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Review

From plant immunity to crop disease resistance

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ABSTRACT

Plant diseases caused by diverse pathogens lead to a serious reduction in crop yield and threaten food security worldwide. Genetic improvement of plant immunity is considered as the most effective and sustainable approach to control crop diseases. In the last decade, our understanding of plant immunity at both molecular and genomic levels has improved greatly. Combined with advances in biotechnologies, particularly clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9-based genome editing, we can now rapidly identify new resistance genes and engineer disease-resistance crop plants like never before. In this review, we summarize the current knowledge of plant immunity and outline existing and new strategies for disease resistance improvement in crop plants. We also discuss existing challenges in this field and suggest directions for future studies.

Introduction

The world population is expected to reach 9.7 billion in 2050 and 11.2 billion in 2100 (United Nations, 2017). Increases in crop yields are not keeping pace with the growing demand. Global demand for agricultural products is projected to grow by 15 percent over the coming decade (OECD/FAO, 2019). However, crop losses caused by plant diseases and pests add great weight to this food challenge. According to recent research, on a global scale, the estimated range of crop losses caused by pathogens and pests is 10.1%–28.1% in wheat, 24.6%–40.9% in rice, 19.5%–41.1% in maize, 8.1%–21.0% in potato, and 11.0%–32.4% in soybean, among which, more than half are caused by diseases (Savary et al., 2019). Application of chemical pesticides has greatly reduced these losses but causes hazardous risks to human health and the environment (Damalas and Eleftherohorinos, 2011). Cultural practices such as removal of tillage, crop rotation, and polycultures can reduce disease outbreaks (Garrett and Mundt, 2000; Zhu et al., 2000), but these practices are not always applicable when arable land is limited. Thus, breeding crops with genetic resistance is unarguably the most effective and sustainable approach to control plant diseases.

Recent advances in the molecular mechanism underlying plant-pathogen interactions and advances in biotechnology are providing powerful theoretical and technological support for breeding crops with disease resistance genetically. Readers are referred to several reviews for detailed advances in plant immunity (Wang and Chai 2020; Zhou and Zhang, 2020; Yuan et al., 2021b; Ngou et al., 2022; Wang et al., 2022). We also recommend recent reviews on the genetic engineering of disease-resistant crop plants (Van Esse et al., 2020; Frailie and Innes, 2021; Liu et al., 2021a). This review summarizes basic principles of plant immunity, the molecular basis of durable resistance, and discusses how to apply this knowledge to improve disease resistance in crop plants.

Molecular basis of plant immunity

Plant immunity is governed by a surveillance system that monitors pathogen invasion (Jones and Dangl, 2006). As such, plants devote resources and energy to growth and development in the absence of threats but quickly mobilize resources and energy to defense when under attack from pathogens. Our knowledge of plant immunity has

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advanced greatly over the past 30 years. Plants employ a layered surveillance system to detect pathogen invasion. Pattern recognition receptors (PRRs) function as the first layer to sense microbe-derived and host-derived immunogenic molecular patterns and activate pattern-triggered immunity (PTI). Various pathogens secrete virulence proteins called effectors into the apoplastic spaces or inside host cells for successful invasion. Intracellular receptors function as the second layer to monitor virulence activities of intracellular effectors and activate more potent immune responses, leading to effector-triggered immunity (ETI). This knowledge is important not only for our understanding of how plants cope with constant assault by numerous pathogens but also crucial for the improvement of crop plants (Fig. 1).

Sensing danger signals at the cell surface

Plant PRRs are either plasma membrane-localized receptor-like kinases (RLKs) or receptor-like proteins (RLPs) (Ngou et al., 2022). PRRs perceive pathogen-associated molecular patterns (PAMPs), apoplastic effector proteins, and plant-derived damage-associated molecular patterns that are produced during pathogen attacks to activate immune responses. In addition, PRRs also perceive plant peptides called phytocytokines that coordinate immune responses and growth in neighboring cells (Gust et al., 2017; Hou et al., 2021). These RLKs and RLPs use highly variable ectodomains to perceive diverse ligands. Often, PRRs belong to gene families undergoing gene expansion and collectively exist in large numbers (from dozens to hundreds) in each plant species. In addition, many PRRs display high degree of variation at levels of cultivar, species, and family (Ngou et al., 2022). Thus, studies on PRRs not only provide insights into how plants perceive complex danger signals from diverse pathogenic organisms but also offer a rich source of disease resistance genes that can be utilized in crop improvement.

Effectors promote pathogenesis

Effector biology is an important area of research that has tremendously enhanced our understanding of plant-pathogen interactions and plant immunity. Pathogenic bacteria, fungi, oomycetes, nematodes, and herbivore insects deliver large repertoires of effector proteins into the apoplastic spaces of host tissues or inside host cells (Dou and Zhou, 2012; Wang et al., 2022). Many effector proteins interfere with the host immune system by multiple strategies including, but are not limited to, modifying PAMPs, competing with PRRs for binding to PAMPs, inhibiting immune signaling components, promoting stomatal opening to facilitate invasion, and interfering with biosynthesis or action of defense hormones (Dou and Zhou, 2012; Wang et al., 2022). Some effectors actively promote water space in the apoplast to assist bacterial growth (Xin et al., 2016). Several bacterial pathogens exemplified by *Xanthomonas campestris* and *X. oryzae oryzae* (*Xoo*) secrete a specific class of intracellular effectors called Transcription Activator-Like Effectors (TALEs) that bind specific promoter sequences called effector-binding elements (EBEs) to activate the transcription of susceptibility (*S*) genes in the host plant for pathogenesis. In addition to *S* genes targeted by TALEs, some other host genes encode proteins that are targeted by and required for the virulence function of effectors are also called *S* genes, because their absence renders plants less susceptible to infection by pathogens carrying these effectors (Garcia-Ruiz et al., 2021). *Mildew resistance locus O* (*MLO*) is one of the well-known *S* genes that encodes a transmembrane protein essential for powdery mildew infection (Kusch and Panstruga, 2017). An ortholog in Arabidopsis, MLO2, is targeted by the *Pseudomonas syringae* (*P. syringae*) effector HopZ2 (Lewis et al., 2012). Loss-of-function mutations of *MLO* protect plants from infection by powdery mildew fungi in various plant species including barley, wheat, tomato, apple, grapevine, and pepper (Kusch and Panstruga, 2017). Many of the mutated *S* genes have also been referred to as "recessive resistance genes" in the literature.

