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REVIEW

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Exploiting susceptibility genes in rice: from molecular mechanism to application

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Abstract

Rice commercial production is seriously threatened by various pathogens. Generally, the susceptibility (*S*) genes in plants are exploited by phytopathogens to promote infection. Dysfunction of *S* genes may result in recessively inheritable durable and broad-spectrum disease resistance. In this review, we summarize the latest research on *S* genes that encode proteins contributing to pathogen infection in rice. The *S* genes in rice are prospective targets of genome engineering to create resistance germplasms. However, the potential pleiotropic effects resulting from the deletion of *S* genes limit their application in resistance breeding. The newly developed CRISPR/Cas9-mediated genome editing system offers a promising approach for developing transgene-free rice varieties with durable disease resistance.

Keywords *Oryza sativa*, Susceptibility genes, Disease resistance, Genome editing, Plant breeding

Background

To fend off pathogen attacks, plants have evolved sophisticated defense mechanisms (Schie and Takken 2014). However, compatible pathogens can disarm multiple layers of plant defenses and successfully infect host plants (Trivedi et al. 2020). Once this compatibility between hosts and pathogens is perturbed, plant-pathogen interactions become incompatible, rendering the plant immune to pathogens (Schie and Takken 2014). In plants, there are two layers of immune systems that become active upon the recognition of microbe- and/or plant-derived molecules and pathogen effectors using extracellular and intracellular immune receptors, respectively (Jones and Dangl 2006; Saijo et al. 2018). The first layer of immunity involves the perception of conserved microbial elicitors, referred to as pathogen-associated molecular patterns (PAMPs) and plant-derived damage-associated molecular patterns (DAMPs) by cell membrane-bound pattern recognition receptors, leading to pattern-triggered immunity (PTI). PTI responses include a remarkable increase in pathogenesis-related (*PR*) gene expression, generation of reactive oxygen species (ROS), and activation of mitogen-activated protein kinase (MAPK) cascades, among others (Couto and Zipfel 2016). The second layer of immunity involves resistance (*R*) genes, whose products can directly or indirectly recognize pathogen effectors, thereby leading to effector-triggered immunity (ETI) (Koseoglou et al. 2022). Nevertheless, pathogen effectors rapidly evolve to incapacitate ETI by escaping surveillance of R proteins (Jones and Dangl 2006).

The relationship between disease resistance and susceptibility is akin to two sides of the same coin (Eckardt 2002). Any plant gene that facilitates a compatible

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interaction with the pathogen is referred to as a susceptibility (*S*) gene (Schie and Takken 2014; Koseoglou et al. 2022). The first *S* gene *Mlo* cloned from barley in 1992 is still in use and confers non-race-specific and durable resistance to powdery mildew in the field (Jørgensen 1992). The concept of *S* genes was later proposed in 2002 following the identification of the *S* gene *PMR6* in *Arabidopsis thaliana* (Eckardt 2002). Since then, hundreds of *S* genes from different plant species have been identified to be involved in three major molecular mechanisms: basic compatibility for host recognition and penetration, sustained compatibility crucial for pathogen expansion and proliferation, and negative regulation of immune signaling, including suppression of salicylic acid (SA) and jasmonic acid (JA) defense signaling, and PTI and ETI responses (Schie and Takken 2014; Deng et al. 2020). Given that *S* genes are exploited by pathogens to promote disease development, it is plausible that disabling *S* genes could lead to relatively durable and potentially broad-spectrum resistance in plants (Pavan et al. 2010; Koseoglou et al. 2022).

Rice (*Oryza sativa* L.), one of the most important staple food crops, feeds over 50% of the world's population. However, sustainable rice production is threatened by various diseases, such as fungal blast, sheath blight, bacterial leaf blight and leaf streak, rice false smut, and viral diseases, which collectively cause up to 30% yield loss. The most effective and environmentally friendly approach to managing these diseases is to utilize host resistance (Liu et al. 2021). However, resistance breeding mainly relies on *R* gene-mediated ETI, a race-specific "gene-for-gene" resistance that is readily broken down by rapidly evolved effectors (Deng et al. 2020). Therefore, novel molecular breeding strategies, such as *S* gene editing, for the control of crop diseases are urgently needed (Pavan et al. 2010). To date, more than a hundred *S* genes have been identified in rice (Additional file 1: Table S1). Here, we focus on the progress in the identification of susceptibility genes in rice and their application in disease resistance improvement.

S genes facilitating basic compatibility in rice

Basic compatibility is implicated in the pre-penetration and penetration stages during pathogen infection. During the early infection, pathogens enter the hosts through natural openings or direct penetration by breaking physical barriers (Fig. 1a, b) (Zaidi et al. 2018). Natural openings, such as stomata and hydathodes, are important for bacterial entry into the apoplast or vasculature (Lahaye and Bonas 2001; Panchal and Melotto 2017). Plants usually close their stomata upon contact with microbes, thus preventing pathogens entry into the leaves and subsequent colonization of host tissues. However, some bacterial pathogens secrete effectors that activate JA signaling, which in turn represses stomatal immunity (Arnaud and Hwang 2015; Panchal and Melotto 2017). For instance, the *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*) effector XopC2 targets and phosphorylates OSK1, a universal adaptor protein of the Skp1-Cullin-F-box complexes, thereby increasing its binding affinity to OsCOI1b to promote the ubiquitination and degradation of JAZ transcription repressors. JA signaling is therefore activated and enhances plant susceptibility by inhibiting stomatal defense in rice (Wang et al. 2021d). In addition, some genes involved in abscisic acid (ABA) accumulation and stomatal closure regulate disease susceptibility through a distinct mechanism (Hu et al. 2022). For instance, mutations in three ABA biosynthesis genes, *OsABA1*, *OsABA2*, and *OsABA3*, confer non-race-specific resistance to *Xanthomonas oryzae* pv. *oryzae* (*Xoo*). The stomata of *osaba1* remain open even after pathogen infection, thus leading to water loss and restricted bacterial growth and spread (Zhang et al. 2018a). Moreover, disruption of *OsSCAR2*, encoding SCAR-LIKE PROTEIN2, improves resistance to *Xoo* due to increased stomatal density and a higher number of semi-open stomata under normal conditions (Rao et al. 2015; Zhang et al. 2018a). Therefore, stomatal defense is disabled by pathogens through different mechanisms.

