via the type III secretion system. It possesses a DNA binding domain that activates host gene transcription of *S* genes to facilitate successful host colonization.

TIR-only protein: a type of protein that lacks canonical NLR architecture. The TIR domain represents a conserved immune module in both prokaryotic and eukaryotic organisms. Signaling regulated by TIR-only proteins is also critical for plant immunity.

TnpB: a transposon-associated RNA-guided endonuclease known to be the ancestral endonuclease of Cas12. The TnpB protein consists of about 400 amino acids and possesses double-strand DNA cleavage activity guided by right-end element RNA. TnpB proteins have been used to develop hypercompact genome editors.

ACKNOWLEDGMENTS

This work was supported by Biological Breeding-National Science and Technology Major Projects (2023ZD04070), the Key R&D Program of Hubei Province (2023BBB171), the National Key R&D Program of China (2022YFA1304402), and Fundamental Research Funds for the Central Universities (2662023PY006, AML2023A05, 2662024ZKPY001) (to G.L.). This work was also supported by the Fundamental Research Funds for the Central Universities (2662023PY006) (to K.X.). This work was also supported by the National Natural Science Foundation of China (32172373 and 32293243) (to G.L. and K.X., respectively) and Hubei Hongshan Laboratory. No conflict of interest is declared. Figures were created with BioRender.

AUTHOR CONTRIBUTIONS

G.L., K.X., Q.Z., S.L., and X.H. planned the review outline. X.H. and S.L. wrote the majority of the manuscript and prepared the figures. Q.Z., P.S., S.L., and X.H. prepared Table 1. Q.Z., D.W., J.W., X.Y., Z.L., R.J.M., Z.K., K.X., and G.L. revised the manuscript. All authors read and approved the final manuscript.

Received: August 28, 2024
Revised: November 1, 2024
Accepted: November 19, 2024
Published: November 20, 2024

REFERENCES

Appiano, M., Catalano, D., Santillán Martínez, M., Lotti, C., Zheng, Z., Visser, R.G.F., Ricciardi, L., Bai, Y., and Pavan, S. (2015). Monocot and dicot MLO powdery mildew susceptibility factors are functionally conserved in spite of the evolution of class-specific molecular features. BMC Plant Biol. **15**:257. https://doi.org/10.1186/s12870-015-0639-6.

Arora, S., Steed, A., Goddard, R., Gaurav, K., O'Hara, T., Schoen, A., Rawat, N., Elkot, A.F., Korolev, A.V., Chinoy, C., et al. (2023). A wheat kinase and immune receptor form host-specificity barriers against the blast fungus. Nat. Plants **9**:385–392. https://doi.org/10.1038/s41477-023-01357-5.

Athiyannan, N., Abrouk, M., Boshoff, W.H.P., Cauet, S., Rodde, N., Kudrna, D., Mohammed, N., Bettgenhaeuser, J., Botha, K.S., Derman, S.S., et al. (2022). Long-read genome sequencing of bread wheat facilitates disease resistance gene cloning. Nat. Genet. **54**:227–231. https://doi.org/10.1038/s41588-022-01022-1.

Bai, Y., Pavan, S., Zheng, Z., Zappel, N.F., Reinstädler, A., Lotti, C., De Giovanni, C., Ricciardi, L., Lindhout, P., Visser, R., et al. (2008). Naturally occurring broad-spectrum powdery mildew resistance in a Central American tomato accession is caused by loss of *Mlo* function. Mol. Plant Microbe Interact. **21**:30–39. https://doi.org/10.1094/mpmi-21-1-0030.

Bettgenhaeuser, J., Hernández-Pinzón, I., Dawson, A.M., Gardiner, M., Green, P., Taylor, J., Smoker, M., Ferguson, J.N., Emmrich, P., Hubbard, A., et al. (2021). The barley immune receptor *Mla* recognizes multiple pathogens and contributes to host range dynamics. Nat. Commun. **12**:6915. https://doi.org/10.1038/s41467-021-27288-3.

Bi, G., Su, M., Li, N., Liang, Y., Dang, S., Xu, J., Hu, M., Wang, J., Zou, M., Deng, Y., et al. (2021). The ZAR1 resistosome is a calcium-permeable channel triggering plant immune signaling. Cell **184**:3528–3541.e12. https://doi.org/10.1016/j.cell.2021.05.003.

Boch, J., and Bonas, U. (2010). *Xanthomonas* AvrBs3 family-type III effectors: Discovery and function. Annu. Rev. Phytopathol. **48**:419–436. https://doi.org/10.1146/annurev-phyto-080508-081936.

Buschges, R., Hollricher, K., Panstruga, R., Simons, G., Wolter, M., Frijters, A., vanDaelen, R., vanderLee, T., Diergaarde, P., Groenendijk, J., et al. (1997). The barley *Mlo* gene: A novel control element of plant pathogen resistance. Cell **88**:695–705. https://doi.org/10.1016/S0092-8674(00)81912-1.

Cai, Q., Qiao, L., Wang, M., He, B., Lin, F.M., Palmquist, J., Huang, S.D., and Jin, H. (2018). Plants send small RNAs in extracellular vesicles to fungal pathogen to silence virulence genes. Science **360**:1126–1129. https://doi.org/10.1126/science.aar4142.

Cao, L., Karapetyan, S., Yoo, H., Chen, T., Mwimba, M., Zhang, X., and Dong, X. (2024). H_2O_2 sulfenylates CHE, linking local infection to the establishment of systemic acquired resistance. Science **385**:1211–1217. https://doi.org/10.1126/science.adj7249.

Chang, H.H.Y., Pannunzio, N.R., Adachi, N., and Lieber, M.R. (2017). Non-homologous DNA end joining and alternative pathways to double-strand break repair. Nat. Rev. Mol. Cell Biol. **18**:495–506. https://doi.org/10.1038/nrm.2017.48.

Chen, B., Zhang, Y., Sun, Z., Liu, Z., Zhang, D., Yang, J., Wang, G., Wu, J., Ke, H., Meng, C., et al. (2021). Tissue-specific expression of *GhnsLTPs* identified via GWAS sophisticatedly coordinates disease and insect resistance by regulating metabolic flux redirection in cotton. Plant J. **107**:831–846. https://doi.org/10.1111/tpj.15349.

Chen, G., Zhang, B., Ding, J., Wang, H., Deng, C., Wang, J., Yang, Q., Pi, Q., Zhang, R., Zhai, H., et al. (2022). Cloning southern corn rust resistant gene *RppK* and its cognate gene *AvrRppK* from *Puccinia polysora*. Nat. Commun. **13**:4392. https://doi.org/10.1038/s41467-022-32026-4.

Chen, L., Luo, J., Jin, M., Yang, N., Liu, X., Peng, Y., Li, W., Phillips, A., Cameron, B., Bernal, J.S., et al. (2022). Genome sequencing reveals evidence of adaptive variation in the genus *Zea*. Nat. Genet. **54**:1736–1745. https://doi.org/10.1038/s41588-022-01184-y.

Chen, X., Shang, J., Chen, D., Lei, C., Zou, Y., Zhai, W., Liu, G., Xu, J., Ling, Z., Cao, G., et al. (2006). A B-lectin receptor kinase gene conferring rice blast resistance. Plant J. **46**:794–804. https://doi.org/10.1111/j.1365-313X.2006.02739.x.

Chen, X.D., Chen, Z., Wythes, G., Zhang, Y., Orr, B.C., Sun, G., Chao, Y.K., Navarro Torres, A., Thao, K., Vallurupalli, M., et al. (2024). Helicase-assisted continuous editing for programmable mutagenesis of endogenous genomes. Science **386**:eadn5876. https://doi.org/10.1126/science.adn5876.

Cheng, S., Feng, C., Wingen, L.U., Cheng, H., Riche, A.B., Jiang, M., Leverington-Waite, M., Huang, Z., Collier, S., Orford, S., et al. (2024). Harnessing landrace diversity empowers wheat breeding. Nature **632**:823–831. https://doi.org/10.1038/s41586-024-07682-9.

Cheng, W., Lin, M., Chu, M., Xiang, G., Guo, J., Jiang, Y., Guan, D., and He, S. (2022). RNAi-based gene silencing of RXLR effectors protects plants against the oomycete pathogen *Phytophthora capsici*. Mol. Plant Microbe Interact. **35**:440–449. https://doi.org/10.1094/MPMI-12-21-0295-R.

Chukwu, S.C., Rafii, M.Y., Ramlee, S.I., Ismail, S.I., Hasan, M.M., Oladosu, Y.A., Magaji, U.G., Akos, I., and Olalekan, K.K. (2019). Bacterial leaf blight resistance in rice: A review of conventional breeding to molecular approach. Mol. Biol. Rep. **46**:1519–1532. https://doi.org/10.1007/s11033-019-04584-2.

Crété, R., Pires, R.N., Barbetti, M.J., and Renton, M. (2020). Rotating and stacking genes can improve crop resistance durability while potentially selecting highly virulent pathogen strains. Sci. Rep. **10**:19752. https://doi.org/10.1038/s41598-020-76788-7.

DeFalco, T.A., and Zipfel, C. (2021). Molecular mechanisms of early plant pattern-triggered immune signaling. Mol. Cell **81**:3449–3467. https://doi.org/10.1016/j.molcel.2021.07.029.

Deng, L., Zhou, Y.L., Cai, Z., Zhu, J., Li, Z., and Bao, Z. (2024). Massively parallel CRISPR-assisted homologous recombination enables saturation editing of full-length endogenous genes in yeast. Sci. Adv. **10**:eadj9382. https://doi.org/10.1126/sciadv.adj9382.

Deng, Y., Ning, Y., Yang, D.L., Zhai, K., Wang, G.L., and He, Z. (2020). Molecular basis of disease resistance and perspectives on breeding strategies for resistance improvement in crops. Mol. Plant **13**:1402–1419. https://doi.org/10.1016/j.molp.2020.09.018.

Deng, Y., Zhai, K., Xie, Z., Yang, D., Zhu, X., Liu, J., Wang, X., Qin, P., Yang, Y., Zhang, G., et al. (2017). Epigenetic regulation of antagonistic receptors confers rice blast resistance with yield balance. Science **355**:962–965. https://doi.org/10.1126/science.aai8898.

Ding, B., Bellizzi, M.d.R., Ning, Y., Meyers, B.C., and Wang, G.L. (2012). HDT701, a histone H4 deacetylase, negatively regulates plant innate immunity by modulating histone H4 acetylation of defense-related genes in rice. Plant Cell **24**:3783–3794. https://doi.org/10.1105/tpc.112.101972.

Ding, Y., Zhang, F., Sun, F., Liu, J., Zhu, Z., He, X., Bai, G., Ni, Z., Sun, Q., and Su, Z. (2023). Loss of *OsHRC* function confers blast resistance without yield penalty in rice. Plant Biotechnol. J. **21**:1516–1518. https://doi.org/10.1111/pbi.14061.