As a result of host–pathogen co-evolution, many apoplastic effectors are recognized as immunogenic signals by PRRs, and intracellular effectors are recognized by nucleotide-binding, leucine-rich repeat receptors (NLRs) (Jones et al., 2016). The pathogen responds by mutations in existing effectors and the acquisition of new effectors to evade recognition by the host plant. Thus, the co-evolution led to an enormously large number of highly diverse immune receptors in

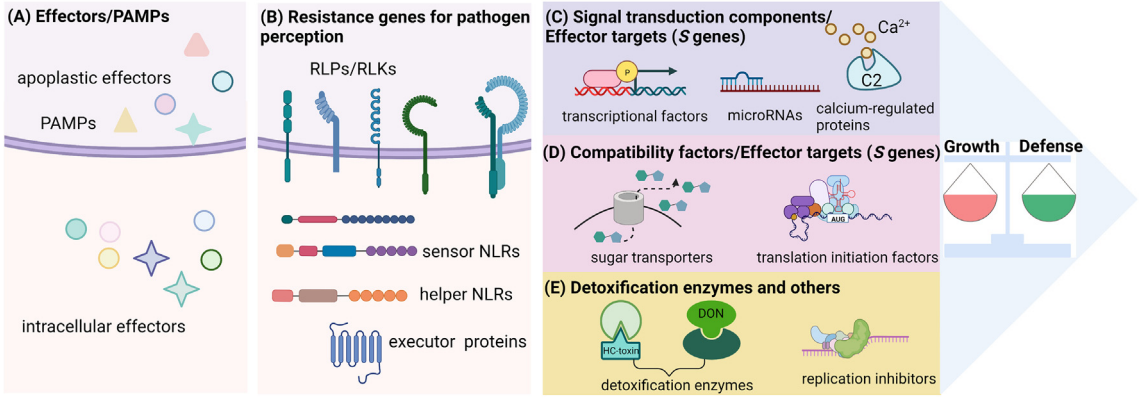

Fig. 1. Pathogen and host players determining disease susceptibility and disease resistance. **A** and **B**: Pathogen-associated molecular patterns (PAMPs) are recognized by surface immune receptors, which are RLKs and RLPs. The recognition of microbial molecules triggers defenses through downstream signaling components, including protein kinases, transcription factors (TFs), miRNAs, calcium-regulated proteins, etc. Pathogen-secreted apoplastic effectors and intracellular effectors, initially evolved as virulence factors, can be recognized by surface immune receptors and nucleotide-binding, leucine-rich repeat receptors (NLRs), respectively. Genes encoding executor proteins use their DNA elements in the promoter to recognize a unique class of intracellular effectors called TALEs, thus functioning as a promoter trap to initiate defenses. Defenses triggered by surface and intracellular immune receptors mutually potentiate each other and operate through similar signal transduction pathways. **C** and **D**: Effectors promote pathogenesis by subverting the host immune system or perturbing other physiological processes. Some of the host genes or their products targeted by effectors are required for disease susceptibility and are thus called susceptibility (*S*) genes. Proteins encoded by *S* genes include immune signaling components (**C**) or compatibility factors, such as sugar transporters and translation elongation factors (**D**). Genes encoding immune receptors (**B**), immune signaling components (**C**), compatibility factors (**D**), and enzymes that detoxify pathogen-produced toxins (**E**) offer a rich source of genes for disease resistance breeding in crop plants. The trade-off between defense and growth is a common problem in disease resistance breeding. However, certain alleles of resistance genes confer disease resistance without a penalty on the yield of crop plants, which are highly valued in disease resistance breeding. RLK, receptor-like kinase; RLP, receptor-like protein; TALE, transcription activator-like effector.

the plant and an equally large number of effector proteins in the pathogen. This concept is important for our understanding of the variation and durability of resistance genes.

Monitoring danger signals within the plant cell

The most prevalent intracellular immune receptors are NLRs with variable N terminal domains. NLRs with an N terminal coiled-coil domain, toll/interlukin-1 receptor domain, and RPW8 domain are called CNLs, TNLs, and RNLs, respectively (Jones et al., 2016). NLRs exist in super families, and each plant genome typically carries several dozens to ~1000 NLR-coding genes, which provide enormous potential in pathogen recognition (Barragan and Weigel, 2021).

Some, but not all, CNLs and TNLs function by sensing their cognate effectors and are thus called sensor NLRs. Some NLRs that are not required for sensing effectors but are instead required for signaling from sensor NLRs are called helper NLRs (Jubic et al., 2019). Sensor NLRs recognize their cognate effectors through multiple modes (Jones et al., 2016). Some sensor NLRs directly bind and recognize cognate effectors. For example, the flax allelic TNLs L5, L6, and L7 directly interact with alleles of the AvrL567 effector of the rust fungus *Melampsora lini* (Dodds et al., 2006). Similarly, alleles of the Arabidopsis TNL protein RPP1 directly interact with different alleles of the *Hyaloperonospora parasitica* effector ATR1 (Steinbrenner et al., 2015). Many sensor NLRs, however, indirectly recognize cognate effectors by recruiting other host proteins (Jones et al., 2016). These host proteins are either virulence targets of effectors or decoys, which are structural but not functional mimics of virulence targets, that are guarded by NLRs (Jones and Dangl, 2006; van der Hoorn and Kamoun, 2008; Zhou and Chai, 2008). Modification of these proteins by effectors serves as a danger signal to activate NLRs. In addition to the canonical domains, a small portion of NLRs have an additional integrated domain (ID) that mimic virulence targets of effector proteins, enabling ID-mediated sensing of effectors by this class of NLRs (Grund et al., 2019). An NLR-ID protein and a helper NLR act in pair and their coding sequences are organized in a head-to-head orientation in the genome (Cesari et al., 2013). For instance, the Arabidopsis NLR-ID protein RRS1 carries a WRKY domain and works with its paired helper NLR RPS4 (Le Roux et al., 2015). The rice sensor NLRs RGA5 and Pik-1, both carry a heavy metal-associated (HMA) domain as ID, activate immunity through their paired NLRs RGA4 and Pik-2, respectively (Cesari et al., 2013; De la Concepcion et al., 2021a). The employment of guardees/decoys allows plants to utilize a relatively small repertoire of NLRs to detect a vast number of pathogen effectors (Jones et al., 2016). IDs and decoys also provide opportunities to engineer plants for expanded effector-recognition specificity and resistance spectrum (Kim et al., 2016; Frailie and Innes, 2021; Liu et al., 2021a).