Unlike phytopathogenic bacteria, many biotrophic filamentous pathogens invade host plants using mechanical pressure exerted from melanized appressoria to penetrate the cell wall and form haustoria, a specialized feeding structure that depends on membrane dynamics. A few *S* genes have been identified to be involved in the early infection steps and in the formation of membrane structures surrounding haustoria (Schie and Takken 2014). The well-known example is the *S* gene *Mildew resistance Locus O* (*MLO*), which is required for powdery mildew penetration into epidermal cells (Appiano et al. 2015). Small G proteins (Rho-GTPase and RAC/ROP) are required for cytoskeleton dynamics and vesicle trafficking. Three RAC/ROP proteins in rice, OsRacB, OsRac4, and OsRac5, have been identified as susceptibility factors for *Magnaporthe oryzae* infection (Jung et al. 2006; Chen et al. 2010). Similar to barley HvRacB, all of them are localized to the plasma membrane and promote susceptibility by regulating cytoskeleton reorganization to form extrahaustorial membrane (Kawano et al. 2014). Mutation of these *S* genes can prevent penetration of adapted pathogens via hampering the formation of haustoria (Opalski et al. 2005). Furthermore, phosphatidylinositol 4,5-bisphosphate ($PtdIns(4,5)P_2$) enriched in biotrophic interfacial complex (BIC) and extra-invasive hyphal membrane (EIHM) structures, which are involved in effector secretion and fungal

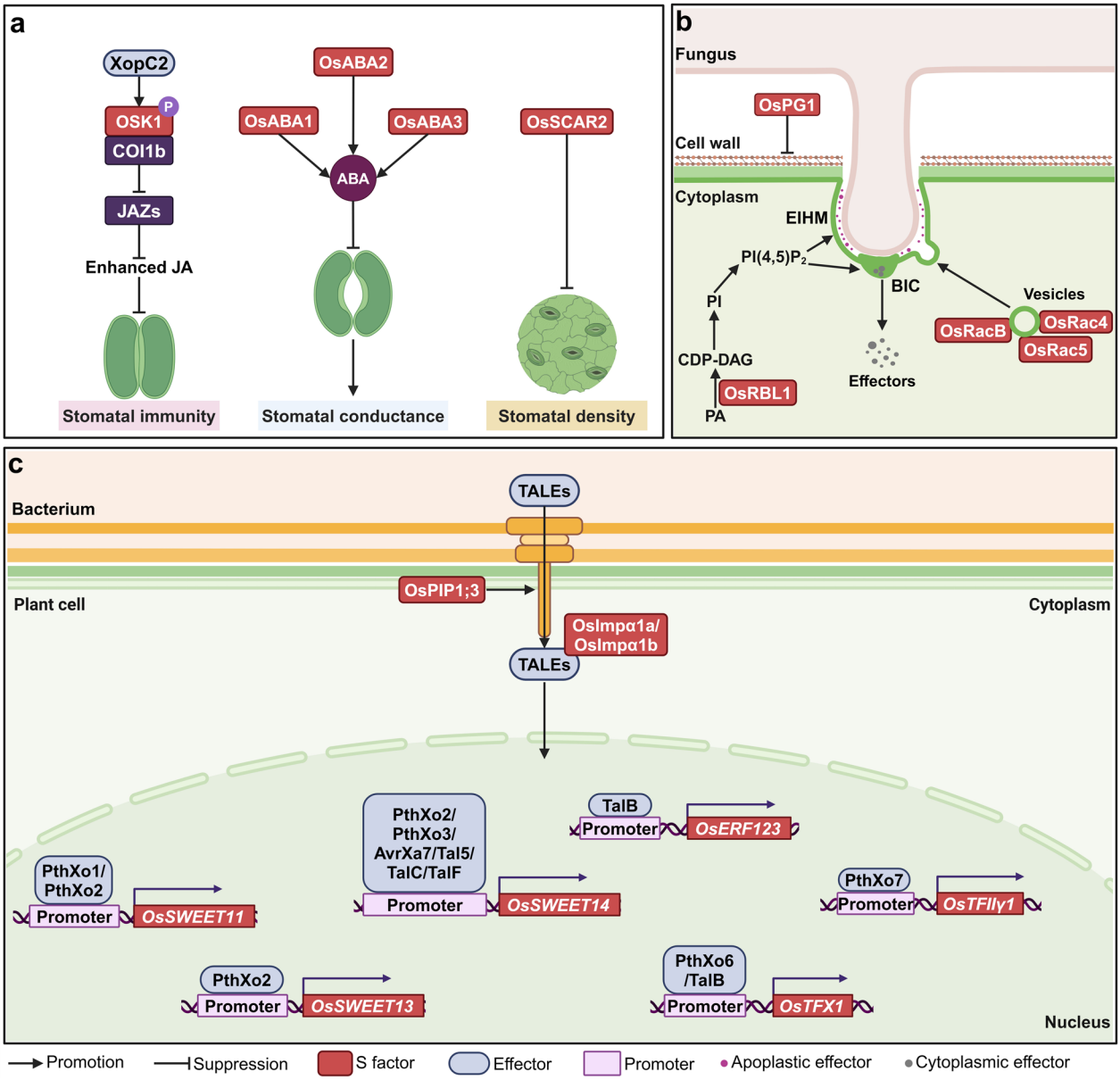

Fig. 1 Susceptibility genes involved in basic compatibility and sustained compatibility during the host-pathogen interactions. **a**, **b** Examples of the *S* genes involved in the early infection process. OSK1, OsABA1/OsABA2/OsABA3, and OsSCAR2 negatively regulate stomatal immunity, stomatal conductance, and stomatal density, respectively. OsPG1, OsRBL1, and OsRacB/OsRac5/OsRac4 are involved in cell wall degradation, effector secretion, and formation of the extrahaustorial membrane, respectively. PA, phosphatidic acid; CDP-DAG, cytidine diphosphate diacylglycerol; PI, phosphatidylinositol; BIC, biotrophic interfacial complex; EIHM, extra-invasive hyphal membrane. **c** Examples of the *S* genes involved in compatible interaction during post-penetration stages of infection. OsPIP1;3 facilitates the secretion of the effector PthoXo1 into the host cytosol. OsImpα1a and OsImpα1b contribute to the translocation of bacterial TALEs into rice nuclei. The promoters of *S* genes, *OsSWEET11*, *OsSWEET13*, *OsSWEET14*, *OsTFX1*, *OsERF123*, and *OsTFIIy1*, are targeted by various effectors. Arrows indicate positive regulation; the blunt-ended line indicates negative regulation. Created with BioRender (www. BioRender.com)

infection, is a disease-susceptibility factor. The cytidine diphosphate diacylglycerol (CDP-DAG) is synthesized by CDP-DAG synthases (CDSs) and is then used to produce PtdIns(4,5)P_2 (Shimada et al. 2019; Qin et al. 2020). Recently, Sha et al. identified an *S* gene *RESISTANCE TO BLAST1* (*RBL1*) encoding a CDP-DAG synthase. Mutation of *RBL1* confers broad-spectrum resistance to various pathogens (Sha et al. 2023). In addition, the change in cell wall structure modulates plant resistance to bacterial blight. For instance, mutation of *OsPG1* encoding a

polygalacturonase causes increased contents of cellulose, pectin, and hemicellulose, thereby enhancing immune responses and resistance against *Xoo* (Cao et al. 2021). In summary, the genes that facilitate pathogen penetration through various mechanisms are a category of *S* genes.