Dinh, H.X., Singh, D., Gomez de la Cruz, D., Hensel, G., Kumlehn, J., Mascher, M., Stein, N., Perovic, D., Ayliffe, M., Moscou, M.J., et al. (2022). The barley leaf rust resistance gene *Rph3* encodes a predicted membrane protein and is induced upon infection by avirulent pathotypes of *Puccinia hordei*. Nat. Commun. **13**:2386. https://doi.org/10.1038/s41467-022-29840-1.

Du, J., Verzaux, E., Chaparro-Garcia, A., Bijsterbosch, G., Keizer, L.C.P., Zhou, J., Liebrand, T.W.H., Xie, C., Govers, F., Robatzek, S., et al. (2015). Elicitin recognition confers enhanced resistance to *Phytophthora infestans* in potato. Nat. Plants **1**:15034. https://doi.org/10.1038/Nplants.2015.34.

Duxbury, Z., Wu, C.H., and Ding, P. (2021). A comparative overview of the intracellular guardians of plants and animals: NLRs in innate immunity and beyond. Annu. Rev. Plant Biol. **72**:155–184. https://doi.org/10.1146/annurev-arplant-080620-104948.

Ercoli, M.F., Luu, D.D., Rim, E.Y., Shigenaga, A., Teixeira de Araujo, A., Jr., Chern, M., Jain, R., Ruan, R., Joe, A., Stewart, V., and Ronald, P. (2022). Plant immunity: Rice XA21-mediated resistance to bacterial infection. Proc. Natl. Acad. Sci. USA **119**:e2121568119. https://doi.org/10.1073/pnas.2121568119.

Fabregas, N., and Fernie, A.R. (2021). The interface of central metabolism with hormone signaling in plants. Curr. Biol. **31**:R1535–R1548. https://doi.org/10.1016/j.cub.2021.09.070.

Fan, J., Bai, P., Ning, Y., Wang, J., Shi, X., Xiong, Y., Zhang, K., He, F., Zhang, C., Wang, R., et al. (2018). The monocot-specific receptor-like kinase SDS2 controls cell death and immunity in rice. Cell Host Microbe **23**:498–510.e5. https://doi.org/10.1016/j.chom.2018.03.003.

Fang, H., Shen, S., Wang, D., Zhang, F., Zhang, C., Wang, Z., Zhou, Q., Wang, R., Tao, H., He, F., et al. (2021). A monocot-specific hydroxycinnamoylputrescine gene cluster contributes to immunity and cell death in rice. Sci. Bull. **66**:2381–2393. https://doi.org/10.1016/j.scib.2021.06.014.

Feng, H., Duan, X., Zhang, Q., Li, X., Wang, B., Huang, L., Wang, X., and Kang, Z. (2014). The target gene of tae-miR164, a novel NAC transcription factor from the NAM subfamily, negatively regulates resistance of wheat to stripe rust. Mol. Plant Pathol. **15**:284–296. https://doi.org/10.1111/mpp.12089.

Feng, J.X., Cao, L., Li, J., Duan, C.J., Luo, X.M., Le, N., Wei, H., Liang, S., Chu, C., Pan, Q., and Tang, J.L. (2011). Involvement of OsNPR1/NH1 in rice basal resistance to blast fungus *Magnaporthe oryzae*. Eur. J. Plant Pathol. **131**:221–235. https://doi.org/10.1007/s10658-011-9801-7.

Feng, Q., Wang, H., Yang, X.M., Hu, Z.W., Zhou, X.H., Xiang, L., Xiong, X.Y., He, X.R., Zhu, Y., Li, G.B., et al. (2022). Osa-miR160a confers broad-spectrum resistance to fungal and bacterial pathogens in rice. New Phytol. **236**:2216–2232. https://doi.org/10.1111/nph.18491.

Förderer, A., Li, E., Lawson, A.W., Deng, Y.N., Sun, Y., Logemann, E., Zhang, X., Wen, J., Han, Z., Chang, J., et al. (2022). A wheat resistosome defines common principles of immune receptor channels. Nature **610**:532–539. https://doi.org/10.1038/s41586-022-05231-w.

Galli, M., Martiny, E., Imani, J., Kumar, N., Koch, A., Steinbrenner, J., and Kogel, K.H. (2022). CRISPR/*SpCas9*-mediated double knockout of barley Microrchidia MORC1 and MORC6a reveals their strong involvement in plant immunity, transcriptional gene silencing and plant growth. Plant Biotechnol. J. **20**:89–102. https://doi.org/10.1111/pbi.13697.

Gao, C. (2021). Genome engineering for crop improvement and future agriculture. Cell **184**:1621–1635. https://doi.org/10.1016/j.cell.2021.01.005.

Gao, C., Tang, D., and Wang, W. (2022). The role of ubiquitination in plant immunity: Fine-tuning immune signaling and beyond. Plant Cell Physiol. **63**:1405–1413. https://doi.org/10.1093/pcp/pcac105.

Gao, M., He, Y., Yin, X., Zhong, X., Yan, B., Wu, Y., Chen, J., Li, X., Zhai, K., Huang, Y., et al. (2021). Ca^{2+} sensor-mediated ROS scavenging suppresses rice immunity and is exploited by a fungal effector. Cell **184**:5391–5404.e17. https://doi.org/10.1016/j.cell.2021.09.009.

Gao, Y., Zhang, C., Han, X., Wang, Z.Y., Ma, L., Yuan, D.P., Wu, J.N., Zhu, X.F., Liu, J.M., Li, D.P., et al. (2018). Inhibition of *OsSWEET11* function in mesophyll cells improves resistance of rice to sheath blight disease. Mol. Plant Pathol. **19**:2149–2161. https://doi.org/10.1111/mpp.12689.

Ge, D., Yeo, I.C., and Shan, L. (2022). Knowing me, knowing you: Self and non-self recognition in plant immunity. Essays Biochem. **66**:447–458. https://doi.org/10.1042/EBC20210095.

Ghosh, P., and Roychoudhury, A. (2024). Plant peptides involved in abiotic and biotic stress responses and reactive oxygen opecies (ROS) signaling. J. Plant Growth Regul. **43**:1410–1427. https://doi.org/10.1007/s00344-023-11194-7.

Gong, Q., Yao, S., Wang, X., and Li, G. (2024). Fine-tuning phosphatidic acid production for optimal plant stress responses. Trends Biochem. Sci. **49**:663–666. https://doi.org/10.1016/j.tibs.2024.05.008.

Gou, J.Y., Li, K., Wu, K., Wang, X., Lin, H., Cantu, D., Uauy, C., Dobon-Alonso, A., Midorikawa, T., Inoue, K., et al. (2015). Wheat stripe rust resistance protein WKS1 reduces the ability of the thylakoid-

associated ascorbate peroxidase to detoxify reactive oxygen species. Plant Cell **27**:1755–1770. https://doi.org/10.1105/tpc.114.134296.

Gu, K., Tian, D., Qiu, C., and Yin, Z. (2009). Transcription activator-like type III effector AvrXa27 depends on OsTFIIAγ5 for the activation of *Xa27* transcription in rice that triggers disease resistance to *Xanthomonas oryzae* pv. *oryzae*. Mol. Plant Pathol. **10**:829–835. https://doi.org/10.1111/j.1364-3703.2009.00567.x.

Gupta, M., Dubey, S., Jain, D., and Chandran, D. (2021). The *Medicago truncatula* sugar transport protein 13 and its Lr67res-like variant confer powdery mildew resistance in legumes via defense modulation. Plant Cell Physiol. **62**:650–667. https://doi.org/10.1093/pcp/pcab021.

Hatta, M.A.M., Arora, S., Ghosh, S., Matny, O., Smedley, M.A., Yu, G., Chakraborty, S., Bhatt, D., Xia, X., Steuernagel, B., et al. (2021). The wheat *Sr22, Sr33, Sr35* and *Sr45* genes confer resistance against stem rust in barley. Plant Biotechnol. J. **19**:273–284. https://doi.org/10.1111/pbi.13460.

He, H., Zhu, S., Zhao, R., Jiang, Z., Ji, Y., Ji, J., Qiu, D., Li, H., and Bie, T. (2018). *Pm21*, encoding a typical CC-NBS-LRR protein, confers broad-spectrum resistance to wheat powdery mildew disease. Mol. Plant **11**:879–882. https://doi.org/10.1016/j.molp.2018.03.004.

Heidersbach, A.J., Dorighi, K.M., Gomez, J.A., Jacobi, A.M., and Haley, B. (2023). A versatile, high-efficiency platform for CRISPR-based gene activation. Nat. Commun. **14**:902. https://doi.org/10.1038/s41467-023-36452-w.

Helliwell, E.E., Lafayette, P., Kronmiller, B.N., Arredondo, F., Duquette, M., Co, A., Vega-Arreguin, J., Porter, S.S., Borrego, E.J., Kolomiets, M.V., et al. (2022). Transgenic soybeans expressing phosphatidylinositol-3-phosphate-binding proteins show enhanced resistance against the oomycete pathogen *Phytophthora sojae*. Front. Microbiol. **13**:923281. https://doi.org/10.3389/fmicb.2022.923281.

Hendelman, A., Zebell, S., Rodriguez-Leal, D., Dukler, N., Robitaille, G., Wu, X., Kostyun, J., Tal, L., Wang, P., Bartlett, M.E., et al. (2021). Conserved pleiotropy of an ancient plant homeobox gene uncovered by *cis*-regulatory dissection. Cell **184**:1724–1739.e16. https://doi.org/10.1016/j.cell.2021.02.001.

Hou, Y., Wang, L., Wang, L., Liu, L., Li, L., Sun, L., Rao, Q., Zhang, J., and Huang, S. (2015). JMJ704 positively regulates rice defense response against *Xanthomonas oryzae* pv. *oryzae* infection via reducing H3K4me2/3 associated with negative disease resistance regulators. BMC Plant Biol. **15**:286. https://doi.org/10.1186/s12870-015-0674-3.

Hu, G., Lei, Y., Liu, J., Hao, M., Zhang, Z., Tang, Y., Chen, A., and Wu, J. (2020). The ghr-miR164 and *GhNAC100* modulate cotton plant resistance against *Verticillium dahlia*. Plant Sci. **293**:110438. https://doi.org/10.1016/j.plantsci.2020.110438.

Huang, S., Jia, A., Song, W., Hessler, G., Meng, Y., Sun, Y., Xu, L., Laessle, H., Jirschitzka, J., Ma, S., et al. (2022). Identification and receptor mechanism of TIR-catalyzed small molecules in plant immunity. Science **377**:eabq3297. https://doi.org/10.1126/science.abq3297.

Huffaker, A., Pearce, G., and Ryan, C.A. (2006). An endogenous peptide signal in activates components of the innate immune response. Proc. Natl. Acad. Sci. USA **103**:10098–10103. https://doi.org/10.1073/pnas.0603727103.

Huffaker, A., Dafoe, N.J., and Schmelz, E.A. (2011). ZmPep1, an ortholog of Arabidopsis Elicitor Peptide 1, regulates maize innate immunity and enhances disease resistance. Plant Physiol. **155**:1325–1338. https://doi.org/10.1104/pp.110.166710.