In addition to NLR proteins, some plants carry ‘‘executor’’ genes that have acquired the same EBE sequences of susceptibility genes that are normally targeted by TALEs, thus function as a promoter trap to initiate defenses (Zhang et al., 2015). The expression of executor genes leads to typical defense responses including hypersensitive response and induction of defense gene expression (Chen et al., 2021), although the underlying mechanism remains unknown.

Immune signaling

Immune receptors do not activate immune responses in the resting state but are rapidly converted to the active state upon a perception of immunogenic signals, which ensures immune activation only in the presence of pathogens. For PRRs, an important mechanism underlying this control is the formation of macromolecular protein complexes upon ligand binding by receptors and co-receptors, leading to the activation of RLKs in the complex (DeFalco and Zipfel, 2021). The receptor complexes also contain receptor-like cytoplasmic kinases, such as BIK1, which are central components mediating phosphorylation relay to activate multiple downstream signaling events including calcium ion flux, production of reactive oxygen species, activation of MAP kinase cascades, transcriptional reprogramming, and production of defense hormones (Liang and Zhou, 2018).

Similar to PRRs, recent advances have shown that plant NLRs, upon activation by effectors, also form macromolecular complexes called resistosomes (Duxbury et al., 2021). The CNL protein ZAR1 forms a pentameric resistosome and its N terminal CC domain in the oligomer is organized into a pore in the PM to conduct calcium ion (Wang et al., 2019; Bi et al., 2021). The TNLs RPP1 and ROQ1 form tetrameric resistosomes in which their N terminal TIR domain becomes an active NADase that produces secondary signal molecules to activate immune signaling (Horsefield et al., 2019; Wan et al., 2019; Ma et al., 2020; Martin et al., 2020). These signaling molecules are thought to activate lipase-like proteins EDS1, PAD4, and SAG101, which then recruit and activate RNLs that form calcium channels in a way similar to the ZAR1 resistosome (Jacob et al., 2021; Sun et al., 2021; Wu et al., 2021). Thus resistosome-mediated calcium flux is likely the earliest signal to initiate ETI.

Recent studies additionally have shown that mutual potentiation of ETI and PTI is necessary to activate strong immune responses, whereas the activation of ETI alone in the absence of PTI only leads to weak immune responses (Ngou et al., 2021; Yuan et al., 2021a; Zhai et al., 2022). Furthermore, EDS1 and the RNL proteins ADR1s associate with PRRs to mediate PTI (Pruitt et al., 2021; Tian et al., 2021). These findings indicate that PTI and ETI converge very early in immune signaling and explain the largely overlapping immune responses in both PTI and ETI.

Regulatory components including, but are not limited to, calcium channels, calcium-binding proteins, NADPH oxidases, protein kinases, transcription factors, microRNAs, and ubiquitin enzymes form a complex signaling network (DeFalco and Zipfel, 2021). The network not only regulates diverse physiological changes, including the production of antimicrobial compounds, cell wall enforcement, and regulated cell death, but also coordinates with growth/development and stress adaptation (Huot et al., 2014; Karasov et al., 2017). Components of this network play key roles in immune homeostasis and are important for balancing disease resistance and yield in crop plants.

Genes conferring durable resistance operate at different levels of the immune system

Over the course of more than 100 years, a large number of disease resistance genes encoding immune receptors, signaling components, compatibility factors, and enzymes that detoxify microbial toxins have been isolated from crop and model plants (Fig. 1). A major challenge in the deployment of disease-resistance genes in crop breeding is a frequent breakdown of disease resistance when new virulent pathogen isolates emerge. However, some resistance genes are known to remain effective for many years or even decades in the field and are thus referred to as durable resistance genes. Some resistance genes confer resistance to numerous isolates of a pathogen or multiple pathogen species and are referred to as broad-spectrum resistance genes, which are likely durable. Below we use several examples to discuss how studies of these genes have offered useful lessons for the molecular basis of durable resistance.

Durable resistance genes involved in pathogen recognition

Resistance genes encoding immune receptors and executors that recognize effectors often offer strong resistance. Because they activate defenses upon pathogen infection and have minimum costs

on the growth and yield of crop plants, thus, they have naturally become the first choice for breeders. However, mutations in pathogen effectors can lead to a rapid loss of resistance conferred by these resistance genes, particularly when monoculture is employed in intensive agriculture (McDonald and Linde, 2002). The majority of NLR genes conferring blast resistance in rice is not durable (Li et al., 2019, 2020; Deng et al., 2020; Gao et al., 2021), likely because of the variations of cognate effector genes in *Magnaporthe oryzae* (*M. oryzae*). Similarly, breakdown of NLR-mediated resistance to rust diseases frequently occurred in wheat (Ellis et al., 2014). As a single NLR gene typically confers resistance to pathogens carrying one or a few specific effectors, mutations in the cognate effector gene in the pathogen can lead to a loss of resistance in the host plant.

However, some effectors are more important than others for the pathogen, and the loss of these effectors imposes a fitness penalty on the pathogen (Leach et al., 2001). These effectors are also referred to as core effectors as they are prevalent in the pathogen population in the field (Bart et al., 2012). NLR genes or executor genes recognizing these effectors often confer durable resistance. For instance, the *Xoo* effector AvrXa7 plays an important role in bacterial virulence, and strains carrying mutations in *AvrXa7* have poor fitness in the rice field (Cruz et al., 2000). Rice varieties carrying the cognate resistance gene *Xa7* display durable resistance in the field. *Xa7* has recently been isolated (Chen et al., 2021; Wang et al., 2021a). *Xa7* is an executor gene, and its promoter possesses the EBE of AvrXa7 (Wang et al., 2021a). The rice *Pi9* gene, which encodes a CNL recognizing the *M. oryzae* effector AvrPi9, confers durable resistance to rice blast (Wu et al., 2015). *AvrPi9* is prevalent in rice blast isolates in the Philippines and China, explaining the durable nature of *Pi9,* although loss of *AvrPi9* in virulent isolates does not appear to cause a fitness penalty to the pathogen. Another rice blast resistance gene, *Pb1*, also encodes a CNL that confers durable panicle blast-resistance (Hayashi et al., 2010). The mechanism of the durability is not clear, but Pb1 has been reported to interact with the rice transcription factor WRKY45 to regulate salicylate-mediated defenses (Inoue et al., 2013). The ability of a small number of NLR genes to confer broad-spectrum resistance is also demonstrated by a study in Arabidopsis (Laflamme et al., 2020). The vast majority of *P. syringae* strains collected around the world carry at least one or more effector alleles that trigger ETI in a single accession of Arabidopsis, Col-0. As few as eight NLR genes from Col-0 are predicted to recognize 96.6% isolates, and two NLRs, ZAR1, and CAR1, together can recognize up to 94.7% isolates. The prevalent presence of these effectors in numerous strains suggests that they are core effectors important for the virulence of *P. syringae*. Of note, ZAR1 recognizes multiple effectors of different bacterial pathogens through a family of adaptor proteins called ZRKs and different decoy proteins (Wang et al., 2015; Martel et al., 2020), and plant species carrying ZAR1 often contain many copies of ZRKs (Gong et al., 2022). The combination of ZRKs and decoy proteins represents a mechanism of broad-spectrum-resistance conferred by a single NLR protein. Future exploitation of genes encoding ZRK and decoy proteins in different plant species may allow breeders to tap into this large potential of pathogen recognition by ZAR1.