S genes facilitating sustained compatibility in rice

Sustained compatibility is implicated in post-penetration stages during infection. After successfully colonizing host cells, some pathogens manipulate host genes to acquire nutrients for proliferation and/or suppress immunity through the secreted effectors to sustain the compatible interaction (Fig. 1c). The SWEET (Sugars will eventually be exported transporters) family proteins play important roles in fructose and sucrose transport and are among the most extensively investigated classes of S factors. Three *SWEET* genes in rice (*OsSWEET11*, *OsSWEET13*, and *OsSWEET14*) have been identified as the targets of the *Xoo*-secreted transcription activator-like effectors (TALEs) (Yang et al. 2006; Antony et al. 2010; Römer et al. 2010; Streubel et al. 2013; Zhou et al. 2015; Xu et al. 2019; Luo et al. 2021; Wu et al. 2022a). TALEs directly bind to effector-binding elements (EBEs) located on the promoter regions of *SWEET* genes and activate gene expression (Römer et al. 2010). These sugar transporters provide nutrients to *Xoo* and enhance rice susceptibility. Furthermore, SWEETs can function in copper transport. OsSWEET11 interacts with two copper transporters, COPT1 and COPT5, to form a copper transporter complex, which contributes to removing copper ions from xylem vessels and thereby supports *Xoo* multiplication (Yuan et al. 2010). In addition, TALEs modulate the expression of other susceptibility genes. For instance, the promoters of *OsTFX1* and *OsERF123* encoding transcription factors and *OsTFIIy1* encoding the small subunit of the transcription factor IIA are the targets of pthXo6, TalB, and pthXo7 in *Xoo*, respectively (Sugio et al. 2007; Tran et al. 2018).

It is assumed that bacteria take advantage of host proteins to form secretion systems by interacting with bacterial translocators (Li et al. 2019). The *Xoo* translocator Hpa1 interacts with aquaporin OsPIP1;3 to facilitate the secretion of the effector PthoXo1 into host cytosol (Wang et al. 2018b). When *OsPIP1;3* is silenced in rice, *Xoo* no longer delivers the effectors into the cytosol of rice cells during infection and the *ospip1;3* mutant exhibits resistance to *Xoo* (Li et al. 2019; Zhang et al. 2019). In addition, the nucleocytoplasmic transporters OsImpα1a and OsImpα1b interact with the secreted TALEs and mediate TALE translocation into cell nuclei. Down-regulation of *OsImpα1a* and *OsImpα1b* disables the translocation of bacterial TALEs into rice nuclei, where they target *SWEET* genes, thus leading to broad-spectrum resistance against TALE-secreting bacteria (Hui et al. 2019). Collectively, these genes involved in effector translocation represent another type of *S* genes.

Negative regulation of plant immunity in rice

Phytohormone in disease susceptibility

Plant defense hormones, such as SA, JA, and ethylene, play important roles in regulating immune responses (Robert-Seilaniantz et al. 2011; Yang et al. 2015). SA contributes to resistance against hemibiotrophic and biotrophic pathogens and plays critical roles in amplifying local immune responses and establishing systemic acquired resistance (Peng et al. 2021). SA is synthesized mainly through the isochorismate synthase (ICS) and phenylalanine ammonia-lyase (PAL) pathways (Maruri-López et al. 2019; Zhang and Li 2019; Peng et al. 2021). The levels of active SA are also regulated by SA modification. The proteins that are involved in SA catabolism may enhance plant susceptibility (Fig. 2a). The salicylic acid 3-hydroxylase (S3H/DLO1) and 5-hydroxylase (S5H/DMR6) hydroxylate SA into 2,3-hydroxyl and 2,5-hydroxyl benzoic acid (2,3-DHBA and 2,5-DHBA), respectively, resulting in decreased SA levels and SA-mediated defense responses. The transgenic plants overexpressing *OsS5H1*, *OsS5H2*, and *OsS5H3*, which have dramatically decreased SA levels and increased 2,5-DHBA contents, are more susceptible to fungal blast and bacterial blight diseases (Zhang et al. 2022c; Liu et al. 2023b). In rice, OsSAH3 (SA hydroxylase 3) only has SA 5-hydroxylase (SA5H) activity, while OsSAH2 shows both SA3H and SA5H activities. Both *ossah2* and *ossah3* mutants confer broad-spectrum disease resistance to hemibiotrophic and necrotrophic pathogens (Liang et al. 2022). $OsF3H_{03g}$ encoding 2-oxoglutarate-dependent dioxygenase negatively regulates resistance to *Xoc* and *Xoo* via directly reducing SA levels. OsUGT74H4, a uridine diphosphate glycosyltransferase protein, may glycosylate and inactivate SA, thus promoting susceptibility to bacterial leaf streak (Wu et al. 2022b). By contrast, the phenylalanine ammonia-lyases (PALs) activate immune responses by converting Phe to *trans*-cinnamic acid, an alternative precursor of SA (Zhang and Li 2019). Disruption of *Bsr-k1* leads to transcriptional activation of multiple *OsPAL* genes and confers broad-spectrum disease resistance in rice (Zhou et al. 2018). Therefore, the genes involved in SA catabolism and modification belong to a category of *S* genes.

JA, a lipid-derived defense hormone, functions as an important signaling molecule to prevent plant infection by necrotrophic pathogens (Fig. 2a). The isoleucine-conjugate of jasmonic acid (JA-Ile) is perceived by coronatine-insensitive 1 (COI1), which mediates 26S proteasome-dependent degradation of JAZ (JA