Jacob, P., Kim, N.H., Wu, F., El-Kasmi, F., Chi, Y., Walton, W.G., Furzer, O.J., Lietzan, A.D., Sunil, S., Kempthorn, K., et al. (2021). Plant "helper" immune receptors are Ca^{2+}-permeable nonselective cation channels. Science **373**:420–425. https://doi.org/10.1126/science.abg7917.

Jia, A., Huang, S., Song, W., Wang, J., Meng, Y., Sun, Y., Xu, L., Laessle, H., Jirschitzka, J., Hou, J., et al. (2022). TIR-catalyzed ADP-ribosylation reactions produce signaling molecules for plant immunity. Science **377**:eabq8180. https://doi.org/10.1126/science.abq8180.

Jia, H., Omar, A.A., Xu, J., Dalmendray, J., Wang, Y., Feng, Y., Wang, W., Hu, Z., Grosser, J.W., and Wang, N. (2024). Generation of transgene-free canker-resistant *Citrus sinensis* cv. Hamlin in the T0 generation through Cas12a/CBE co-editing. Front. Plant Sci. **15**:1385768. https://doi.org/10.3389/fpls.2024.1385768.

Jiang, G.H., Xia, Z.H., Zhou, Y.L., Wan, J., Li, D.Y., Chen, R.S., Zhai, W.X., and Zhu, L.H. (2006). Testifying the rice bacterial blight resistance gene *xa5* by genetic complementation and further analyzing *xa5 (Xa5)* in comparison with its homolog *TFIIAγ1*. Mol. Genet. Genom. **275**:354–366. https://doi.org/10.1007/s00438-005-0091-7.

Jing, Y., Zou, X., Sun, C., Qin, X., and Zheng, X. (2023). Danger-associate peptide regulates root immunity in *Arabidopsis*. Biochem. Biophys. Res. Commun. **663**:163–170. https://doi.org/10.1016/j.bbrc.2023.04.091.

Johansson, O.N., Fantozzi, E., Fahlberg, P., Nilsson, A.K., Buhot, N., Tör, M., and Andersson, M.X. (2014). Role of the penetration-resistance genes *PEN1, PEN2* and *PEN3* in the hypersensitive response and race-specific resistance in *Arabidopsis thaliana*. Plant J. **79**:466–476. https://doi.org/10.1111/tpj.12571.

Jones, J.D.G., Staskawicz, B.J., and Dangl, J.L. (2024). The plant immune system: From discovery to deployment. Cell **187**:2095–2116. https://doi.org/10.1016/j.cell.2024.03.045.

Jordan, T., Seeholzer, S., Schwizer, S., Töller, A., Somssich, I.E., and Keller, B. (2011). The wheat homologue exhibits an evolutionarily conserved function against powdery mildew in both wheat and barley. Plant J. **65**:610–621. https://doi.org/10.1111/j.1365-313X.2010.04445.x.

Jubic, L.M., Saile, S., Furzer, O.J., El Kasmi, F., and Dangl, J.L. (2019). Help wanted: Helper NLRs and plant immune responses. Curr. Opin. Plant Biol. **50**:82–94. https://doi.org/10.1016/j.pbi.2019.03.013.

Karmakar, S., Das, P., Panda, D., Xie, K., Baig, M.J., and Molla, K.A. (2022). A detailed landscape of CRISPR-Cas-mediated plant disease and pest management. Plant Sci. **323**:111376. https://doi.org/10.1016/j.plantsci.2022.111376.

Karmakar, S., Panda, D., Panda, S., Dash, M., Saha, R., Das, P., Avinash, S.P., Shih, J., Yang, Y., Nayak, A.K., et al. (2024). A miniature alternative to Cas9 and Cas12: Transposon-associated TnpB mediates targeted genome editing in plants. Plant Biotechnol. J. **22**:2950–2953. https://doi.org/10.1111/pbi.14416.

Karvelis, T., Druteika, G., Bigelyte, G., Budre, K., Zedaveinyte, R., Silanskas, A., Kazlauskas, D., Venclovas, Č., and Siksnys, V. (2021). Transposon-associated TnpB is a programmable RNA-guided DNA endonuclease. Nature **599**:692–696. https://doi.org/10.1038/s41586-021-04058-1.

Klymiuk, V., Yaniv, E., Huang, L., Raats, D., Fatiukha, A., Chen, S., Feng, L., Frenkel, Z., Krugman, T., Lidzbarsky, G., et al. (2018). Cloning of the wheat *Yr15* resistance gene sheds light on the plant tandem kinase-pseudokinase family. Nat. Commun. **9**:3735. https://doi.org/10.1038/s41467-018-06138-9.

Kourelis, J., Marchal, C., Posbeyikian, A., Harant, A., and Kamoun, S. (2023). NLR immune receptor-nanobody fusions confer plant disease resistance. Science **379**:934–939. https://doi.org/10.1126/science.abn4116.

Krattinger, S.G., Kang, J., Bräunlich, S., Boni, R., Chauhan, H., Selter, L.L., Robinson, M.D., Schmid, M.W., Wiederhold, E., Hensel, G., et al. (2019). Abscisic acid is a substrate of the ABC transporter encoded by the durable wheat disease resistance gene *Lr34*. New Phytol. **223**:853–866. https://doi.org/10.1111/nph.15815.

Kumar, A., Partap, M., and Warghat, A.R. (2024). Jasmonic acid: A versatile phytohormone regulating growth, physiology, and biochemical responses. J. Plant Growth Regul. https://doi.org/10.1007/s00344-024-11376-x.

Kusch, S., and Panstruga, R. (2017). mlo-based resistance: An apparently universal "Weapon" to defeat powdery mildew disease. Mol. Plant Microbe Interact. **30**:179–189. https://doi.org/10.1094/Mpmi-12-16-0255-Cr.

Lacombe, S., Rougon-Cardoso, A., Sherwood, E., Peeters, N., Dahlbeck, D., van Esse, H.P., Smoker, M., Rallapalli, G., Thomma, B.P.H.J., Staskawicz, B., et al. (2010). Interfamily transfer of a plant pattern-recognition receptor confers broad-spectrum bacterial resistance. Nat. Biotechnol. **28**:365–369. https://doi.org/10.1038/nbt.1613.

Lapin, D., and Van den Ackerveken, G. (2013). Susceptibility to plant disease: More than a failure of host immunity. Trends Plant Sci. **18**:546–554. https://doi.org/10.1016/j.tplants.2013.05.005.

Lee, O.S., Lee, B., Park, N., Koo, J.C., Kim, Y.H., Prasad D, T., Karigar, C., Chun, H.J., Jeong, B.R., Kim, D.H., et al. (2003). Pn-AMPs, the hevein-like proteins from *Pharbitis nil* confers disease resistance against phytopathogenic fungi in tomato, *Lycopersicum esculentum*. Phytochemistry **62**:1073–1079. https://doi.org/10.1016/S0031-9422(02)00668-4.

Li, B., Sun, C., Li, J., and Gao, C. (2024). Targeted genome-modification tools and their advanced applications in crop breeding. Nat. Rev. Genet. **25**:603–622. https://doi.org/10.1038/s41576-024-00720-2.

Li, C., Zhang, R., Meng, X., Chen, S., Zong, Y., Lu, C., Qiu, J.L., Chen, Y.H., Li, J., and Gao, C. (2020). Targeted, random mutagenesis of plant genes with dual cytosine and adenine base editors. Nat. Biotechnol. **38**:875–882. https://doi.org/10.1038/s41587-019-0393-7.

Li, C., Wu, J., Fu, S., Xu, Y., Wang, Y., Yang, X., Lan, Y., Lin, F., Du, L., Zhou, T., and Zhou, X. (2024). Development of a transgenic rice line with strong and broad resistance against four devastating rice viruses through expressing a single hairpin RNA construct. Plant Biotechnol. J. **22**:2142–2144. https://doi.org/10.1111/pbi.14334.

Li, C., Zhou, Z., Xiong, X., Li, C., Li, C., Shen, E., Wang, J., Zha, W., Wu, B., Chen, H., et al. (2024). Development of a multi-resistance and high-yield rice variety using multigene transformation and gene editing. Plant Biotechnol. J. **22**:3118–3120. https://doi.org/10.1111/pbi.14434.

Li, G., Xu, Z., Wang, J., Mu, C., Zhou, Z., Li, M., Hao, Z., Zhang, D., Yong, H., Han, J., et al. (2024). Gene pyramiding of *ZmGLK36* and *ZmGDIα-hel* for rough dwarf disease resistance in maize. Mol. Breed. **44**:25. https://doi.org/10.1007/s11032-024-01466-9.

Li, J., Meng, X., Zong, Y., Chen, K., Zhang, H., Liu, J., Li, J., and Gao, C. (2016). Gene replacements and insertions in rice by intron targeting using CRISPR-Cas9. Nat. Plants **2**:16139. https://doi.org/10.1038/nplants.2016.139.

Li, J., Chen, M., Fan, T., Mu, X., Gao, J., Wang, Y., Jing, T., Shi, C., Niu, H., Zhen, S., et al. (2022). Underlying mechanism of accelerated cell death and multiple disease resistance in a maize *lethal leaf spot 1* allele. J. Exp. Bot. **73**:3991–4007. https://doi.org/10.1093/jxb/erac116.

Li, J., Fan, T., Zhang, Y., Xing, Y., Chen, M., Wang, Y., Gao, J., Zhang, N., Tian, J., Zhao, C., et al. (2023). Characterization and fine mapping of a maize lesion mimic mutant (*Les8*) with enhanced resistance to *Curvularia* leaf spot and southern leaf blight. Theor. Appl. Genet. **137**:7. https://doi.org/10.1007/s00122-023-04511-x.

Li, J., Hu, S., Jian, W., Xie, C., and Yang, X. (2021). Plant antimicrobial peptides: Structures, functions, and applications. Bot. Stud. **62**:5. https://doi.org/10.1186/s40529-021-00312-x.

Li, M., Dong, L., Zhu, K., Wu, Q., Chen, Y., Lu, P., Guo, G., Zhang, H., Zhang, P., Li, B., et al. (2022). Provoking a silent *R* gene in wheat genome confers resistance to powdery mildew. Plant Biotechnol. J. **20**:2039–2041. https://doi.org/10.1111/pbi.13903.

Li, Q., Wang, Y., Hou, Z., Zong, H., Wang, X., Zhang, Y.E., Wang, H., Chen, H., Wang, W., and Duan, K. (2024). Genome editing in plants using the TnpB transposase system. aBIOTECH **5**:225–230. https://doi.org/10.1007/s42994-024-00172-6.

Li, S., Lin, D., Zhang, Y., Deng, M., Chen, Y., Lv, B., Li, B., Lei, Y., Wang, Y., Zhao, L., et al. (2022). Genome-edited powdery mildew resistance in wheat without growth penalties. Nature **602**:455–460. https://doi.org/10.1038/s41586-022-04395-9.