Another excellent example of durable disease resistance conferred by NLR-coding genes is illustrated by the study of *Pigm*, which has been deployed in the field for decades against rice blast (Deng et al., 2017). The *PigmR* in the *Pigm* locus encodes a CNL and confers broad-spectrum resistance to rice blast, but at the same time, it reduces yield if activated in reproductive tissues. Interestingly, the *Pigm* locus also encodes a closely related protein, PigmS, that can interact with PigmR to inhibit the resistance function of the latter. *PigmS* is tightly regulated by an epigenetic mechanism that restricts its expression to leaves but not reproductive tissues. Thus, rice lines carrying both *PigmR* and *PigmS* show normal yield. The mechanism underlying PigmR-mediated durable resistance has been recently elucidated. PigmR directly interacts with a novel RRM-domain transcription factor family to activate the expression of defense genes (Zhai et al., 2019). PigmR additionally interacts with the rice deubiquitinase PICI1, a positive regulator of ethylene biosynthesis and PTI, to prevent AvrPi9-mediated degradation of PICI1 (Zhai et al., 2022). Thus, PigmR synchronizes both ETI and PTI during fungal infection. While it remains unknown whether Pigm recognizes a conserved or unique effector that is prevalent in *M. oryzae,* the studies will surely inspire future efforts in developing durable resistance and high-yield crops.

PAMPs are often conserved among diverse isolates of one or more pathogen groups, and PRRs recognize that PAMPs offer disease resistance to multiple pathogen species. As PAMPs often are functionally important moiety of pathogen molecules, mutations that evade recognition by PRRs are likely to cause a fitness penalty on the pathogen. Thus, the broad-spectrum resistance conferred by PRRs is likely to be durable as well. An excellent example is the successful transfer of the Arabidopsis PRR EFR into a number of crop plants with increased disease resistance to multiple bacterial pathogens (Lacombe et al., 2010; Liu et al., 2021a). Some apoplastic effectors secreted by bacterial, fungal, and oomycete pathogens are also widely distributed among numerous pathogen species. PRRs perceive these immunogenic molecules therefore contribute to broad-spectrum resistance to diverse pathogens. The glycoside hydrolase 12 (GH12) protein XEG1 is such an apoplastic effector widely distributed among different microbial taxa and can be recognized by the *Nicotiana benthamiana* (*N. benthamiana*) RLP protein RXEG1 (Wang et al., 2018b). RXEG1 thus holds great potential as a broad-spectrum resistance protein.

A common practice for breeding durable disease-resistance crops is stacking of multiple resistance genes in a single cultivar, as has been demonstrated in wheat, rice, and potato (Zhu et al., 2012; Ellis et al., 2014; Fukuoka et al., 2015; Ghislain et al., 2019). However, combining multiple resistance genes into a cultivar is time-consuming and can be technically difficult. A recent study shows that the transgenic approach offers a powerful alternative to genetic crossing. Five resistance genes were transformed into bread wheat by using a single cassette (Luo et al., 2021). The resulting lines are highly resistant to highly aggressive *Puccinia graminis* f. sp. *tritici* isolates from around the world and show excellent field resistance. Because these transgenes are integrated into the genome as a single locus, they can be easily mobilized to other elite cultivars by crossing.

Durable resistance genes encoding immune signaling components

A significant number of disease resistance genes isolated to date encode signaling components of the plant immune network. Genetic variations in these components often lead to heightened basal resistance that is broad-spectrum and/or durable. However, elevated defenses can have pleiotropic effects on the growth and yield of crop plants. Past analyses of these genes have been focused on both durable resistance and defense-growth trade-off.

Loss-of-function mutations of *MLO* in barley lead to durable resistance to powdery mildew (Buschges et al., 1997). Mutations in *MLO* similarly cause resistance to powdery multiple mildew fungi in wheat, tomato, and Arabidopsis plants (Bhat et al., 2005; Bai et al., 2008; Wang et al., 2014). Analyses of the *mlo* resistance in Arabidopsis suggest that *MLO* is a negative regulator of immune signaling pathway mediated by *PEN1*, a syntaxin required to restrict fungal penetration (Bhat et al., 2005). While simultaneous mutations in all three homologous *MLO* alleles in hexaploid wheat are highly resistant to powdery mildew, the resulting plants display reduced plant growth and yield (Wang et al., 2014; Li et al., 2022). While it is not clear

whether the pleiotropic effects are caused by increased defenses, the deletion of a 304-kb genomic fragment adjacent to *MLO-B1*, which leads to increased expression of a tonoplast monosaccharide transporter gene, could circumvent these pleiotropic effects, although the exact mechanism remains unknown (Li et al., 2022).

The SQUAMOSA promoter binding protein-like (SPL) transcription factor IPA1 of rice (also known as OsSPL14) confers resistance to multiple *M*. *oryzae* isolates (Wang et al., 2018a). Importantly, it acts as a switch between normal growth and defense, sustaining a balance between yield and immunity (Jiao et al., 2010; Wang et al., 2018a). In healthy plants, IPA1 activates the expression of genes that control tillering and yield. However, during infection by pathogens like *M*. *oryzae*, IPA1 is phosphorylated and switches its target to *WRKY45*, which encodes a transcription factor regulating defenses. Thus, IPA1 promotes both yield and disease resistance, providing an excellent paradigm in which plants maintain a balance between immunity and growth. Similarly, the rice heterotrimeric G protein OsXLG3 plays a positive role in both immunity and growth (Zhao et al., 2022). Components that positively regulate both plant immunity and growth may be particularly desirable for improving disease resistance in crop plants.