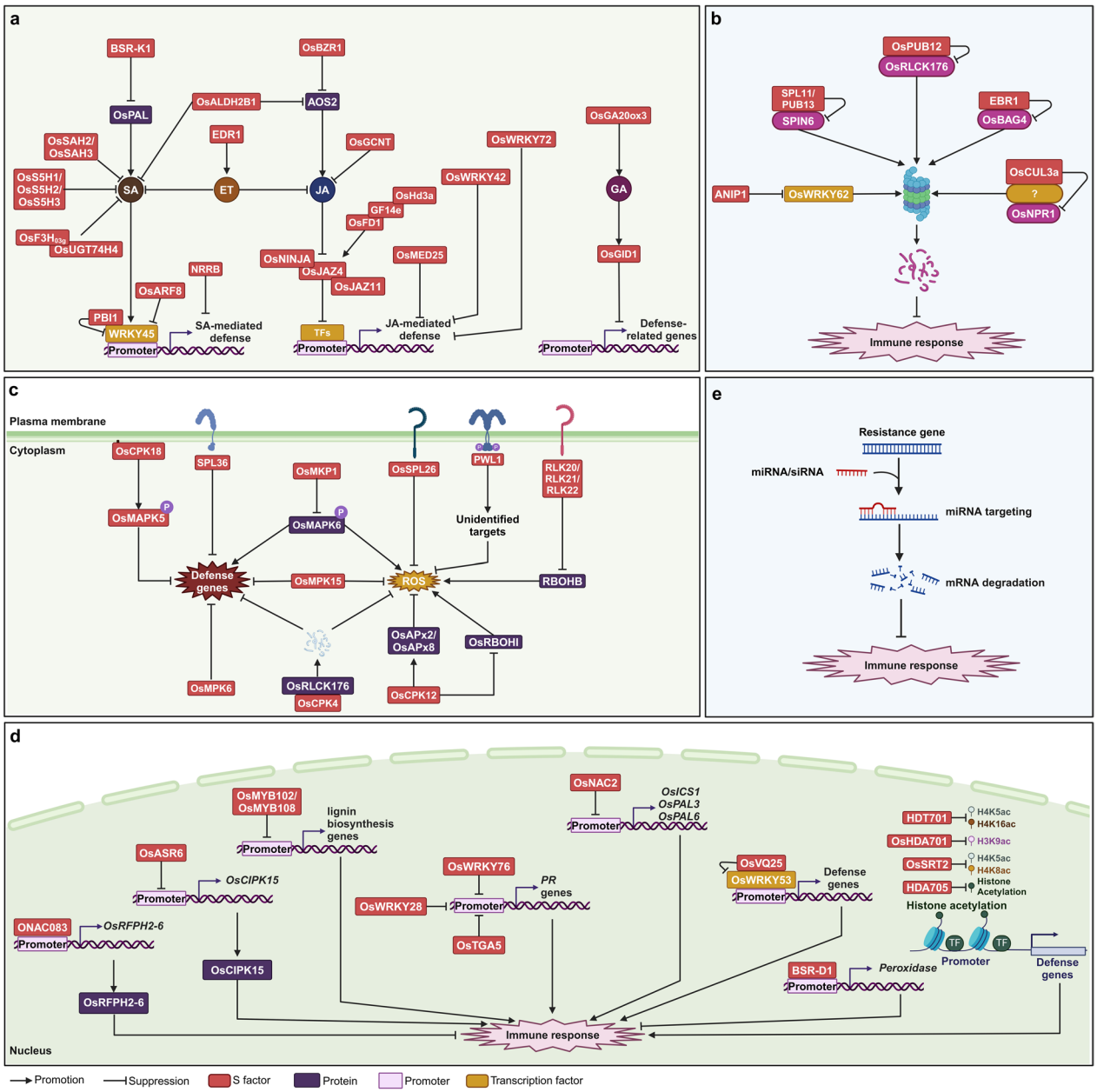

Fig. 2 Susceptibility genes involved in negative regulation of plant immunity. **a** Examples of the *S* genes involved in hormone-mediated defenses. BSR-K1, OsSAH2, OsSAH3, OsS5H1, OsS5H2, OsS5H3, OsF3H$_{03g}$, OsUGT74H4, PBI1, OsARF8, and NRRB suppress SA-mediated defenses. OsBZR1, OsGCNT, OsNINJA1, OsJAZ4, OsJAZ11, OsHd3a, GF14c, OsFD1, OsMED25, OsWRKY42, and OsWRKY72 suppress JA-mediated defenses. OsALDH2B1 suppresses both JA- and SA-mediated defenses. EDR1 suppresses JA- and SA-mediated defenses by activation of ethylene biosynthesis. OsGA20ox3 and OsGID1, involved in GA-mediated signaling, suppress the expression of defense-related genes. **b** Examples of the *S* genes encoding E3 ligases involved in disease susceptibility. The E3 ligases SPL11/ PUB13, OsPUB12, EBR1, and OsCUL3a inhibit immune responses through degrading the substrate proteins SPIN6, OsRLCK176, OsBAG4, and OsNPR1, respectively. ANIP1 negatively regulates resistance to fungal blast via promoting the degradation of OsWRKY62. **c** Examples of the *S* genes encoding protein kinases and phosphatases. OsCPK18, OsMAPK5, SPL36, OsMPK6, OsMPK15, OsCPK4, OsCPK12, PWL1, OsSPL26, RLK20, RLK21, and RLK22 are protein kinases. OsMKP1 is a phosphatase. **d** Examples of the *S* genes encoding transcription regulators. ONAC083, OsASR6, OsMYB102, OsMYB108, OsWRKY28, OsWRKY76, OsTGA5, OsNAC2, and BSR-D1 are transcription factors. OsVQ25 is a cofactor, inhibiting the activity of transcription factor OsWRKY53. HDT701, OsHDA701, HDA705, and OsSRT2 are involved in histone modifications. **e** Examples of microRNA genes involved in disease susceptibility. Arrows indicate positive regulation; the blunt-ended line indicates negative regulation. Created with BioRender (www. BioRender.com)

ZIM-domain) family proteins. JAZ proteins function as transcriptional repressors of the JA signaling pathway and are involved in disease susceptibility caused by necrotrophic pathogens (Berens et al. 2017). For instance, JA- and ethylene-mediated responses are constitutively activated in *Arabidopsis thaliana jaz* decuple mutant, which shows resistance to a necrotrophic fungal pathogen (Guo et al. 2018). OsJAZ4 negatively regulates defenses against viral infection by suppressing JA signaling in rice (He et al. 2020). Furthermore, some proteins mediate rice susceptibility by transcriptionally regulating *JAZ* genes. OsFD1, a basic leucine zipper (bZIP) transcription factor in rice, binds to the promoters of *JAZ* genes and activates their expression. OsHd3a collaborating with GF14e (G-box factor 14-3-3) enhances OsFD1-mediated transcriptional activation of *JAZ* gene expression, thus attenuating rice resistance to *Xoo* and *Xoc* (Ke et al. 2019). NOVEL INTERACTOR OF JAZ (NINJA), a JAZ-interacting adaptor protein, negatively regulates OsMYC2-mediated JA signaling and resistance to *Xoo* in rice (Kashihara et al. 2019). Besides, a novel *Oryza sativa* beta-1,6-N-acetylglucosaminyl transferase (OsGCNT) acts as a negative regulator of defense responses and immunity-associated premature leaf senescence probably by changing the JA metabolic pathway (Xu et al. 2018). OsBZR1, a positive regulator of rice BR signaling, negatively regulates resistance to *Xoo* by suppressing JA signaling (Ke et al. 2020). The aldehyde dehydrogenase OsALDH2B1 also functions as a transcriptional regulator of several biological processes mediated by brassinolide, G protein, JA, and SA signaling pathways. The *osaldh2b1* knockout mutant exhibits enhanced broad-spectrum resistance to pathogens (Ke et al. 2020). MEDIATOR25 (OsMED25), a subunit of the multiprotein complex in rice, negatively regulates resistance to bacterial blight. The expressing levels of OsMYC2-independent JA-responsive defense-related genes were upregulated in the *osmed25* mutant (Suzuki et al. 2022).