Li, W., Chern, M., Yin, J., Wang, J., and Chen, X. (2019). Recent advances in broad-spectrum resistance to the rice blast disease. Curr. Opin. Plant Biol. **50**:114–120. https://doi.org/10.1016/j.pbi.2019.03.015.

Li, W., Zhu, Z., Chern, M., Yin, J., Yang, C., Ran, L., Cheng, M., He, M., Wang, K., Wang, J., et al. (2017). A natural allele of a transcription factor in rice confers broad-spectrum blast resistance. Cell **170**:114–126.e15. https://doi.org/10.1016/j.cell.2017.06.008.

Li, X., Huang, R., Liu, J., Xu, G., and Yuan, M. (2021). Engineering false smut resistance rice via host-induced gene silencing of two chitin synthase genes of *Ustilaginoidea virens*. Plant Biotechnol. J. **19**:2386–2388. https://doi.org/10.1111/pbi.13711.

Li, X., Niu, G., Fan, Y., Liu, W., Wu, Q., Yu, C., Wang, J., Xiao, Y., Hou, L., Jin, D., et al. (2023). Synthetic dual hormone-responsive promoters enable engineering of plants with broad-spectrum resistance. Plant Commun. **4**:100596. https://doi.org/10.1016/j.xplc.2023.100596.

Li, Y., Xia, Q., Kou, H., Wang, D., Lin, X., Wu, Y., Xu, C., Xing, S., and Liu, B. (2011). Induced *Pib* expression and resistance to *Magnaporthe grisea* are compromised by cytosine demethylation at critical promoter regions in rice. J. Integr. Plant Biol. **53**:814–823. https://doi.org/10.1111/j.1744-7909.2011.01070.x.

Li, Y., Huang, C., Liu, Y., Zeng, J., Yu, H., Tong, Z., Yuan, X., Sui, X., Fang, D., Xiao, B., et al. (2023). CRISPR/Cas9-mediated seamless gene replacement in protoplasts expands the resistance spectrum to TMV-U1 strain in regenerated *Nicotiana tabacum*. Plant Biotechnol. J. **21**:2641–2653. https://doi.org/10.1111/pbi.14159.

Li, Y., Leveau, A., Zhao, Q., Feng, Q., Lu, H., Miao, J., Xue, Z., Martin, A.C., Wegel, E., Wang, J., et al. (2021). Subtelomeric assembly of a multi-gene pathway for antimicrobial defense compounds in cereals. Nat. Commun. **12**:2563. https://doi.org/10.1038/s41467-021-22920-8.

Liang, H., Zheng, J., Duan, X., Sheng, B., Jia, S., Wang, D., Ouyang, J., Li, J., Li, L., Tian, W., et al. (2000). A transgenic wheat with a stilbene synthase gene resistant to powdery mildew obtained by biolistic method. Chin. Sci. Bull. **45**:634–638. https://doi.org/10.1007/Bf02886041.

Liu, F., Cai, S., Ma, Z., Yue, H., Xing, L., Wang, Y., Feng, S., Wang, L., Dai, L., Wan, H., et al. (2023). RVE2, a new regulatory factor in jasmonic acid pathway, orchestrates resistance to Verticillium wilt. Plant Biotechnol. J. **21**:2507–2524. https://doi.org/10.1111/pbi.14149.

Liu, J.Z., Horstman, H.D., Braun, E., Graham, M.A., Zhang, C., Navarre, D., Qiu, W.L., Lee, Y., Nettleton, D., Hill, J.H., and Whitham, S.A. (2011). Soybean homologs of MPK4 negatively regulate defense responses and positively regulate growth and development. Plant Physiol. **157**:1363–1378. https://doi.org/10.1104/pp.111.185686.

Liu, L., Gallagher, J., Arevalo, E.D., Chen, R., Skopelitis, T., Wu, Q., Bartlett, M., and Jackson, D. (2021). Enhancing grain-yield-related

traits by CRISPR-Cas9 promoter editing of maize *CLE* genes. Nat. Plants **7**:287–294. https://doi.org/10.1038/s41477-021-00858-5.

Liu, M., Li, Y.J., Zhu, Y.X., Sun, Y., and Wang, G.F. (2021). Maize nicotinate *N*-methyltransferase interacts with the NLR protein Rp1-D21 and modulates the hypersensitive response. Mol. Plant Pathol. **22**:564–579. https://doi.org/10.1111/mpp.13044.

Liu, P., Panda, K., Edwards, S.A., Swanson, R., Yi, H., Pandesha, P., Hung, Y.H., Klaas, G., Ye, X., Collins, M.V., et al. (2024). Transposase-assisted target-site integration for efficient plant genome engineering. Nature **631**:593–600. https://doi.org/10.1038/s41586-024-07613-8.

Liu, Q., Ning, Y., Zhang, Y., Yu, N., Zhao, C., Zhan, X., Wu, W., Chen, D., Wei, X., Wang, G.L., et al. (2017). OsCUL3a negatively regulates cell death and immunity by degrading OsNPR1 in rice. Plant Cell **29**:345–359. https://doi.org/10.1105/tpc.16.00650.

Liu, X., Meng, G., Wang, M., Qian, Z., Zhang, Y., and Yang, W. (2021). Tomato SlPUB24 enhances resistance to *Xanthomonas euvesicatoria* pv. *perforans* race T3. Hortic. Res. **8**:30. https://doi.org/10.1038/s41438-021-00468-4.

Liu, Y., Zhang, X., Yuan, G., Wang, D., Zheng, Y., Ma, M., Guo, L., Bhadauria, V., Peng, Y.L., and Liu, J. (2021). A designer rice NLR immune receptor confers resistance to the rice blast fungus carrying noncorresponding avirulence effectors. Proc. Natl. Acad. Sci. USA **118**:e2110751118. https://doi.org/10.1073/pnas.2110751118.

Lopez-Gomollon, S., and Baulcombe, D.C. (2022). Roles of RNA silencing in viral and non-viral plant immunity and in the crosstalk between disease resistance systems. Nat. Rev. Mol. Cell Biol. **23**:645–662. https://doi.org/10.1038/s41580-022-00496-5.

Lu, P., Guo, L., Wang, Z., Li, B., Li, J., Li, Y., Qiu, D., Shi, W., Yang, L., Wang, N., et al. (2020). A rare gain of function mutation in a wheat tandem kinase confers resistance to powdery mildew. Nat. Commun. **11**:680. https://doi.org/10.1038/s41467-020-14294-0.

Luan, Q.L., Zhu, Y.X., Ma, S., Sun, Y., Liu, X.Y., Liu, M., Balint-Kurti, P.J., and Wang, G.F. (2021). Maize metacaspases modulate the defense response mediated by the NLR protein Rp1-D21 likely by affecting its subcellular localization. Plant J. **105**:151–166. https://doi.org/10.1111/tpj.15047.

Luo, D., Sun, W., Cai, J., Hu, G., Zhang, D., Zhang, X., Larkin, R.M., Zhang, J., Yang, C., Ye, Z., and Wang, T. (2023). SlBBX20 attenuates JA signalling and regulates resistance to *Botrytis cinerea* by inhibiting SlMED25 in tomato. Plant Biotechnol. J. **21**:792–805. https://doi.org/10.1111/pbi.13997.

Luo, M., Xie, L., Chakraborty, S., Wang, A., Matny, O., Jugovich, M., Kolmer, J.A., Richardson, T., Bhatt, D., Hoque, M., et al. (2021). A five-transgene cassette confers broad-spectrum resistance to a fungal rust pathogen in wheat. Nat. Biotechnol. **39**:561–566. https://doi.org/10.1038/s41587-020-00770-x.

Lv, Z., Chen, W., Fang, S., Dong, B., Wang, X., Zhang, L., Xue, J., and Chen, W. (2024). Targeted mutagenesis in Arabidopsis and medicinal plants using transposon-associated TnpB. J. Integr. Plant Biol. **66**:2083–2086. https://doi.org/10.1111/jipb.13758.

Ma, S., Lapin, D., Liu, L., Sun, Y., Song, W., Zhang, X., Logemann, E., Yu, D., Wang, J., Jirschitzka, J., et al. (2020). Direct pathogen-induced assembly of an NLR immune receptor complex to form a holoenzyme. Science **370**:eabe3069. https://doi.org/10.1126/science.abe3069.

Ma, Y., Guo, Z., Xia, B., Zhang, Y., Liu, X., Yu, Y., Tang, N., Tong, X., Wang, M., Ye, X., et al. (2022). Identification of antimicrobial peptides from the human gut microbiome using deep learning. Nat. Biotechnol. **40**:921–931. https://doi.org/10.1038/s41587-022-01226-0.

Martin, R., Qi, T., Zhang, H., Liu, F., King, M., Toth, C., Nogales, E., and Staskawicz, B.J. (2020). Structure of the activated ROQ1 resistosome directly recognizing the pathogen effector XopQ. Science **370**:eabd9993. https://doi.org/10.1126/science.abd9993.

Mazier, M., Flamain, F., Nicolaï, M., Sarnette, V., and Caranta, C. (2011). Knock-down of both *eIF4E1* and *eIF4E2* genes confers broad-spectrum resistance against potyviruses in tomato. PLoS One **6**:e29595. https://doi.org/10.1371/journal.pone.0029595.

Meng, F., Yang, C., Cao, J., Chen, H., Pang, J., Zhao, Q., Wang, Z., Qing Fu, Z., and Liu, J. (2020). A bHLH transcription activator regulates defense signaling by nucleo-cytosolic trafficking in rice. J. Integr. Plant Biol. **62**:1552–1573. https://doi.org/10.1111/jipb.12922.

Meng, F., He, Y., Chen, J., Long, X., Wang, H., Zhu, M., Liu, S., Cai, Q., and Zhang, Z. (2021). Analysis of natural variation of the rice blast resistance gene *Pike* and identification of a novel allele *Pikg*. Mol. Genet. Genom. **296**:939–952. https://doi.org/10.1007/s00438-021-01795-w.

Milne, R.J., Dibley, K.E., Schnippenkoetter, W., Mascher, M., Lui, A.C.W., Wang, L., Lo, C., Ashton, A.R., Ryan, P.R., and Lagudah, E.S. (2019). The wheat *Lr67* gene from the sugar transport protein 13 family confers multipathogen resistance in barley. Plant Physiol. **179**:1285–1297. https://doi.org/10.1104/pp.18.00945.

Nekrasov, V., Wang, C., Win, J., Lanz, C., Weigel, D., and Kamoun, S. (2017). Rapid generation of a transgene-free powdery mildew resistant tomato by genome deletion. Sci. Rep. **7**:482. https://doi.org/10.1038/s41598-017-00578-x.

Ngou, B.P.M., Ahn, H.K., Ding, P., and Jones, J.D.G. (2021). Mutual potentiation of plant immunity by cell-surface and intracellular receptors. Nature **592**:110–115. https://doi.org/10.1038/s41586-021-03315-7.