In addition to regulatory proteins, some microRNAs also play an important role in the regulation of broad-spectrum resistance (Tang et al., 2021; Wang et al., 2021b). For example, microRNA168 (miR168) targets Argonaute1 (AGO1), a major component of the RNA-induced silencing complex to negatively regulate plant growth and immunity. Suppression of miR168 by a target-mimic (MIM168) not only improves grain yield and shortens the flowering time in rice, but also enhances immunity to many *M*. *oryzae* isolates (Wang et al., 2021b). Genetic manipulations of microRNAs hold promise in crop improvement.

Although components of the immune signaling network are generally conserved, there exists a great deal of genetic diversity among different haplotypes. Some of the haplotypes harbor subtle mutations that enhance the output of immune responses with minimal or no costs on the growth and yield of crop plants. The *ipa1-1D*, a natural allele of *IPA1*, displays not only improved disease resistance but also improved agronomic traits (Wang et al., 2018a). The rice *Bsr-d1* gene encoding a C2H2-type transcription factor negatively regulates immune responses to *M. oryzae* (Li et al., 2017). The *bsr-d1*, a natural allele discovered from resistant rice germplasm, carries a single base change in the promoter. This generates a high-affinity binding site for the transcription factor *MYBS1* to suppress the transcription of *Bsr-d1*, leading to enhanced defense output and broad-spectrum resistance to *M*, *oryzae* (Li et al., 2017). The *bsr-d1* allele does not affect the yield of rice plants, indicating that this allele could be particularly important for rice breeding. Similarly, a natural variation of the rice PICI1 deubiquitinase mainly retained in *japonica* confers enhanced blast resistance without impacting yield traits (Zhai et al., 2022). Furthermore, the rice *ROD1* gene encoding a C2-domain Ca^{2+} sensor is a negative regulator of ROS production during pathogen infection (Gao et al., 2021). Mutations in *ROD1* can lead to broad-spectrum resistance to both *M*. *oryzae* and *Rhizoctonia oryzae*. A natural *ROD1* allele carrying a single SNP^{1A} that is prevalent in *indica* rice enhances resistance without yield penalty. These examples indicate that variations in immune signaling components can be exploited for increased broad-spectrum disease resistance without a negative impact on agronomic traits in crop plants. Deep mining superior alleles of these genes in germplasms may provide valuable resources for broad-spectrum resistance.

Other durable resistance genes

A small number of resistance genes do not appear to be involved in pathogen perception or immune signaling. Some reported resistance genes encode enzymes that detoxify toxins produced by the pathogen. For example, the first cloned resistance gene *Hm1* encodes an enzyme that inactivates the *Helminthosporium carbonum* toxin produced by the fungus to permit infection and confers maize resistance (Johal and Briggs, 1992). Fusarium head blight resistance gene *Fhb7* encodes a glutathione S-transferase (GST) enzyme that detoxifies deoxynivalenol (DON toxin), a virulence factor of the pathogen and a major contaminant of grains (Wang et al., 2020). As these proteins target important virulence factors, they may confer durable resistance. Notably, *Fhb7* only exists in the *Thinopyrum* genus (wild relatives of wheat), while absent from the rest of the grass genomes (Wang et al., 2020). Introgression of *Fhb7* into cultivated wheat led to excellent protection against Fusarium head blight. This example indicates that exploring wild relatives of crop plants can offer a source of resistance genes that do not normally exist in crop plants.

Genes conferring durable resistance go beyond the categories mentioned above. In wheat, the well-known durable resistance genes *Lr67* and *Lr34* confer resistance to multiple pathogens including leaf rust, stripe rust, stem rust, and powdery mildew, whereas *Yr36* confers broad-spectrum resistance to stripe rust races at high temperatures. *Lr67*, *Lr34*, and *Yr36* encode a hexose transporter, an ABC transporter with abscisic acid-transporting activity, and a protein with a kinase and a putative START lipid-binding domain, respectively (Fu et al., 2009; Krattinger et al., 2009, 2019; Moore et al., 2015). The hexose transporter activity of the Lr67 protein is associated with susceptible variant, whereas the resistant variant dominantly inhibits such activity. Whether these proteins are defense signaling components or susceptibility factors remains unknown. In addition, many recessive resistance genes often confer broad-spectrum and/or durable disease resistance (Pavan et al.,

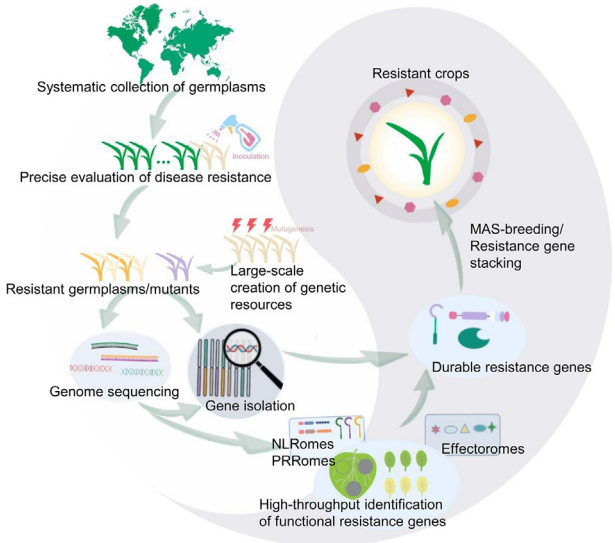

Fig. 2. Strategies to identify resistance genes and their utilization in breeding. Genetic diversity hosted by natural germplasms and those created by mutagenesis are evaluated for disease resistance. Subsequent identification of resistance genes can be carried out by a variety of approaches. Sequencing-based BSA and GWAS greatly facilitate the rapid dissection of genotype−phenotype associations and gene cloning. Pan-genome analyses allow the construction of NLRomes and PRRomes. These NLRs and PRRs can be experimentally tested against pathogen effectors to accelerate the identification of functional disease resistance genes. Pan-genome analyses of effectoromes help the identification of core effectors that are likely vital for pathogen fitness, thus will help the prediction of the durability of disease resistance genes that target these effectors. The newly identified resistance genes can be introduced into crops by marker-assisted (MAS) breeding and resistance gene stacking. BSA, bulk segregant analysis; GWAS, genome-wide association study; PRR, pattern recognition receptor.

2010; Li et al., 2019; Deng et al., 2020), it remains to be determined whether these represent loss-of-function alleles of *S* genes.