Ethylene, a third classical defense hormone, positively or negatively regulates disease resistance depending on the nutrient types and environmental conditions (De Vleesschauwer et al. 2013). Rice *EDR1* (enhanced disease resistance), encoding a putative MAPK kinase kinase, is essential for susceptibility to bacterial diseases through promoting the synthesis of ethylene, which in turn suppresses SA- and JA-associated defense signaling (Shen et al. 2011). In addition, other phytohormones, such as gibberellins (GAs), is also involved in defense responses (Fig. 2a) (Berens et al. 2017). The gibberellin 20-oxidase (GA20ox) catalyzes consecutive steps of oxidation in the late part of the GA biosynthetic pathway. The RNA interference lines of gene *OsGA20ox3* have higher resistance to rice blast and bacterial blight and increased expression of defense-related genes (Qin et al. 2013). The GA receptor gene *GID1* mutant shows enhanced resistance to *M. oryzae* and has more PBZ1 and PR10 proteins (Tanaka et al. 2006).

Role of E3 ligases in disease susceptibility

Ubiquitination, a common type of post-translational protein modification, is involved in the selective degradation of proteins in eukaryotic cells. The modification is sequentially catalyzed by three kinds of enzymes: E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and ubiquitin E3 ligase (Vierstra 2009; Buetow and Huang 2016). The ubiquitin–proteasome system (UPS) often contributes to enhanced disease susceptibility by degrading positive regulators of immune signaling in plants (Fig. 2b) (Vierstra 2009; Buetow and Huang 2016; Wang et al. 2022b). For instance, multiple ubiquitin E3 ligases are negative regulators of rice immunity. The plant U-box (PUB) E3 ligase SPL11/PUB13 functions in tandem with the SPL11-interacting protein 6 (SPIN6), a Rho GTPase-activating protein, to negatively modulate the small GTPase OsRac1-mediated immune signaling (Yin et al. 2000; Liu et al. 2015). Another PUB E3 ligase, OsPUB12, negatively regulates immunity by interacting with and ubiquitinating OsRLCK176 to promote its degradation in rice (Mou et al. 2024). The mutation of a RING-type E3 ligase gene *enhanced blight and blast resistance 1* (*EBR1*) causes enhanced broad-spectrum resistance to bacterial and fungal diseases. EBR1 directly interacts with and degrades OsBAG4, which is required to trigger programmed cell death (PCD) and enhances resistance to pathogen infection (You et al. 2016). OsCUL3a, a component of a Cullin3-based RING E3 ubiquitin ligase (CRL3), not only attenuates PAMP-induced ROS burst and *PR* gene expression but also negatively regulates resistance to *M. oryzae* and *Xoo* by interacting with and degrading OsNPR1 (NON-EXPRESSOR OF PATHOGENESIS-RELATED GENES 1) in rice (Liu et al. 2017). In addition, some UPS regulators negatively regulate plant immunity. For instance, AvrPi9-interacting protein (ANIP1), a rice ubiquitin-like domain-containing protein (UDP), negatively modulates resistance against the rice blast fungus via facilitating 26S proteasome-mediated degradation of OsWRKY62 (Shi et al. 2023b). OsDjA6, a chaperone DnaJ protein, directly associates with the E3 ligase OsZFP1 to assist with the UPS for protein quality control in eukaryotes. Silencing of *OsDjA6* enhances rice resistance to *M. oryzae* through activating ROS accumulation and expression of *PR* genes (Zhong et al. 2018). Therefore, the genes involved in protein ubiquitination represent a group of *S* genes.

Protein kinases and phosphatases in disease susceptibility

Reversible protein phosphorylation mediated by various types of protein kinases and phosphatases plays a key role in regulating plant immunity (Park et al. 2012; Mithoe and Menke 2018; Zhang et al. 2018b; Kong et al. 2021). Multiple groups of protein kinases, such as calcium-dependent protein kinases (CDPKs or CPKs), mitogen-activated protein kinases (MAPKs or MPKs), and receptor-like kinases (RLKs), positively or negatively regulate plant defenses (Fig. 2c) (Berriri et al. 2012; Kong et al. 2012; Schie and Takken 2014; Wang et al. 2018a). OsCPK4 negatively regulates resistance to bacterial blight and blast disease by promoting the degradation of OsRLCK176 (Wang et al. 2018a). Overexpression of *OsCPK12* leads to a lower level of H_2O_2 accumulation and enhances susceptibility to the rice blast fungus due to the decreased expression level of NADPH oxidase gene *OsRBOHI* and increased expression levels of *OsAPx2* and *OsAPx8* encoding ROS scavenging enzymes (Asano et al. 2012). OsCPK18 is a negative regulator of defense gene expression and represses susceptibility to fungal blast in rice through phosphorylating and activating OsMAPK5 (Xie et al. 2014). Although the activated MAPK cascade is one of the early defense responses, not all MAPKs play positive roles in PTI. For example, OsMAPK5, OsMPK6, and OsMPK15 act as negative regulators of resistance to both fungal and bacterial pathogens (Xiong and Yang 2003; Hong et al. 2019; Wang et al. 2021a; Zheng et al. 2022a), while OsMPK17 only negatively regulates XA21-mediated resistance to *Xoo* (Zhu et al. 2022). On the other hand, MAPK cascades that positively regulate plant immunity can be repressed by the MAPK phosphatases (MKPs). OsMKP1, which targets and dephosphorylates OsMAPK6, positively regulates vascular defense against *Xoo* through activating lignin biosynthesis while negatively regulating resistance to the mesophyll pathogen *Xoc* through inhibiting SA and ROS signaling pathways (Lin et al. 2022). Likewise, some RLKs positively modulate plant immunity, while others negatively regulate defense responses. Individual mutations of *RLK20*, *RLK21*, and *RLK22* confer enhanced broad-spectrum resistance against multiple *Xoo* strains by promoting RBOHD-mediated H_2O_2 production in rice (Mei et al. 2022). Premature withered leaf 1 (PWL1), a G-type lectin receptor-like kinase, also suppresses resistance to *X. oryzae* in rice (Xu et al. 2023). The deletion of RLK genes *OsSPL26* and *SPL36* causes spontaneous leaf lesions, indicating that these kinases negatively regulate cell death and immunity in rice (Rao et al. 2021; Shang et al. 2022). Interestingly, NRRB, a receptor-like cytoplasmic kinase (RLCK), suppresses immunity to bacterial leaf streak (BLS) in rice (Guo et al. 2014). However, the molecular mechanisms through which receptor-like kinases negatively regulate plant immunity remain largely unclear.