Nishimura, M.T., Anderson, R.G., Cherkis, K.A., Law, T.F., Liu, Q.L., Machius, M., Nimchuk, Z.L., Yang, L., Chung, E.H., El Kasmi, F., et al. (2017). TIR-only protein RBA1 recognizes a pathogen effector to regulate cell death in *Arabidopsis*. Proc. Natl. Acad. Sci. USA **114**:E2053–E2062. https://doi.org/10.1073/pnas.1620973114.

Nowack, M.K., Holmes, D.R., and Lahaye, T. (2022). TALE-induced cell death executors: an origin outside immunity? Trends Plant Sci. **27**:536–548. https://doi.org/10.1016/j.tplants.2021.11.003.

Oliva, R., Ji, C., Atienza-Grande, G., Huguet-Tapia, J.C., Perez-Quintero, A., Li, T., Eom, J.S., Li, C., Nguyen, H., Liu, B., et al. (2019). Broad-spectrum resistance to bacterial blight in rice using genome editing. Nat. Biotechnol. **37**:1344–1350. https://doi.org/10.1038/s41587-019-0267-z.

Omolehin, O., Raruang, Y., Hu, D., Han, Z.Q., Wei, Q., Wang, K., Rajasekaran, K., Cary, J.W., and Chen, Z.Y. (2021). Resistance to aflatoxin accumulation in maize mediated by host-induced silencing of the *Aspergillus flavus* alkaline protease (*alk*) gene. J. Fungi **7**:904. https://doi.org/10.3390/jof7110904.

Parween, D., Sultan, E., Dalei, K., and Sahu, B.B. (2021). Arabidopsis nonhost resistance gene *PENETRATION 2* is involved in disruption of cushion formation by *Rhizoctonia solani* during early infection process. Australas Plant Path **50**:281–292. https://doi.org/10.1007/s13313-020-00768-8.

Qiao, Y., Jiang, W., Lee, J., Park, B., Choi, M.S., Piao, R., Woo, M.O., Roh, J.H., Han, L., Paek, N.C., et al. (2010). SPL28 encodes a clathrin-associated adaptor protein complex 1, medium subunit μ1 (AP1M1) and is responsible for spotted leaf and early senescence in rice (*Oryza sativa*). New Phytol. **185**:258–274. https://doi.org/10.1111/j.1469-8137.2009.03047.x.

Qin, P., Fan, S., Deng, L., Zhong, G., Zhang, S., Li, M., Chen, W., Wang, G., Tu, B., Wang, Y., et al. (2018). *LML1*, encoding a conserved eukaryotic release factor 1 protein, regulates cell death and pathogen resistance by forming a conserved complex with *SPL33* in rice. Plant Cell Physiol. **59**:887–902. https://doi.org/10.1093/pcp/pcy056.

Ramasamy, M., Rajkumar, M.S., Bedre, R., Irigoyen, S., Berg-Falloure, K., Kolomiets, M.V., and Mandadi, K.K. (2024). Genome editing of *NPR3* confers potato resistance to *Candidatus* Liberibacter spp. Plant Biotechnol. J. **22**:2635–2637. https://doi.org/10.1111/pbi.14378.

Ramirez-Prado, J.S., Abulfaraj, A.A., Rayapuram, N., Benhamed, M., and Hirt, H. (2018). Plant immunity: From signaling to epigenetic control of defense. Trends Plant Sci. **23**:833–844. https://doi.org/10.1016/j.tplants.2018.06.004.

Remick, B.C., Gaidt, M.M., and Vance, R.E. (2023). Effector-triggered immunity. Annu. Rev. Immunol. **41**:453–481. https://doi.org/10.1146/annurev-immunol-101721-031732.

Ren, B., Yan, F., Kuang, Y., Li, N., Zhang, D., Zhou, X., Lin, H., and Zhou, H. (2018). Improved base editor for efficiently inducing genetic variations in rice with CRISPR/Cas9-guided hyperactive hAID mutant. Mol. Plant **11**:623–626. https://doi.org/10.1016/j.molp.2018.01.005.

Robatzek, S., Chinchilla, D., and Boller, T. (2006). Ligand-induced endocytosis of the pattern recognition receptor FLS2 in *Arabidopsis*. Genes Dev. **20**:537–542. https://doi.org/10.1101/gad.366506.

Rodríguez-Leal, D., Lemmon, Z.H., Man, J., Bartlett, M.E., and Lippman, Z.B. (2017). Engineering quantitative trait variation for crop improvement by genome editing. Cell **171**:470–480.e8. https://doi.org/10.1016/j.cell.2017.08.030.

Römer, P., Recht, S., Strauß, T., Elsaesser, J., Schornack, S., Boch, J., Wang, S., and Lahaye, T. (2010). Promoter elements of rice susceptibility genes are bound and activated by specific TAL effectors from the bacterial blight pathogen, *Xanthomonas oryzae* pv. *oryzae*. New Phytol. **187**:1048–1057. https://doi.org/10.1111/j.1469-8137.2010.03217.x.

Romer, P., Hahn, S., Jordan, T., Strauss, T., Bonas, U., and Lahaye, T. (2007). Plant pathogen recognition mediated by promoter activation of the pepper *Bs3* resistance gene. Science **318**:645–648. https://doi.org/10.1126/science.1144958.

Rosa, C., Kuo, Y.W., Wuriyanghan, H., and Falk, B.W. (2018). RNA interference mechanisms and applications in plant pathology. Annu. Rev. Phytopathol. **56**:581–610. https://doi.org/10.1146/annurev-phyto-080417-050044.

Rui, L., and Wang, W. (2024). Fortify the defense frontline: MAPKs phosphorylate receptor-like cytoplasmic kinase to maintain plant resistance in soybean. Stress Biol. **4**:22. https://doi.org/10.1007/s44154-024-00164-y.

Saintenac, C., Cambon, F., Aouini, L., Verstappen, E., Ghaffary, S.M.T., Poucet, T., Marande, W., Berges, H., Xu, S., Jaouannet, M., et al. (2021). A wheat cysteine-rich receptor-like kinase confers broad-spectrum resistance against Septoria tritici blotch. Nat. Commun. **12**:433. https://doi.org/10.1038/s41467-020-20685-0.

Saijo, Y., Loo, E.P.I., and Yasuda, S. (2018). Pattern recognition receptors and signaling in plant-microbe interactions. Plant J. **93**:592–613. https://doi.org/10.1111/tpj.13808.

Salcedo, A., Rutter, W., Wang, S., Akhunova, A., Bolus, S., Chao, S., Anderson, N., De Soto, M.F., Rouse, M., Szabo, L., et al. (2017). Variation in the *AvrSr35* gene determines *Sr35* resistance against wheat stem rust race Ug99. Science **358**:1604–1606. https://doi.org/10.1126/science.aao7294.

Sánchez-Martín, J., Widrig, V., Herren, G., Wicker, T., Zbinden, H., Gronnier, J., Spörri, L., Praz, C.R., Heuberger, M., Kolodziej, M.C., et al. (2021). Wheat *Pm4* resistance to powdery mildew is controlled by alternative splice variants encoding chimeric proteins. Nat. Plants **7**:327–341. https://doi.org/10.1038/s41477-021-00869-2.

Sawada, K., Hasegawa, M., Tokuda, L., Kameyama, J., Kodama, O., Kohchi, T., Yoshida, K., and Shinmyo, A. (2004). Enhanced resistance to blast fungus and bacterial blight in transgenic rice constitutively expressing *OsSBP*, a rice homologue of mammalian selenium-binding proteins. Biosci. Biotechnol. Biochem. **68**:873–880. https://doi.org/10.1271/bbb.68.873.

Schaefer, S.C., Gasic, K., Cammue, B., Broekaert, W., van Damme, E.J.M., Peumans, W.J., and Korban, S.S. (2005). Enhanced resistance to early blight in transgenic tomato lines expressing heterologous plant defense genes. Planta **222**:858–866. https://doi.org/10.1007/s00425-005-0026-x.

Schnippenkoetter, W., Lo, C., Liu, G., Dibley, K., Chan, W.L., White, J., Milne, R., Zwart, A., Kwong, E., Keller, B., et al. (2017). The wheat Lr34 multipathogen resistance gene confers resistance to anthracnose and rust in sorghum. Plant Biotechnol. J. **15**:1387–1396. https://doi.org/10.1111/pbi.12723.

Sha, G., Sun, P., Kong, X., Han, X., Sun, Q., Fouillen, L., Zhao, J., Li, Y., Yang, L., Wang, Y., et al. (2023). Genome editing of a rice CDP-DAG synthase confers multipathogen resistance. Nature **618**:1017–1023. https://doi.org/10.1038/s41586-023-06205-2.

Shen, Q., Pu, Q., Liang, J., Mao, H., Liu, J., and Wang, Q. (2019). CYP71Z18 overexpression confers elevated blast resistance in transgenic rice. Plant Mol. Biol. **100**:579–589. https://doi.org/10.1007/s11103-019-00881-3.

Shen, S., Peng, M., Fang, H., Wang, Z., Zhou, S., Jing, X., Zhang, M., Yang, C., Guo, H., Li, Y., et al. (2021). An *Oryza*-specific hydroxycinnamoyl tyramine gene cluster contributes to enhanced disease resistance. Sci. Bull. **66**:2369–2380. https://doi.org/10.1016/j.scib.2021.03.015.

Shi, J., An, H.L., Zhang, L., Gao, Z., and Guo, X.Q. (2010). *GhMPK7*, a novel multiple stress-responsive cotton group C MAPK gene, has a role in broad spectrum disease resistance and plant development. Plant Mol. Biol. **74**:1–17. https://doi.org/10.1007/s11103-010-9661-0.

Shimono, M., Koga, H., Akagi, A., Hayashi, N., Goto, S., Sawada, M., Kurihara, T., Matsushita, A., Sugano, S., Jiang, C.J., et al. (2012). Rice *WRKY45* plays important roles in fungal and bacterial disease resistance. Mol. Plant Pathol. **13**:83–94. https://doi.org/10.1111/j.1364-3703.2011.00732.x.

Si, X., Zhang, H., Wang, Y., Chen, K., and Gao, C. (2020). Manipulating gene translation in plants by CRISPR-Cas9-mediated genome editing of upstream open reading frames. Nat. Protoc. **15**:338–363. https://doi.org/10.1038/s41596-019-0238-3.

Skoppek, C.I., Punt, W., Heinrichs, M., Ordon, F., Wehner, G., Boch, J., and Streubel, J. (2022). The barley HvSTP13GR mutant triggers resistance against biotrophic fungi. Mol. Plant Pathol. **23**:278–290. https://doi.org/10.1111/mpp.13161.

Song, W., Liu, L., Yu, D., Bernardy, H., Jirschitzka, J., Huang, S., Jia, A., Jemielniak, W., Acker, J., Laessle, H., et al. (2024). Substrate-induced condensation activates plant TIR domain proteins. Nature **627**:847–853. https://doi.org/10.1038/s41586-024-07183-9.

Spoel, S.H., Johnson, J.S., and Dong, X. (2007). Regulation of tradeoffs between plant defenses against pathogens with different lifestyles. Proc. Natl. Acad. Sci. USA **104**:18842–18847. https://doi.org/10.1073/pnas.0708139104.