Strategies for identifying and engineering new resistance genes

The rapid advance in our understanding of the plant immune system and the development of new biotechnologies have provided unprecedented tools for breeding disease-resistant crop plants. Not only we can rapidly identify and deploy useful resistance genes using cross-based breeding (Fig. 2) but also we are able to engineer crop plants with novel resistance that never existed in traditional breeding (Fig. 3).

Systematic collection and large-scale creation of genetic resources

Germplasms with vast genetic diversity provide a foundation for genetic improvements in disease resistance in crop plants. Systematic collection of germplasms, including wild relatives and local cultivars, and subsequent evaluation of their disease resistance traits are essential for the identification of novel genes and alleles to be used in breeding. A total of ~7.4 million accessions are stored in more than 1750 genebanks worldwide (FAO, 2010). Access and effective use of these germplasm repositories have greatly expedited the identification of novel resistance genes. A large-scale screen has identified numerous blast-resistant rice accessions using germplasms and information from IRRI (Vasudevan et al., 2014). Of which 289 showed broad-spectrum resistance against multiple blast isolates. A screen of 19,460 wheat genotypes obtained 163 accessions with resistance to powdery mildew, among which 18 showed resistances to multiple diseases (Vikas et al., 2020). Wild relatives are of particular interest since a large amount of genetic diversity has been lost in domesticated varieties (estimated about 75%) after the migration of crops from their centers of origin or during modern breeding (Abbo et al., 2014; Bohra et al., 2022). The main limitation for use of wild relatives by the breeders in the past is the extraordinary length of time in classical breeding, but the recently developed genome editing technologies make it possible for de novo domestication in wild relatives in just a few generations (Li et al., 2018; Yu et al., 2021). It can be envisioned that wild relatives with excellent disease resistance traits could be edited to incorporate desirable domestication traits.

Besides the utilization of natural resources, large-scale creation of genetic resources by mutagenesis is also irreplaceable in the isolation of valuable resistance gene alleles which can be utilized in crop breeding. This approach complements the utilization of natural germplasms as it enables the acquisition of crop attributes that either does not exist in nature or have been lost during evolution (Novak and Brunner, 1992). Mutations can be randomly induced by chemical agents (e.g., ethyl methanesulfonate [EMS], sodium azide), physical treatments (e.g., fast-neutron irradiation, Gamma-rays) and insertional mutagenesis (e.g., T-DNA insertion, transposon and retrotransposon mutagenesis) (Viana et al., 2019). Targeted mutations can be created by employing genome editing tools such as zinc-finger nucleases, transcription activator-like effector nucleases (TALEN), and CRISPR/Cas9. Both the random and targeted mutagenesis can lead to gene gain or loss of function mutations and give rise to desired traits. The *bsr-k1* locus that displays broad-spectrum resistance was isolated from an EMS-induced rice mutant population and is considered as a reasonable candidate for breeding broad-spectrum resistance crop without yield penalties since the *bsr-k1* mutant maintains major agronomic traits (Ning and Wang, 2018; Zhou et al., 2018).

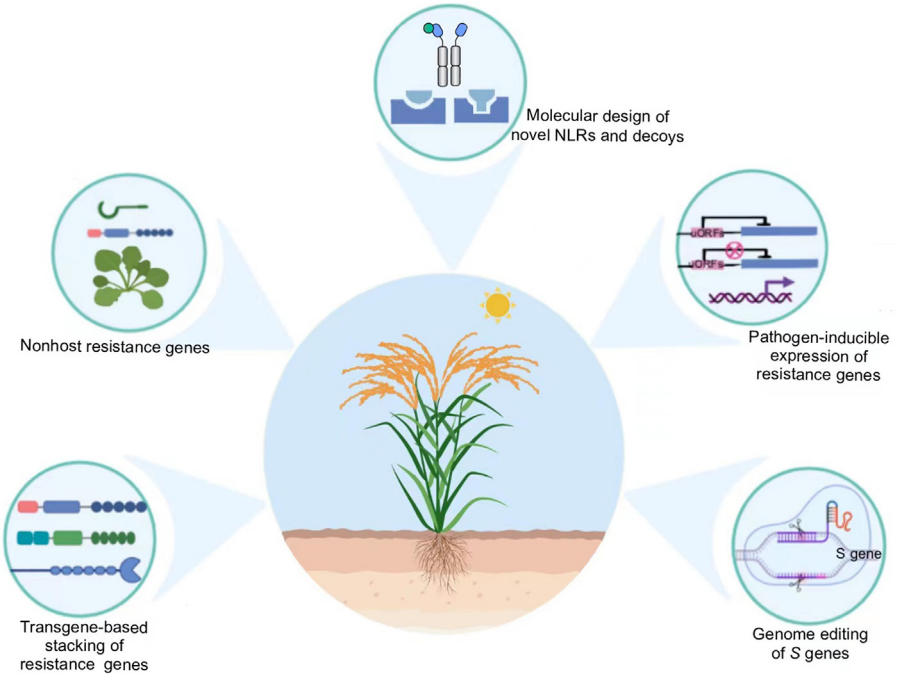

Fig. 3. Strategies for engineering disease resistance in crop plants. Transgene-based stacking of resistance genes can be achieved by constructing multiple resistance genes into a single cassette for gene transformation. As these transgenes are integrated into the genome as a single locus, they can be easily mobilized to other elite cultivars by crossing to offer strong and broad-spectrum resistance. Gene transformation also enables the cross-species transfer of nonhost resistance genes that do not exist in crop plants. We can also engineer existing NLRs or their decoys to generate novel pathogen-recognition specificity. Pathogen-inducible transcriptional or translational control of resistance genes in crop plants can minimize the trade-off between defense and growth. Gene editing of the *S* gene can rapidly generate durable disease resistance in crop plants.

Strategies for identifying new resistance genes

Many strategies have been employed for gene isolation. The map-based or positional cloning strategy is an established approach but labor-intensive and time-consuming. In the post-genomic era, multiple new approaches for effective gene isolation have emerged. These include comparative genomic analysis, bulked segregant analysis (BSA) and genome-wide association study (GWAS) (Tibbs et al., 2021; Li and Xu, 2022). BSA is more suitable for isolating causal genes from mutants, while GWAS is more feasible for capturing genes from natural populations of germplasm. Advances in sequencing, omics, and computational biology will also accelerate the cloning of disease-resistant genes. Nowadays, high-quality reference genome sequences are available for all major cereal crop species. A series of technologies emerged facilitating the dissection of genotype–phenotype associations and gene cloning. Resistance gene enrichment sequencing (RenSeq) works by designing a capture array that allows for the enrichment of NLR sequences specifically (Jupe et al., 2013). RenSeq and its descendants, such as dRenSeq, MutRenSeq, SMRT RenSeq, and AgRenSeq, have proved to be powerful tools for rapid cloning of NLR coding genes even in very large and complex genomes like wheat and barley (Steuernagel et al., 2016; Witek et al., 2016; Armstrong et al., 2019; Arora et al., 2019). Guided by a similar concept, RLP/KSeq was developed for RLP/RLK gene enrichment sequencing (Lin et al., 2020). RenSeq combined with RLP/KSeq will greatly facilitate the large-scale identification of new NLRs and PRRs.