Transcription regulators in disease susceptibility

Immune homeostasis is mediated by different types of transcription factors (TFs) in the WRKY, AP2/ERF (apetala2/ethylene-response element binding factor), bHLH (basic-helix-loop-helix), TGA (TGACG-binding), MYB (v-myb avian myeloblastosis viral oncogene homolog), NAC (for NAM, ATAF1/2, and CUC2) families, and so on (Fig. 2d) (Tsuda and Somssich 2015). WRKY proteins belong to one of the largest TF families in plants and balance plant immunity (Jiang et al. 2017). OsWRKY28 and OsWRKY62 function as PAMP-responsive transcriptional repressors to inhibit rice resistance against blast fungus and *Xoo*, respectively (Peng et al. 2008; Chujo et al. 2013). Likewise, OsWRKY42 and OsWRKY72 suppress JA signaling and negatively regulate defense responses to *M. oryzae* and *Xoo*, respectively (Cheng et al. 2015; Hou et al. 2019). Overexpression of *OsWRKY76* in rice leads to a significantly increased susceptibility to *M. oryzae* through suppressing the expression of *PR* and phytoalexin synthetic genes (Yokotani et al. 2013). The auxin response factors (ARFs) represent another family of transcription factors, many of which act as susceptibility factors for diverse diseases in rice. For instance, OsARF8, OsARF18, and OsARF22 negatively regulate broad-spectrum resistance against *M. oryzae* and *Xoo* (Feng et al. 2022). Interestingly, OsARF8 also negatively contributes to disease resistance to the necrotrophic pathogen *Rhizoctonia solani* (Feng et al. 2022).

Other types of transcription factors have been successively identified as negative immune regulators (Fig. 2d). OsASR6, a plant-specific ASR (abscisic acid, stress, and ripening) transcription factor, alleviates resistance to bacterial leaf blight and leaf streak diseases by suppressing *OsCIPK15* expression in rice (Guo et al. 2022). OsTGA5 functions as a negative regulator of rice resistance against blast fungus by repressing the expression of *PR* genes and the accumulation of endogenous SA (Niu et al. 2022). The NAC transcription factor ONAC083 negatively contributes to rice immunity against *M. oryzae* by directly activating the transcription of *OsRFPH2-6* encoding a RING-H2 finger protein that negatively regulates rice resistance to *M. oryzae* (Bi et al. 2023). OsNAC2 acts as a repressor of bacterial leaf blight resistance by inhibiting the expression of SA biosynthesis-related genes in rice (Zhong et al. 2024). When *OsMYB102* and *OsMYB108* are knocked out, the mutant plants generate more lignin and exhibit increased resistance to *Xoo* (Lin et al. 2022). Inhibited expression of rice *bsr-d1*, encoding a C2H2-type transcription factor, increases hydrogen peroxide accumulation and enhances resistance to *M. oryzae* (Li

et al. 2017a; Zhu et al. 2020b). *OsERF922* disruption confers broad-spectrum resistance to rice blast, bacterial blight and leaf streak diseases (Wang et al. 2016; Zhou et al. 2022). Interestingly, VASCULAR PLANT ONE ZINC-FINGER 1 (OsVOZ1), a plant specific one-zinc-finger-type transcription factor, negatively regulates PTI and enhances susceptibility to *M. oryzae*, but positively contributes to ETI signaling (Wang et al. 2021c).

Some cofactors have been identified to be suppressors of defense responses through inhibiting the transcriptional activity or regulating the stability of TFs in rice (Fig. 2d). OsVQ25, a valine-glutamine (VQ) motif-containing protein, hampers species-non-specific broad-spectrum resistance by interaction with OsWRKY53 and repression of its transcriptional activity (Hao et al. 2022). PBI1, comprised of a four-helix bundle, plays a negative role in defense responses to *Xoo* by interacting with and inhibiting the transcription activity of WRKY45, a key regulator of rice immunity (Ichimaru et al. 2022). Additionally, chromatin modifications such as histone acetylation play crucial roles in the regulation of defense gene expression (Fig. 2d). Multiple histone deacetylases, including HDT701, OsHDA701, HDA705, and OsSRT2, negatively regulate rice immunity against *Ustilaginoidea virens*, *M. oryzae*, and *Xoo* (Ding et al. 2012; Chen et al. 2021, 2022a, 2024). Collectively, more and more transcription factors and regulators are identified to promote disease susceptibility.

MicroRNAs in disease susceptibility

In response to pathogen attacks, plants have developed a multiple-layered immune system, composed of proteins and RNAs, to defend against pathogens (Song et al. 2019). Especially, microRNAs function as important regulators to inhibit the expression of target genes by DNA methylation, mRNA cleavage, and translational inhibition after binding to the target DNA or RNA sites (Fig. 2e) (Song et al. 2021b; Zhan and Meyers 2023). Until now, at least 18 microRNAs and/or small interfering RNA (siRNA) have been identified as negative regulators of disease resistance by targeting defense genes in rice, including miR167d, miR168, miR11117, miR1873, miR396, miR169, miR156, miR529, miR319, miR164a, miR1871, miR439, miR1432, miR530, miR535, miR444.2, miR2118, and siR109944 (Li et al. 2017b, 2021b, c, 2022b, Chandran et al. 2018; Zhang et al. 2018c, 2020; Qiao et al. 2020; Zhao et al. 2020; Zhou et al. 2020; Lu et al. 2021; Wang et al. 2018c, 2021b; Zhang et al. 2022b; Feng et al. 2023; Gao et al. 2023; Hui et al. 2023; Zhu et al. 2023). Generally, these microRNA and siRNA genes are also candidate *S* genes for gene editing to breed resistant varieties.

Other proteins in disease susceptibility

Hypersensitive responses (HR), a type of programmed cell death, prevent pathogens from spreading to uninfected cells (Coll et al. 2011). Lesion mimic mutants (LMMs) display spontaneous immune responses and HR-like necrotic lesions without pathogens invasion (Yan et al. 2022; Zhang et al. 2022a). LMMs are typically generated by the disruption of genes encoding potent suppressors of plant immunity (Shi et al. 2023a). The identified LMM genes in rice encode various functional proteins and are involved in various immune responses, such as ROS generation, SA signaling pathway, activation of defense-related genes, chlorophyll metabolism, and chloroplast development. For example, eukaryotic elongation factor 1 alpha (eEF1A) plays an important role in protein translation and has been implicated in PCD (Wang et al. 2017; Li et al. 2020). Two eukaryotic translation elongation factor 1A like proteins LMM5.1/SPL33 and LMM5.4 negatively regulate cell death and disease resistance to *Xoo* and *M. oryzae*, as the gene mutants exhibit constitutively activated basal defenses, including *PR* gene expression and ROS production in rice (Wang et al. 2017; Zhao et al. 2017). Two conserved eukaryotic release factor 1 proteins, LML1 and OsPELOTA (originally termed HM47), also negatively regulate cell death and disease resistance in rice by forming complexes with LMM5.1/SPL33 (Feng et al. 2013; Qin et al. 2018; Zhang et al. 2018d). In addition, RLIN1 (putative coproporphyrinogen III oxidase) (Sun et al. 2011), LMM8 (encoding protoporphyrinogen IX oxidase) (Zhao et al. 2023), SPL32 (a ferredoxin-dependent glutamate synthase, Fd-GOGAT) (Sun et al. 2017), and SDR7-6 (a short-chain alcohol dehydrogenase/reductase family protein) (Zheng et al. 2022b) participate in PCD by regulating the metabolism of chlorophyll and glutamate. The proteins associated with transcription and post-translational modification also contribute to cell death, including OsLSD1 (zinc finger protein) (Wang et al. 2005), OsUbc13 (ubiquitin-conjugating enzyme) (Liu et al. 2023a), OsUBP2 (ubiquitin-specific protease 2) (Jiang et al. 2022), and SPL5 (RNA splicing protein) (Jin et al. 2015). Mutation of LMM genes causes intense immune responses, which may affect normal plant growth. Therefore, precise gene editing of LMM genes is necessary to utilize them for resistance breeding.