Springmann, M., Clark, M., Mason-D'Croz, D., Wiebe, K., Bodirsky, B.L., Lassaletta, L., de Vries, W., Vermeulen, S.J., Herrero, M., Carlson, K.M., et al. (2018). Options for keeping the food system within environmental limits. Nature **562**:519–525. https://doi.org/10.1038/s41586-018-0594-0.

Stukenbrock, E., and Gurr, S. (2023). Address the growing urgency of fungal disease in crops. Nature **617**:31–34. https://doi.org/10.1038/d41586-023-01465-4.

Su, X., Lu, G., Li, X., Rehman, L., Liu, W., Sun, G., Guo, H., Wang, G., and Cheng, H. (2020). Host-induced gene silencing of an adenylate

kinase gene involved in fungal energy metabolism improves plant resistance to *Verticillium dahliae*. Biomolecules **10**:127. https://doi.org/10.3390/biom10010127.

Su, X., Wang, Q., Zhang, T., Ge, X., Liu, W., Guo, H., Wang, X., Sun, Z., Li, Z., and Cheng, H. (2024). A *Verticillium dahliae* exoglucanase as potential HIGS target interacts with a cotton cysteine protease to confer resistance to cotton Verticillium wilt. Plant Biotechnol. J. **22**:2107–2109. https://doi.org/10.1111/pbi.14330.

Sun, C., Lei, Y., Li, B., Gao, Q., Li, Y., Cao, W., Yang, C., Li, H., Wang, Z., Li, Y., et al. (2024). Precise integration of large DNA sequences in plant genomes using PrimeRoot editors. Nat. Biotechnol. **42**:316–327. https://doi.org/10.1038/s41587-023-01769-w.

Sun, K., Schipper, D., Jacobsen, E., Visser, R.G.F., Govers, F., Bouwmeester, K., and Bai, Y. (2022). Silencing susceptibility genes in potato hinders primary infection of *Phytophthora infestans* at different stages. Hortic. Res. **9**:uhab058. https://doi.org/10.1093/hr/uhab058.

Sun, P., Han, X., Milne, R.J., and Li, G. (2024). Trans-crop applications of atypical *R* genes for multipathogen resistance. Trends Plant Sci. **29**:1103–1112. https://doi.org/10.1016/j.tplants.2024.05.004.

Suzuki, K., Tsunekawa, Y., Hernandez-Benitez, R., Wu, J., Zhu, J., Kim, E.J., Hatanaka, F., Yamamoto, M., Araoka, T., Li, Z., et al. (2016). *In vivo* genome editing via CRISPR/Cas9 mediated homology-independent targeted integration. Nature **540**:144–149. https://doi.org/10.1038/nature20565.

Tang, J., Gu, X., Liu, J., and He, Z. (2021). Roles of small RNAs in crop disease resistance. Stress Biol. **1**:6. https://doi.org/10.1007/s44154-021-00005-2.

Tao, H., Shi, X., He, F., Wang, D., Xiao, N., Fang, H., Wang, R., Zhang, F., Wang, M., Li, A., et al. (2021). Engineering broad-spectrum disease-resistant rice by editing multiple susceptibility genes. J. Integr. Plant Biol. **63**:1639–1648. https://doi.org/10.1111/jipb.13145.

Tian, D., Wang, J., Zeng, X., Gu, K., Qiu, C., Yang, X., Zhou, Z., Goh, M., Luo, Y., Murata-Hori, M., et al. (2014). The rice TAL effector-dependent resistance protein XA10 triggers cell death and calcium depletion in the endoplasmic reticulum. Plant Cell **26**:497–515. https://doi.org/10.1105/tpc.113.119255.

Thomazella, D.P.d.T., Seong, K., Mackelprang, R., et al. (2021). Loss of function of a *DMR6* ortholog in tomato confers broad-spectrum disease resistance. Proc. Natl. Acad. Sci. USA **118**:e2026152118. https://doi.org/10.1073/pnas.2026152118.

Tian, J., Tang, Z., Niu, R., Zhou, Y., Yang, D., Chen, D., Luo, M., Mou, R., Yuan, M., and Xu, G. (2024). Engineering disease-resistant plants with alternative translation efficiency by switching uORF types through CRISPR. Sci. China Life Sci. **67**:1715–1726. https://doi.org/10.1007/s11427-024-2588-9.

van Dijk, M., Morley, T., Rau, M.L., and Saghai, Y. (2021). A meta-analysis of projected global food demand and population at risk of hunger for the period 2010-2050. Nat. Food **2**:494–501. https://doi.org/10.1038/s43016-021-00322-9.

van Schie, C.C.N., and Takken, F.L.W. (2014). Susceptibility genes 101: How to be a good host. Annu. Rev. Phytopathol. **52**:551–581. https://doi.org/10.1146/annurev-phyto-102313-045854.

Varshney, R.K., Roorkiwal, M., Sun, S., Bajaj, P., Chitikineni, A., Thudi, M., Singh, N.P., Du, X., Upadhyaya, H.D., Khan, A.W., et al. (2021). A chickpea genetic variation map based on the sequencing of 3,366 genomes. Nature **599**:622–627. https://doi.org/10.1038/s41586-021-04066-1.

Vora, Z., Pandya, J., Sangh, C., and Vaikuntapu, P.R. (2023). The evolving landscape of global regulations on genome-edited crops. J Plant Biochem Biot **32**:831–845. https://doi.org/10.1007/s13562-023-00863-z.

Walkowiak, S., Gao, L., Monat, C., Haberer, G., Kassa, M.T., Brinton, J., Ramirez-Gonzalez, R.H., Kolodziej, M.C., Delorean, E., Thambugala, D., et al. (2020). Multiple wheat genomes reveal global variation in modern breeding. Nature **588**:277–283. https://doi.org/10.1038/s41586-020-2961-x.

Wang, C., Zhang, X., Fan, Y., Gao, Y., Zhu, Q., Zheng, C., Qin, T., Li, Y., Che, J., Zhang, M., et al. (2015). XA23 is an executor R protein and confers broad-spectrum disease resistance in rice. Mol. Plant **8**:290–302. https://doi.org/10.1016/j.molp.2014.10.010.

Wang, F., Zhang, H., Liu, H., Wu, C., Wan, Y., Zhu, L., Yang, J., Cai, P., Chen, J., and Ge, T. (2024). Combating wheat yellow mosaic virus through microbial interactions and hormone pathway modulations. Microbiome **12**:200. https://doi.org/10.1186/s40168-024-01911-z.

Wang, H., Chen, Q., and Feng, W. (2024). The emerging role of *2OGDs* as candidate targets for engineering crops with broad-spectrum disease resistance. Plants **13**:1129. https://doi.org/10.3390/plants13081129.

Wang, H., Sun, S., Ge, W., Zhao, L., Hou, B., Wang, K., Lyu, Z., Chen, L., Xu, S., Guo, J., et al. (2020). Horizontal gene transfer of *Fhb7* from fungus underlies *Fusarium* head blight resistance in wheat. Science **368**:eaba5435. https://doi.org/10.1126/science.aba5435.

Wang, H., Hou, J., Ye, P., Hu, L., Huang, J., Dai, Z., Zhang, B., Dai, S., Que, J., Min, H., et al. (2021). A teosinte-derived allele of a MYB transcription repressor confers multiple disease resistance in maize. Mol. Plant **14**:1846–1863. https://doi.org/10.1016/j.molp.2021.07.008.

Wang, J., Zhou, L., Shi, H., Chern, M., Yu, H., Yi, H., He, M., Yin, J., Zhu, X., Li, Y., et al. (2018). A single transcription factor promotes both yield and immunity in rice. Science **361**:1026–1028. https://doi.org/10.1126/science.aat7675.

Wang, J., Hu, M., Wang, J., Qi, J., Han, Z., Wang, G., Qi, Y., Wang, H.W., Zhou, J.M., and Chai, J. (2019). Reconstitution and structure of a plant NLR resistosome conferring immunity. Science **364**:eaav5870. https://doi.org/10.1126/science.aav5870.

Wang, M., Wu, L., Mei, Y., Zhao, Y., Ma, Z., Zhang, X., and Chen, Y. (2020). Host-induced gene silencing of multiple genes of *Fusarium graminearum* enhances resistance to Fusarium head blight in wheat. Plant Biotechnol. J. **18**:2373–2375. https://doi.org/10.1111/pbi.13401.

Wang, M., Li, S., Li, H., Song, C., Xie, W., Zuo, S., Zhou, X., Zhou, C., Ji, Z., and Zhou, H. (2024). Genome editing of a dominant resistance gene for broad-spectrum resistance to bacterial diseases in rice without growth penalty. Plant Biotechnol. J. **22**:529–531. https://doi.org/10.1111/pbi.14233.

Wang, N., Tang, C., Fan, X., He, M., Gan, P., Zhang, S., Hu, Z., Wang, X., Yan, T., Shu, W., et al. (2022). Inactivation of a wheat protein kinase gene confers broad-spectrum resistance to rust fungi. Cell **185**:2961–2974.e19. https://doi.org/10.1016/j.cell.2022.06.027.

Wang, R., Li, C., Li, Q., Ai, Y., Huang, Z., Sun, X., Zhou, J., Zhou, Y., and Liang, Y. (2022). Tomato receptor-like cytosolic kinase RIPK confers broad-spectrum disease resistance without yield penalties. Hortic. Res. **9**:uhac207. https://doi.org/10.1093/hr/uhac207.

Wang, S., Lei, C., Wang, J., Ma, J., Tang, S., Wang, C., Zhao, K., Tian, P., Zhang, H., Qi, C., et al. (2017). *SPL33*, encoding an eEF1A-like protein, negatively regulates cell death and defense responses in rice. J. Exp. Bot. **68**:899–913. https://doi.org/10.1093/jxb/erx001.

Wang, W., Qin, L., Zhang, W., Tang, L., Zhang, C., Dong, X., Miao, P., Shen, M., Du, H., Cheng, H., et al. (2023). WeiTsing, a pericycle-expressed ion channel, safeguards the stele to confer clubroot resistance. Cell **186**:2656–2671.e18. https://doi.org/10.1016/j.cell.2023.05.023.

Wang, Y., Cheng, X., Shan, Q., Zhang, Y., Liu, J., Gao, C., and Qiu, J.L. (2014). Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew. Nat. Biotechnol. **32**:947–951. https://doi.org/10.1038/nbt.2969.

Wang, Z., Xia, Y., Lin, S., Wang, Y., Guo, B., Song, X., Ding, S., Zheng, L., Feng, R., Chen, S., et al. (2018). Osa-miR164a targets *OsNAC60* and negatively regulates rice immunity against the blast fungus *Magnaporthe oryzae*. Plant J. **95**:584–597. https://doi.org/10.1111/tpj.13972.

Wang, Z., Zhou, L., Lan, Y., Li, X., Wang, J., Dong, J., Guo, W., Jing, D., Liu, Q., Zhang, S., et al. (2022). An aspartic protease 47 causes quantitative recessive resistance to rice black-streaked dwarf virus disease and southern rice black-streaked dwarf virus disease. New Phytol. **233**:2520–2533. https://doi.org/10.1111/nph.17961.