Genomic sequencing of an individual cultivar/accession cannot reveal the true extent of NLR or PRR diversity within a plant species. Recent pan-genome studies have shown that the number of NLR genes within a plant species can exceed several times that found in a single variety (Barragan and Weigel, 2021). The entirety of NLR genes within a species is thus called pan-NLRome, and entirety of PRR-coding genes within a species is called pan-PRRome. Several pan-NLRomes studies have already been reported and provided useful information on our understanding NLR genes (Van de Weyer et al., 2019; Seong et al., 2020; Barragan and Weigel, 2021). The information on pan-NLRome and pan-PRRome will greatly help our effort in isolating functional NLR genes. Useful NLR-coding resistance genes are likely those function as sensor NLRs. NLR genes in the head-to-head organization in the genome, particularly those carrying ID, are excellent candidates. Furthermore, structural modeling of recognition surface has led to new methodologies for the identification of candidate sensor NLRs (Prigozhin and Krasileva, 2021).

It remains a daunting task to assign function to individual genes encoding NLRs and PRRs. Pan-genome studies in bacterial, fungal and oomycete pathogens allowed the construction of the effectorome (the entirety of effectors of a pathogen species), which has greatly facilitated the understanding of plant-pathogen interaction and contributed to the identification of functional resistance genes (Wang et al., 2011; Bart et al., 2012; Okmen et al., 2018; Laflamme et al., 2020; Seong and Krasileva, 2021). In particular, core effectors shared by the majority of pathogen strains are likely vital for pathogen infection (Bart et al., 2012). Plants carrying resistance genes that target core effectors may provide durable resistance. Future efforts are needed to develop high-throughput tests of NLR-effector pairs. Pan-PRRome can also be experimentally exploited by systematically testing its ability to recognize apoplastic effectors. Screening of a collection of wild *Solanum* germplasms for their response to the *Phytophthora infestans* apoplastic effector INF1 and subsequent cloning identified the receptor protein ELR, an RLP protein (Du et al., 2015). Using this pathosystem as a model, a combination of effectorome and pan-PRRome analyses coupled with an experimental test allowed rapid identification of an apoplastic effector SCR74 in *P. infestans* and mapping of the cognate receptor gene in a wild *Solanum* species (Lin et al., 2020).

As mentioned above, many PRRs and NLRs vary across different plant species. Transfer of these genes across different species may allow the utilization of non-host resistance (NHR), which refers to the resistance of an entire plant species against all isolates of a non-adapted pathogen (Lee et al., 2016). For example, *EFR* is restricted to the plant *Brassicaceae* family and absent from plant species such as those in the *Solanaceae* and *Poaceae* families (Zipfel et al., 2006). In this situation, interspecies transfer of PRRs can be used to confer resistance to the previously unrecognized pathogen. Besides EFR, the maize *Rxo1* gene has been introduced into the rice as a transgene to confer high-level resistance to bacterial leaf streak disease (Zhao et al., 2005). A recent study reported that Arabidopsis MKP1 confers NHR to rice pathogen *Xoo* through a protein phosphorylation-mediated vascular defense signaling, which also functions in rice resistance to *Xoo* (Lin et al., 2022). A deeper understanding of this pathway may offer new means to utilize Arabidopsis NHR against *Xoo* in rice.

Engineering disease resistant plants by editing *S* genes

Genome editing offers great power for engineering disease resistance in crop plants, and *S* genes are ideal targets for such an approach. An excellent example is the successful editing of rice *S* genes targeted by *Xoo* TALEs. The rice *S* genes *OsSWEET11/13/14* encode a class of sugar transporters required for *Xoo* virulence. Editing of EBEs in *OsSWEET11/13*/14 by TALEN, an earlier genome editing technology, and/or CRISPR/Cas9 endow rice lines with robust, broad-spectrum resistance to bacterial blight with no deleterious effects on other traits (Blanvillain-Baufumé et al., 2017; Oliva et al., 2019; Xu et al., 2019). The broadly conserved *S* gene *translation initiation factor 4E* (e*IF4E*), which is required for the cellular infection cycle of potyviruses, offers another successful example of disease resistance engineering by gene editing (Garcia-Ruiz et al., 2021). The eIF4E protein binds 5′-capped RNAs, which is required for translational initiation of the viral proteins (Schmitt-Keichinger, 2019). Silencing *eIF4E* in tomato or cucumber provided broad-spectrum resistance to potyviruses (Mazier et al., 2011; Chandrasekaran et al., 2016). Similarly, simultaneously mutating all three copies of the *S* gene *TaEDR1* by CRISPR/Cas9 enhances powdery mildew resistance in the bread wheat (Zhang et al., 2017).

Loss of function of *S* genes sometimes leads to deleterious effects on plant growth and yield. In addition to mutations of the wheat *MLOs* mentioned above, knocking out the pepper *S* gene *Bs5* and tomato *S* gene *eIF4E1* also leads to defects in growth and/or reproduction (Van Esse et al., 2020). However, it is now possible to engineer broad-spectrum resistance to powdery mildew in elite wheat cultivars while retaining high yield traits by simultaneously mutating the three copies of the *MLO* gene and deleting the 304-kb fragment in elite wheat cultivars in a single step using CRISPR/Cas9 (Li et al., 2022). Similarly, the introduction of six nonsynonymous mutations in *eIF4E1* increased resistance without affecting plant development and agronomic traits (Bastet et al., 2018). Thus, careful genetic manipulations of *S* genes or generation of second-site mutations enable better exploitation of *S* genes for crop improvements.