In addition, some unclassified proteins negatively regulate plant immunity. For instance, phytochrome B (PhyB) negatively regulates resistance to rice sheath blight caused by *R. solani* through interacting with and inhibiting BZR1-NAC028-CAD8B signaling in rice (Yuan et al. 2022). Ca^{2+}, as a second messenger, rapidly accumulates in the cytoplasm and is perceived by Ca^{2+} sensors to activate immune responses. However, Ca^{2+} sensor ROD1

(RESISTANCE OF RICE TO DISEASES1) facilitates ROS scavenging and suppresses rice immunity through directly interacting with a catalase CatB and enhancing its activity (Gao et al. 2021). In addition, such proteins as receptor-like protein OsBAP1 (Wang et al. 2023a), copper metallochaperone heavy metal-associated plant protein04 (OsHPP04) (Song et al. 2021a; Huang et al. 2023), P-loop NTPase OsYchF1 (Cheung et al. 2016), OsFKBP12 (a rice immunophilin homolog) (Cheung et al. 2020), and nodule inception (NIN)-like protein OsNLP2 (Chen et al. 2022b) in rice also negatively modulate immunity against pathogens, but the underlying mechanisms are yet unclear.

Engineering *S* genes for disease resistance in rice

In contrast to traditional breeding for disease resistance, which is time-consuming and laborious, genome editing techniques have been successfully developed as fast, convenient, and effective tools to introduce precise and predictable genome modifications into plant genomes to enhance resistance against a range of pathogens (Li et al. 2022a; Bishnoi et al. 2023). During the past 30 years, meganucleases, transcription activator-like effector nucleases (TALENs), zinc-finger nucleases (ZFNs), and clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system have been developed for genome editing (Gao 2021). Among these techniques, CRISPR/Cas9 has gained popularity due to its ease of use, affordability, and high success rate in engineering crop genomes (Zhu et al. 2020a; Gao 2021; Wang et al. 2022a; Sha et al. 2023). In the CRISPR/Cas9 system, Cas9 targets specific genomic loci guided by a single guide RNA (sgRNA) and cleaves double-stranded DNA, resulting in DNA double-strand breaks (DSBs) at target sites. This process triggers nonhomologous end joining (NHEJ) repair pathways, during which nucleotide deletions or insertions are often introduced into the target genes and thereby cause frameshift mutations (Li et al. 2021a). Therefore, the CRISPR/Cas9 technology makes it easy to knock out *S* genes, thus conferring broad-spectrum and durable disease resistance. To date, the CRISPR/Cas9 system has been widely used to improve major crops, such as rice, maize, and wheat (Oliva et al. 2019). One of the most representative and successful examples is the susceptibility gene *RBL1* in rice. The loss-of-function mutant of *RBL1*, in which 29-bp deletion partially overlaps the ninth exon–intron junction and causes an in-frame deletion of the ninth exon, exhibits resistance to *M. oryzae* and *Xoo*, but has an about 20-fold yield loss. However, the $rbl1^{\Delta 12}$ line with a 12-bp deletion in the second exon of *RBL1* generated via CRISPR/Cas9 technology displays broad-spectrum disease resistance to multiple pathogens without evident yield penalty (Sha et al. 2023). Moreover, individual disruptions of *OsSRT2*, *OsBDR1*, and *OsPUB12* by CRISPR/Cas9 also confer resistance to multiple rice pathogens (Wang et al. 2023b; Chen et al. 2024; Mou et al. 2024). In addition, CRISPR/Cas9 technology can also be used to edit the promoters of candidate *S* genes for the development of resistant rice varieties. For instance, *OsSWEETs*, potential susceptibility genes, are required for sugar efflux and are involved in seed filling and male fertility, respectively (Yang et al. 2018; Wu et al. 2022a). The mutations of EBEs in the *OsSWEET11*, *OsSWEET13*, *OsSWEET14*, and *OsSULRT3;6* promoters generated through CRISPR/Cas9 prevent binding by TAL effectors and result in rice resistance to bacterial pathogens without yield penalty (Oliva et al. 2019; Xu et al. 2021a).

Although a variety of *S* genes have been identified in rice, not all can be directly engineered to create disease-resistant cultivars. Some *S* genes are required for pathogen invasion and plant physiology (Schie and Takken 2014). The major challenge to utilize *S* genes in resistance breeding is a tight linkage between adverse pleiotropic effects and disease resistance (Koseoglou et al. 2022; Bishnoi et al. 2023). However, this difficulty might be solved by precise genome editing instead of completely disrupting the *S* genes. Recently, CRISPR/Cas9-based precise genome editing tools, such as base editor and prime editor, have been invented to allow for transition, transversion, and targeted DNA deletions and insertions (Gao 2021; Li et al. 2021a). Base editors mainly rely on a catalytically impaired Cas9 (nCas9 D10A) nuclease for targeting specific sites and a deaminase acting on single-stranded DNA (ssDNA) so that the editors can create point mutations rather than DSBs (Rees and Liu 2018). Cytosine base editors (CBEs) and adenine base editors (ABEs) are two major types of base editors. The cytidine deaminase in CBE and deoxyadenosine deaminase in ABE catalyze the transitions of C to T and A to G at ssDNA at target sites, respectively (Molla et al. 2021). The base editors have been increasingly used to improve various crop plants, including rice. *Pi-d2* in rice encodes a receptor-like kinase and confers gene-for-gene resistance against the fungal blast strain ZB15 (Chen et al. 2006). The amino acid substitution at position 441 causes Pi-d2 to lose resistance to blast disease. The improved base editors introduce a G to A mutation in endogenous *pi-d2*, which rescues its biological functions (Ren et al. 2018). Similarly, the mutation of *ROD1* encoding a Ca^{2+}-sensor confers resistance against the bacterial pathogen *Xoo* and fungal pathogens *M. oryzae* and *Rhizoctonia solani*, but simultaneously impedes rice growth and development. A natural *ROD1* variant, *ROD1* ($SNP1^{A}$) with 1 bp substitute at 133 bp downstream of ATG, resulting in a mutation from proline to threonine, shows an enhanced