Watson, J.L., Juergens, D., Bennett, N.R., Trippe, B.L., Yim, J., Eisenach, H.E., Ahern, W., Borst, A.J., Ragotte, R.J., Milles, L.F., et al. (2023). De novo design of protein structure and function with RFdiffusion. Nature **620**:1089–1100. https://doi.org/10.1038/s41586-023-06415-8.

Wei, X., Chen, M., Zhang, Q., Gong, J., Liu, J., Yong, K., Wang, Q., Fan, J., Chen, S., Hua, H., et al. (2024). Genomic investigation of 18,421 lines reveals the genetic architecture of rice. Science **385**:eadm8762. https://doi.org/10.1126/science.adm8762.

Wei, Y., Wu, J., Chen, Y., Fan, K., Yu, X., Li, X., Zhao, Y., Li, Y., Lv, G., Song, G., et al. (2023). Efficacy and safety of PL-5 (peceleganan) spray for wound infections: A phase IIb randomized clinical trial. Ann. Surg. **277**:43–49. https://doi.org/10.1097/SLA.0000000000005508.

Wei, Y., Li, Y., Li, X., Zhao, Y., Xu, J., Wang, H., Rong, X., Xiong, J., Chen, X., Luo, G., et al. (2024). Peceleganan spray for the treatment of skin wound infections: A randomized clinical trial. JAMA Netw. Open **7**:e2415310. https://doi.org/10.1001/jamanetworkopen.2024.15310.

Wu, Q., Cui, Y., Jin, X., Wang, G., Yan, L., Zhong, C., Yu, M., Li, W., Wang, Y., Wang, L., et al. (2022). The CC-NB-LRR protein BSR1 from *Brachypodium* confers resistance to *Barley stripe mosaic virus* in gramineous plants by recognising TGB1 movement protein. New Phytol. **236**:2233–2248. https://doi.org/10.1111/nph.18457.

Wu, Y., Xiao, N., Chen, Y., Yu, L., Pan, C., Li, Y., Zhang, X., Huang, N., Ji, H., Dai, Z., et al. (2019). Comprehensive evaluation of resistance effects of pyramiding lines with different broad-spectrum resistance genes against *Magnaporthe oryzae* in rice (*Oryza sativa* L.). Rice **12**:11. https://doi.org/10.1186/s12284-019-0264-3.

Xiao, N., Wu, Y., Pan, C., Yu, L., Chen, Y., Liu, G., Li, Y., Zhang, X., Wang, Z., Dai, Z., et al. (2016). Improving of rice blast resistances in *Japonica* by pyramiding major *R* genes. Front. Plant Sci. **7**:1918. https://doi.org/10.3389/fpls.2016.01918.

Xiao, N., Wu, Y., Zhang, X., Hao, Z., Chen, Z., Yang, Z., Cai, Y., Wang, R., Yu, L., Wang, Z., et al. (2023). *Pijx* confers broad-spectrum seedling and panicle blast resistance by promoting the degradation of ATP β subunit and OsRbohC-mediated ROS burst in rice. Mol. Plant **16**:1832–1846. https://doi.org/10.1016/j.molp.2023.10.001.

Xie, H., Gan, P., Lü, S., Tang, T., Li, C., Chen, C., Guan, X., Zhu, Z., Ye, Y., Huang, X., et al. (2024). Development of marker-free transgenic rice exhibiting stable and enhanced resistance to Rice ragged stunt virus and Rice grassy stunt virus via RNA interference. Plant Biotechnol. J. **22**:2327–2329. https://doi.org/10.1111/pbi.14347.

Xie, S.S., and Duan, C.G. (2023). Epigenetic regulation of plant immunity: From chromatin codes to plant disease resistance. aBIOTECH **4**:124–139. https://doi.org/10.1007/s42994-023-00101-z.

Xu, G., Yuan, M., Ai, C., Liu, L., Zhuang, E., Karapetyan, S., Wang, S., and Dong, X. (2017). uORF-mediated translation allows engineered plant disease resistance without fitness costs. Nature **545**:491–494. https://doi.org/10.1038/nature22372.

Xu, H.Y., Zhang, C., Li, Z.C., Wang, Z.R., Jiang, X.X., Shi, Y.F., Tian, S.N., Braun, E., Mei, Y., Qiu, W.L., et al. (2018). The MAPK kinase kinase GmMEKK1 regulates cell death and defense responses. Plant Physiol. **178**:907–922. https://doi.org/10.1104/pp.18.00903.

Xu, Y., Bai, L., Liu, M., Liu, Y., Peng, S., Hu, P., Wang, D., Liu, Q., Yan, S., Gao, L., et al. (2023). Identification of two novel rice *S* genes through combination of association and transcription analyses with gene-editing technology. Plant Biotechnol. J. **21**:1628–1641. https://doi.org/10.1111/pbi.14064.

Xu, Z., Zhou, Z., Cheng, Z., Zhou, Y., Wang, F., Li, M., Li, G., Li, W., Du, Q., Wang, K., et al. (2023). A transcription factor *ZmGLK36* confers broad resistance to maize rough dwarf disease in cereal crops. Nat. Plants **9**:1720–1733. https://doi.org/10.1038/s41477-023-01514-w.

Xue, C., Qiu, F., Wang, Y., Li, B., Zhao, K.T., Chen, K., and Gao, C. (2023). Tuning plant phenotypes by precise, graded downregulation of gene expression. Nat. Biotechnol. **41**:1758–1764. https://doi.org/10.1038/s41587-023-01707-w.

Yang, C., Wang, E., and Liu, J. (2022). CERK1, more than a co-receptor in plant-microbe interactions. New Phytol. **234**:1606–1613. https://doi.org/10.1111/nph.18074.

Yang, C., Li, W., Cao, J., Meng, F., Yu, Y., Huang, J., Jiang, L., Liu, M., Zhang, Z., Chen, X., et al. (2017). Activation of ethylene signaling pathways enhances disease resistance by regulating ROS and phytoalexin production in rice. Plant J. **89**:338–353. https://doi.org/10.1111/tpj.13388.

Yang, K., Yan, Q., Wang, Y., Peng, H., Jing, M., and Dou, D. (2022). GmPAO-mediated polyamine catabolism enhances soybean *Phytophthora* resistance without growth penalty. Phytopathol. Res. **4**:35. https://doi.org/10.1186/s42483-022-00139-9.

Yang, K., Yan, Q., Wang, Y., Zhu, W., Wang, X., Li, X., Peng, H., Zhou, Y., Jing, M., and Dou, D. (2023). Engineering crop *Phytophthora* resistance by targeting pathogen-derived PI3P for enhanced catabolism. Plant Commun. **4**:100460. https://doi.org/10.1016/j.xplc.2022.100460.

Yang, Q., He, Y., Kabahuma, M., Chaya, T., Kelly, A., Borrego, E., Bian, Y., El Kasmi, F., Yang, L., Teixeira, P., et al. (2017). A gene encoding maize caffeoyl-CoA *O*-methyltransferase confers quantitative resistance to multiple pathogens. Nat. Genet. **49**:1364–1372. https://doi.org/10.1038/ng.3919.

Yang, X.M., Zhao, J.H., Xiong, X.Y., Hu, Z.W., Sun, J.F., Su, H., Liu, Y.J., Xiang, L., Zhu, Y., Li, J.L., et al. (2024). Broad-spectrum resistance gene *RPW8.1* balances immunity and growth via feedback regulation of WRKYs. Plant Biotechnol. J. **22**:116–130. https://doi.org/10.1111/pbi.14172.

Yao, Q., Shen, R., Shao, Y., Tian, Y., Han, P., Zhang, X., Zhu, J.K., and Lu, Y. (2024). Efficient and multiplex gene upregulation in plants through CRISPR-Cas-mediated knockin of enhancers. Mol. Plant **17**:1472–1483. https://doi.org/10.1016/j.molp.2024.07.009.

Ye, J., Zhong, T., Zhang, D., Ma, C., Wang, L., Yao, L., Zhang, Q., Zhu, M., and Xu, M. (2019). The auxin-regulated protein ZmAuxRP1 coordinates the balance between root growth and stalk rot disease resistance in maize. Mol. Plant **12**:360–373. https://doi.org/10.1016/j.molp.2018.10.005.

Yu, X., Xie, Y., Luo, D., Liu, H., de Oliveira, M.V.V., Qi, P., Kim, S.I., Ortiz-Morea, F.A., Liu, J., Chen, Y., et al. (2023). A phospho-switch constrains BTL2-mediated phytocytokine signaling in plant immunity. Cell **186**:2329–2344.e20. https://doi.org/10.1016/j.cell.2023.04.027.

Yuan, M., Jiang, Z., Bi, G., Nomura, K., Liu, M., Wang, Y., Cai, B., Zhou, J.M., He, S.Y., and Xin, X.F. (2021). Pattern-recognition receptors are required for NLR-mediated plant immunity. Nature **592**:105–109. https://doi.org/10.1038/s41586-021-03316-6.

Zaka, A., Grande, G., Coronejo, T., Quibod, I.L., Chen, C.W., Chang, S.J., Szurek, B., Arif, M., Cruz, C.V., and Oliva, R. (2018). Natural variations in the promoter of *OsSWEET13* and *OsSWEET14* expand the range of resistance against *Xanthomonas oryzae* pv. *oryzae*. PLoS One **13**:e0203711. https://doi.org/10.1371/journal.pone.0203711.

Zavaliev, R., Mohan, R., Chen, T., and Dong, X. (2020). Formation of NPR1 condensates promotes cell survival during the plant immune response. Cell **182**:1093–1108.e18. https://doi.org/10.1016/j.cell.2020.07.016.

Zeng, X., Luo, Y., Vu, N.T.Q., Shen, S., Xia, K., and Zhang, M. (2020). CRISPR/Cas9-mediated mutation of *OsSWEET14* in rice cv. Zhonghua11 confers resistance to *Xanthomonas oryzae* pv. *oryzae* without yield penalty. BMC Plant Biol. **20**:313. https://doi.org/10.1186/s12870-020-02524-y.

Zhai, K.R., Deng, Y.W., Liang, D., Tang, J., Liu, J., Yan, B.X., Yin, X., Lin, H., Chen, F.D., Yang, D.Y., et al. (2019). RRM transcription factors interact with NLRs and regulate boad-spectrum blast resistance in rice. Mol Cell **74**:996–1009.e1007. https://doi.org/10.1016/j.molcel.2019.03.013.

Zhai, K., Liang, D., Li, H., Jiao, F., Yan, B., Liu, J., Lei, Z., Huang, L., Gong, X., Wang, X., et al. (2022). NLRs guard metabolism to coordinate pattern- and effector-triggered immunity. Nature **601**:245–251. https://doi.org/10.1038/s41586-021-04219-2.