Engineering pathogen-inducible crop resistance

Creating pathogen-inducible transcriptional or translational control can minimize the trade-off between defense and growth in crop plants. Expression of *IPA1* under control of the pathogen-inducible promoter of *OsHEN1* improved both rice yield and disease resistance (Liu et al., 2019). Upstream open reading frames (uORFs) are

cis-acting elements located upstream of the primary open reading frame. They primarily inhibit the translation initiation of the downstream primary ORF through ribosome stalling (Von Arnim et al., 2014). Upon immune induction, global translational reprogramming occurs to allow a stringent pathogen-inducible expression of defense proteins (Xu et al., 2017). This mechanism has been exploited for the engineering of disease-resistant Arabidopsis and rice plants by fusing pathogen-inducible uORFs with *snc1-1*, which encodes an autoactivated TNL, and *NPR1*, which encodes a receptor of salicylate (Xu et al., 2017). Importantly, the engineered plants conferred broad-spectrum disease resistance without compromising plant fitness in the laboratory or in the field. Similarly, controlled expression of *AtLecRK-VI.2*, which encodes an RLK involved in PTI, by combining a pathogen-inducible uORF with a pathogen-inducible promoter in transgenic *N. benthamiana* plants conferred resistance to *Phytophthora capsici* with no apparent suppression to plant growth (Ai et al., 2022). Thus, utilization of pathogen-responsive uORFs and promoters offers a powerful strategy for engineering disease resistance in crop plants.

Generation of new recognition specificity of NLRs by engineering

Engineering NLR or decoys has emerged as a promising approach to expand NLR recognition specificity and durability. The Arabidopsis CNL RPS5 indirectly recognizes *P. syringae* effector AvrPphB, a cysteine protease, through the decoy protein PBS1, a protein kinase (Shao et al., 2003; DeYoung et al., 2012). AvrPphB cleaves PBS1 at a specific site, this likely causes a conformational change that activates RPS5. Replacing the AvrPphB proteolytic target site with viral protease target sites in PBS1 allowed RPS5 to recognize tobacco etches virus and turnip mosaic virus (Kim et al., 2016). This strategy has been improved and successfully applied to soybean for virus resistance (Pottinger et al., 2020). While these studies have focused on the recognition of pathogen proteases, a deep understanding of how decoys interact with NLR proteins and how their modification by pathogen effectors leads to an appropriate conformational change to trigger NLR activation may provide instruction for better engineering of NLRs with expanded recognition repertoire.

For NLR-ID proteins, modifications in ID can also expand effector recognition specificity. Targeted engineering of the effector-binding interface in the HMA domain of Pik-1 and RGA5 allowed new recognition specificity to effectors that do not normally activate these NLRs (De la Concepcion et al., 2019, 2021a; Liu et al., 2021b; Cesari et al., 2022). For paired NLRs, it is worth noting that only matching pairs can mount effective immune responses, whereas mismatched pairs can lead to autoimmune phenotypes in the absence of pathogen effectors or no immune action (De la Concepcion et al., 2021b; Yang et al., 2022).

While studies discussed above succeeded in the limited expansion of NLR recognition capacity, a recent study suggests NLRs can be engineered to recognize any intracellular effectors. The Kamoun lab tested the idea that the minimal antigen-binding fragment of single-domain heavy chain antibodies (nanobodies) of camelid can be integrated into the sensor NLR protein Pik-1 in place of ID to trigger ETI in response to the corresponding antigen (Kourelis et al., 2021). A screen of a number of anti-Green Fluorescent Protein (GFP) and anti-mCherry nanobodies fused to Pik-1, called Pikobodies, identified several such fragments that specifically activated HR in *N. benthamiana* plants in response to GFP or mCherry. These Pikobodies can successfully activate HR when plants are infected with Potato virus X expressing GFP or mCherry. Given that nanobodies can be readily generated to bind virtually any antigen, Pikobodies represent a new avenue to generate any needed resistance genes against pathogen or pest that delivers effectors inside host plant cells. This exciting technology is of enormous importance for crop diseases lacking resistance genes.

Knowledge gap and future directions

As discussed above, plants perceive pathogen invasion by membrane-bound and intracellular immune receptors to activate immune responses against pathogenic microbes (Fig. 1). Considerable advances have been made on mechanisms by which plant surveillance system monitors pathogen invasion and activates robust immune responses. Genes encoding immune receptors and signaling components have proven useful in breeding disease-resistant crop plants. Molecular bases underlying durable resistance are being discovered, and it is clear that resistance genes recognizing effectors that are prevalent and/or critical for the fitness of pathogens are excellent candidates for durable resistance genes. Rapid advances in pan-genome analyses of immune receptor genes in crop plants and effector genes in pathogens will surely expand the repertoire of useful disease resistance genes. For diseases that lack major resistance genes in cultivated plants, exploration of wild relatives and even unrelated plant species provides a useful solution. Key nodes in immune signal transduction also offer valuable sources of durable resistance. Altered expression or activity of these genes often lead to elevated resistance to pathogens in a nonspecific manner but may cause deleterious effects on the growth and yield of crop plants. Certain alleles of these genes have been identified that increase disease resistance without adverse effects on yield. Disease resistance genes encoding immune signaling components are often identified as QTLs and confer incomplete disease resistance. However, it is possible to stack these resistance genes with genes encoding immune receptors to achieve strong resistance. Comprehensive mining of germplasms and the generation of new germplasms will further increase our arsenal in the combat against major diseases in crop plants.

In addition to exploiting genetic diversity in germplasms, advances in plant immunity and biotechnology have opened up new avenues to rapidly engineer disease resistance in crop plants (Figs. 2 and 3). We can now engineer NLR proteins with new recognition specificity never existed in nature. This is particularly important for crop diseases that lack resistance genes, such as sheath blight caused by *Rhizoctonia solani* and false smut caused by *Ustilaginoidea virens* in rice and *Fusarium* head blight in wheat. Some of the technical difficulties lie in the proper design of synthetic NLR proteins that remain inactive in the resting state and strictly activate ETI upon detection of effectors (Kourelis et al., 2021). Continued studies of NLR structures using cryo-EM and AlphaFold (Jumper et al., 2021) or AlphaFold-Multimer (Evans et al., 2021) may eventually allow us to design functional NLRs with greater precision. We can also exploit *S* genes or genes encoding negative immune regulators by gene editing to rapidly generate new resistance in elite cultivars of crops. The limitation is the paucity of useful *S* genes that can be mutated with minimum adverse effects on crop plants. An important knowledge gap is a comprehensive understanding of molecular bases underlying the coordination of disease resistance and other agronomic traits. Future studies that close this gap will allow us to better exploit plant immunity at levels of pathogen recognition and signal transduction for the protection of crops.

Conflict of interest

The authors declare no conflict of interest.

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