disease resistance without affecting agronomic traits (Gao et al. 2021). Hence, the susceptible *ROD1* variant is a promising candidate target for precise genome editing for resistance breeding. In some cases, no suitable protospacer adjacent motifs (PAMs) are available for *Streptococcus pyogenes* Cas9 (SpCas9). Therefore, a series of Cas9 variants with broad PAM compatibility and high DNA specificity, such as Cas9n-NG and SpRYCas9, have been engineered to generate new CBEs and ABEs (Li et al. 2021a). SpRYn-based ABE can efficiently induce A to G transition, even at non-G PAM sites. Many *S* genes in rice, including *OsCPK4* and *Brs-k1*, have been successfully edited by these novel editing tools, SpRY-based CBE and ABE (Xu et al. 2021b). Furthermore, based on cytidine deamination and base excision repair (BER), the APOBEC-Cas9 fusion-induced deletion systems (AFIDs), through which multiple base pairs can be precisely deleted, have been developed. The mutants with the 1- to 2-bp precision deletions in the EBEs of AvrXa7 and PthXo3 at the TATA box of the *OsSWEET14* promoter were generated using AFID-3. The deletion mutants exhibit increased resistance to *Xoo* with no impact on plant development (Wang et al. 2020). Recently, PrimeRoot, a genome editing system, made it possible to insert large DNA fragments into plant genomes. A 4.9-kb cassette comprising *PigmR* is precisely inserted into genomic safe harbor in rice, which increases disease resistance of the mutant to fungal blast (Sun et al. 2024). Considering that genetically modified organisms are not readily accepted globally, the generation of transgene-free crop varieties is required. Two transgene-free genome editing methods including CRISPR/Cas9 RNA (in vitro transcripts of *Cas9* and sgRNA) and RNP (ribonucleoprotein, composed of Cas9 protein and in-vitro-transcribed sgRNA) have been designed to create the mutants (Ran et al. 2017). These newly developed technologies will greatly promote the application of *S* genes in rice disease resistance breeding.

Simultaneous editing of multiple susceptibility genes by CRISPR/Cas9-based genome editing technologies is another strategy to create rice germplasm with high and broad-spectrum disease resistance. For instance, the *S* genes *Pi21* and *Bsr-d1* are involved in susceptibility to fungal blast, while *Xa5* mediates susceptibility to bacterial blight. When the three *S* genes are knocked out, the mutants show enhanced resistance to rice blast and bacterial blight (Tao et al. 2021). Likewise, the triple-gene mutants of *Bsr-d1*, *Pi21*, and *ERF922* created by CRISPR/Cas9-mediated gene editing exhibit higher blast resistance than the *bsr-d1* and *pi21* single-gene mutants (Zhou et al. 2022). In addition, some *S* genes may play distinct, even opposite roles in resistance to different types of pathogens. For example, OsBZR1 positively regulates resistance to the necrotrophic pathogen *R. solani* negatively mediates resistance to the hemibiotrophic pathogen *Xoo* (Ke et al. 2020; Yuan et al. 2022). Besides, the *osmkp1* knockout mutant exhibits increased susceptibility to the vascular pathogen *Xoo* due to diminished lignin accumulation but shows enhanced resistance to the nonvascular pathogen *Xoc*, which colonizes in the intercellular spaces of mesophyll cells (Lin et al. 2022). In conclusion, the fitness of *S* gene-edited crop plants should be investigated for tolerance to diverse biotic and abiotic stresses, besides pleiotropic effects on growth, yield, and fertility.

Conclusion and perspectives

We comprehensively summarize diverse *S* genes that facilitate pathogen infection and disease susceptibility in rice. These genes show promise for use in molecular design breeding to enhance rice resistance. Editing *S* gene might confer more durable disease resistance than *R* gene-mediated resistance. However, *S* genes not only contribute to pathogen invasion but also play a role in physiology, growth and development, and other types of resistance in plants. Therefore, it is very important to extensively identify and analyze the functions of *S* genes and avoid possible pleiotropic effects of *S*-gene editing on rice growth and development. The development of efficient and precise CRISPR/Cas9-based technologies in plants contributes to the application of *S* genes in rice resistance breeding. Nonetheless, there are still several challenges to overcome in *S* gene editing for rice resistance breeding. The key functional sites of *S* genes should be explicit and are usually selected to target loci for precise genome editing. Achieving precision editing requires an understanding of the functions and molecular mechanisms of *S* genes, as well as identifying key sites of *S* genes associated with specific target traits. Another challenge is to improve the efficiency and specificity of genome editing. Although base editors, CBE and ABE, can convert C·G into T·A and A·T into G·C substitutions, other base editors that can create transversions, such as C·G to G·C, should be developed. Off-target mutations also pose a significant concern in genome editing. Thus, new editors with higher specificity and more effective methods to detect off-target mutations in genome are in urgent need. With the discovery of more *S* genes, the emergence of novel, precise genome editing tools, and the integration of artificial intelligence, gene editing is expected to greatly accelerate disease resistance breeding in rice.

Abbreviations

ABA	Abscisic acid
BLS	Bacterial leaf streak
CDPKs or CPKs	Calcium-dependent protein kinases
CRISPR/Cas	Clustered regularly interspaced palindromic repeats (CRISPR)/CRISPR-associated protein

DAMPs	Damage-associated molecular patterns
EBEs	Effector-binding elements
ETI	Effector-triggered immunity
GA	Gibberellin
HR	Hypersensitive responses
JA	Jasmonic acid
LMMs	Lesion mimic mutants
MAPKs or MPKs	Mitogen-activated protein kinase
MKPs	MAPK phosphatases
PAMPs	Pathogen-associated molecular patterns
PCD	Programmed cell death
PR gene	Pathogenesis-related gene
PTI	Pattern-triggered immunity
R genes	Resistance genes
RLCK	Receptor-like cytoplasmic kinase
RLKs	Receptor-like kinases
ROS	Reactive oxygen species
S genes	Susceptibility genes
SA	Salicylic acid
sgRNA	Single guide RNA
siRNA	Small interfering RNA
SWEET	Sugars will eventually be exported transporters
TALEs	Transcription activator-like effectors
TFs	Transcription factors
UPS	Ubiquitin proteasome system

Supplementary Information

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Additional file 1: Table S1. The susceptibility genes characterized in rice.

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NN and WS conceived the concept. NN, HC, JX, SP, ZL, JP, and LZ participated in writing the manuscript. WS revised and finalized the manuscript. All authors read and approved the final manuscript.

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