Zhang, H., Zhang, Q., Zhai, H., Gao, S., Yang, L., Wang, Z., Xu, Y., Huo, J., Ren, Z., Zhao, N., et al. (2020). IbBBX24 promotes the jasmonic acid pathway and enhances Fusarium wilt resistance in sweet potato. Plant Cell **32**:1102–1123. https://doi.org/10.1105/tpc.19.00641.

Zhang, J., Hewitt, T.C., Boshoff, W.H.P., Dundas, I., Upadhyaya, N., Li, J., Patpour, M., Chandramohan, S., Pretorius, Z.A., Hovmøller, M., et al. (2021). A recombined *Sr26* and *Sr61* disease resistance gene stack in wheat encodes unrelated *NLR* genes. Nat. Commun. **12**:3378. https://doi.org/10.1038/s41467-021-23738-0.

Zhang, R., Tang, X., He, Y., Li, Y., Wang, W., Wang, Y., Wang, D., Zheng, X., Qi, Y., and Zhang, Y. (2024). IsDge10 is a hypercompact TnpB nuclease that confers efficient genome editing in rice. Plant Commun. **5**:101068. https://doi.org/10.1016/j.xplc.2024.101068.

Zhang, X., Liu, Y., Yuan, G., Wang, S., Wang, D., Zhu, T., Wu, X., Ma, M., Guo, L., Guo, H., et al. (2024). The synthetic NLR RGA5^{HMA5} requires multiple interfaces within and outside the integrated domain for effector recognition. Nat. Commun. **15**:1104. https://doi.org/10.1038/s41467-024-45380-2.

Zhang, Y.-Z., Man, J., Xu, D., Wen, L., Li, Y., Deng, M., Jiang, Q.-T., Xu, Q., Chen, G.-Y., and Wei, Y.-M. (2024). Investigating the mechanisms of isochorismate synthase: An approach to improve salicylic acid synthesis and increase resistance to Fusarium head blight in wheat. The Crop Journal **12**:1054–1063. https://doi.org/10.1016/j.cj.2024.05.012.

Zhang, Y., Li, D., Zhang, H., Hong, Y., Huang, L., Liu, S., Li, X., Ouyang, Z., and Song, F. (2015). Tomato histone H2B monoubiquitination enzymes SlHUB1 and SlHUB2 contribute to disease resistance against *Botrytis cinerea* through modulating the balance between SA- and JA/ET-mediated signaling pathways. BMC Plant Biol. **15**:252. https://doi.org/10.1186/s12870-015-0614-2.

Zhang, Y., Zhang, Y., Ge, X., Yuan, Y., Jin, Y., Wang, Y., Zhao, L., Han, X., Hu, W., Yang, L., et al. (2023). Genome-wide association analysis reveals a novel pathway mediated by a dual-TIR domain protein for pathogen resistance in cotton. Genome Biol. **24**:111. https://doi.org/10.1186/s13059-023-02950-9.

Zhang, Y.M., Zheng, L., and Xie, K. (2023). CRISPR/dCas9-mediated gene silencing in two plant fungal pathogens. mSphere **8**:e0059422. https://doi.org/10.1128/msphere.00594-22.

Zhang, Z.L., Wang, X.J., Lu, J.B., Lu, H.B., Ye, Z.X., Xu, Z.T., Zhang, C., Chen, J.P., Li, J.M., Zhang, C.X., and Huang, H.J. (2024). Cross-kingdom RNA interference mediated by insect salivary microRNAs may suppress plant immunity. Proc. Natl. Acad. Sci. USA **121**:e2318783121. https://doi.org/10.1073/pnas.2318783121.

Zhao, J., Chen, Y., Ding, Z., Zhou, Y., Bi, R., Qin, Z., Yang, L., Sun, P., Sun, Q., Chen, G., et al. (2024). Identification of propranolol and derivatives that are chemical inhibitors of phosphatidate phosphatase as potential broad-spectrum fungicides. Plant Commun. **5**:100679. https://doi.org/10.1016/j.xplc.2023.100679.

Zhao, J., Liu, P., Li, C., Wang, Y., Guo, L., Jiang, G., and Zhai, W. (2017). *LMM5.1* and *LMM5.4*, two eukaryotic translation elongation factor 1A-like gene family members, negatively affect cell death and disease resistance in rice. J Genet Genomics **44**:107–118. https://doi.org/10.1016/j.jgg.2016.12.005.

Zhao, J.H., Huang, Y.Y., Wang, H., Yang, X.M., Li, Y., Pu, M., Zhou, S.X., Zhang, J.W., Zhao, Z.X., Li, G.B., et al. (2023). *Golovinomyces cichoracearum* effector-associated nuclear localization of RPW8.2 amplifies its expression to boost immunity in *Arabidopsis*. New Phytol. **238**:367–382. https://doi.org/10.1111/nph.18682.

Zhao, Y., Zhu, X., Shi, C.M., Xu, G., Zuo, S., Shi, Y., Cao, W., Kang, H., Liu, W., Wang, R., et al. (2024). OsEIL2 balances rice immune responses against (hemi)biotrophic and necrotrophic pathogens via the salicylic acid and jasmonic acid synergism. New Phytol. **243**:362–380. https://doi.org/10.1111/nph.19809.

Zheng, L., Gao, S., Bai, Y., Zeng, H., and Shi, H. (2024). NF-YC15 transcription factor activates ethylene biosynthesis and improves cassava disease resistance. Plant Biotechnol. J. **22**:2424–2434. https://doi.org/10.1111/pbi.14355.

Zheng, W., Li, S., Liu, Z., Zhou, Q., Feng, Y., and Chai, S. (2020). Molecular marker assisted gene stacking for disease resistance and quality genes in the dwarf mutant of an elite common wheat cultivar Xiaoyan22. BMC Genet. **21**:45. https://doi.org/10.1186/s12863-020-00854-2.

Zhi, P., Kong, L., Liu, J., Zhang, X., Wang, X., Li, H., Sun, M., Li, Y., and Chang, C. (2020). Histone deacetylase TaHDT701 functions in TaHDA6-TaHOS15 complex to regulate wheat defense responses to *Blumeria graminis* f.sp. *tritici*. Int. J. Mol. Sci. **21**:2640. https://doi.org/10.3390/ijms21072640.

Zhou, J., Peng, Z., Long, J., Sosso, D., Liu, B., Eom, J.S., Huang, S., Liu, S., Vera Cruz, C., Frommer, W.B., et al. (2015). Gene targeting by the TAL effector PthXo2 reveals cryptic resistance gene for bacterial blight of rice. Plant J. **82**:632–643. https://doi.org/10.1111/tpj.12838.

Zhou, J., Liu, G., Zhao, Y., Zhang, R., Tang, X., Li, L., Jia, X., Guo, Y., Wu, Y., Han, Y., et al. (2023). An efficient CRISPR-Cas12a promoter editing system for crop improvement. Nat. Plants **9**:588–604. https://doi.org/10.1038/s41477-023-01384-2.

Zhou, J., Wang, X., He, Y., Sang, T., Wang, P., Dai, S., Zhang, S., and Meng, X. (2020). Differential phosphorylation of the transcription factor WRKY33 by the protein kinases CPK5/CPK6 and MPK3/MPK6 cooperatively regulates camalexin biosynthesis in Arabidopsis. Plant Cell **32**:2621–2638. https://doi.org/10.1105/tpc.19.00971.

Zhou, J., Mu, Q., Wang, X., Zhang, J., Yu, H., Huang, T., He, Y., Dai, S., and Meng, X. (2022). Multilayered synergistic regulation of phytoalexin biosynthesis by ethylene, jasmonate, and MAPK signaling pathways in Arabidopsis. Plant Cell **34**:3066–3087. https://doi.org/10.1093/plcell/koac139.

Zhou, J.M., and Zhang, Y. (2020). Plant immunity: Danger perception and signaling. Cell **181**:978–989. https://doi.org/10.1016/j.cell.2020.04.028.

Zhou, X., Liao, H., Chern, M., Yin, J., Chen, Y., Wang, J., Zhu, X., Chen, Z., Yuan, C., Zhao, W., et al. (2018). Loss of function of a rice TPR-domain RNA-binding protein confers broad-spectrum disease resistance. Proc. Natl. Acad. Sci. USA **115**:3174–3179. https://doi.org/10.1073/pnas.1705927115.

Zhou, Y., Lei, F., Wang, Q., He, W., Yuan, B., and Yuan, W. (2020). Identification of novel alleles of the rice blast-resistance gene *Pi9*

through sequence-based allele mining. Rice **13**:80. https://doi.org/10.1186/s12284-020-00442-z.

Zhou, Y., Yang, K., Yan, Q., Wang, X., Cheng, M., Si, J., Xue, X., Shen, D., Jing, M., Tyler, B.M., and Dou, D. (2021). Targeting of antimicrobial proteins to the hyphal surface amplifies protection of crop plants against *Phytophthora* pathogens. Mol. Plant **14**:1391–1403. https://doi.org/10.1016/j.molp.2021.05.007.

Zhou, Y., Xu, S., Jiang, N., Zhao, X., Bai, Z., Liu, J., Yao, W., Tang, Q., Xiao, G., Lv, C., et al. (2022). Engineering of rice varieties with enhanced resistances to both blast and bacterial blight diseases via CRISPR/Cas9. Plant Biotechnol. J. **20**:876–885. https://doi.org/10.1111/pbi.13766.

Zhu, H., Li, C., and Gao, C. (2020). Applications of CRISPR-Cas in agriculture and plant biotechnology. Nat. Rev. Mol. Cell Biol. **21**:661–677. https://doi.org/10.1038/s41580-020-00288-9.

Zhu, M., Jiang, L., Bai, B., Zhao, W., Chen, X., Li, J., Liu, Y., Chen, Z., Wang, B., Wang, C., et al. (2017). The intracellular immune receptor Sw-5b confers broad-spectrum resistance to tospoviruses through recognition of a conserved 21-amino acid viral effector epitope. Plant Cell **29**:2214–2232. https://doi.org/10.1105/tpc.17.00180.

Zhu, X., Qi, T., Yang, Q., He, F., Tan, C., Ma, W., Voegele, R.T., Kang, Z., and Guo, J. (2017). Host-induced gene silencing of the MAPKK gene *PsFUZ7* confers stable resistance to wheat stripe rust. Plant Physiol. **175**:1853–1863. https://doi.org/10.1104/pp.17.01223.

Zhu, X., Zhao, J., Abbas, H.M.K., Liu, Y., Cheng, M., Huang, J., Cheng, W., Wang, B., Bai, C., Wang, G., and Dong, W. (2018). Pyramiding of nine transgenes in maize generates high-level resistance against necrotrophic maize pathogens. Theor. Appl. Genet. **131**:2145–2156. https://doi.org/10.1007/s00122-018-3143-1.

Zong, Y., Liu, Y., Xue, C., Li, B., Li, X., Wang, Y., Li, J., Liu, G., Huang, X., Cao, X., and Gao, C. (2022). An engineered prime editor with enhanced editing efficiency in plants. Nat. Biotechnol. **40**:1394–1402. https://doi.org/10.1038/s41587-022-01254-w.