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Molecular Basis of Disease Resistance and Perspectives on Breeding Strategies for Resistance Improvement in Crops

Yiwen Deng[1,5], Yuese Ning[2,5], Dong-Lei Yang[3,5], Keran Zhai[1], Guo-Liang Wang[4,*] and Zuhua He[1,*]

[1]National Key Laboratory of Plant Molecular Genetics, CAS Center for Excellence in Molecular Plant Sciences/Shanghai Institute of Plant Physiology & Ecology, Chinese Academy of Sciences, Shanghai 200032, China

[2]State Key Laboratory for Biology of Plant Diseases and Insect Pests, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China

[3]State Key Laboratory of Crop Genetics and Germplasm Enhancement, Nanjing Agricultural University, Nanjing 210095, China

[4]Department of Plant Pathology, Ohio State University, Columbus, OH 43210, USA

[5]These authors contributed equally to this article.

***Correspondence: Guo-Liang Wang (wang.620@osu.edu), Zuhua He (zhhe@sibs.ac.cn)**

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ABSTRACT

Crop diseases are major factors responsible for substantial yield losses worldwide, which affects global food security. The use of resistance (*R*) genes is an effective and sustainable approach to controlling crop diseases. Here, we review recent advances on *R* gene studies in the major crops and related wild species. Current understanding of the molecular mechanisms underlying *R* gene activation and signaling, and susceptibility (*S*) gene-mediated resistance in crops are summarized and discussed. Furthermore, we propose some new strategies for *R* gene discovery, how to balance resistance and yield, and how to generate crops with broad-spectrum disease resistance. With the rapid development of new genome-editing technologies and the availability of increasing crop genome sequences, the goal of breeding next-generation crops with durable resistance to pathogens is achievable, and will be a key step toward increasing crop production in a sustainable way.

Key words: resistance gene, resistance improvement, molecular basis of disease resistance, crop immunity

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INTRODUCTION

The steady growth of the worldwide population necessitates a substantial increase in crop productivity. Improvement of disease resistance in crops has great potential to increase productivity by preventing the huge losses caused by pathogenic fungi, bacteria, nematodes, oomycetes, and viruses. Indeed, estimated average global yield losses due to diseases and pests range from 11% to 30% (Savary et al., 2019). On the other hand, most modern varieties, which have been selected for enhancement of yield values, are relatively more susceptible to pathogens under high fertilizer inputs. In addition, new pathogen variants often cause greater threat to crops. For example, the new highly virulent races of the wheat stem rust fungus, Ug99 (Singh et al., 2011), and wheat blast (Cruz and Valent, 2017; Ceresini et al., 2018), have caused serious damage to wheat production. Breeding of disease-resistant cultivars is the most economical, eco-friendly measure for disease control in agriculture. Therefore, a deep understanding of plant–pathogen interactions and the immune machinery in crops is critical for the development of crop breeding strategies that improve disease resistance (Dangl et al., 2013; Nelson et al., 2018; Li et al., 2020).

Plant disease resistance is typically divided into complete resistance (qualitative resistance) and partial resistance (quantitative resistance). Complete resistance is usually controlled by resistance genes (*R*), which typically, but not always, encode surface immune receptors (such as receptor-like kinases [RLKs]) or intracellular immune receptors (such as nucleotide-binding leucine-rich repeat proteins [NLRs]), which can detect conserved pathogenic molecules or cognate effectors/avirulence (Avr) proteins directly or indirectly (Jones and Dangl, 2006; St Clair, 2010). However, most *R*-mediated resistance belong to race-specific ''gene-for-gene'' resistance (Flor, 1971), which can easily be

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broken down in the field because pathogens can evolve to evade host recognition by mutating the cognate Avr gene, thus forcing plant breeders to continually seek new *R* genes for control of crop diseases. By contrast, partial resistance, controlled by quantitative resistance loci (QTL) with minor effects, is considered as durable and broad-spectrum resistance (BSR) against various pathogen races. However, it is difficult to use single QTLs in crop breeding because of their minor effects. Therefore, the discovery of genes underlying BSR in crops has been a major breeding objective. For a more comprehensive discussion of different genes involved in BSR in crops, please refer to our recent review (Li et al., 2020).

In the last three decades, impressive progress in deciphering plant immune mechanisms has been made, particularly in the model plant *Arabidopsis*. Most of the proposed resistance models were based on the results in *Arabidopsis*. During the co-evolution of crop plants and pathogens in the field and breeding selection by humans, *R* genes identified in various crops might adopt different mechanisms of immune activation and signaling. In particular, the immune machinery in crops is likely somehow different from that in the model plant *Arabidopsis* owing to extensive domestication and breeding selection (Soltis et al., 2018), especially the *NLR* genes have been positively selected in rice (Huang et al., 2010). In this perspective article, we focus on summarizing recent progress on isolation of *R* genes and the current understanding of resistance mechanisms, new insights and approaches to balance between disease resistance and yield, and utilization of susceptibility genes for resistance improvement in crops. Finally, we propose new breeding strategies for improving disease resistance in crops.

Current Understanding of Plant Immunity

Over the past 30 years, a fundamental framework for the plant immune system has been established along with the identification and characterization of genes that encode immune receptors, pathogen-associated molecular patterns (PAMPs), pathogen Avr proteins/effectors, and key signaling components of plant immune responses. Our current understanding of the plant immune system indicates a two-tiered plant immune machinery: PAMP-triggered immunity (PTI) and effector-triggered immunity (ETI) (Abramovitch et al., 2006; Jones and Dangl, 2006; Couto and Zipfel, 2016; Boutrot and Zipfel, 2017; Saijo et al., 2018), although this simple classification has been challenged by the lack of a clear distinction between PTI and ETI in some cases (Thomma et al., 2011). The widely recognized zigzag evolutionary model of plant innate immunity recapitulates the stepwise co-evolution of the host and microbes (Jones and Dangl, 2006). PTI is a basic defense response activated by plasma member-anchored pattern recognition receptors (PRRs), which detect conserved PAMPs, such as flagellin, elongation factor Tu (EF-Tu), and chitin (Miya et al., 2007; Zipfel et al., 2004, 2006). PTI tends to be effective in preventing infection by a vast majority of microbes, and most PTI-related pathways share highly similar signaling modules. Therefore, the simultaneous activation of multiple PRR pathways is likely to increase the robustness of overall plant defense against pathogen infection (Couto and Zipfel, 2016; Saijo et al., 2018).

However, pathogens can secrete a plethora of effectors into the host cell to suppress host PTI, which leads to effector-triggered susceptibility (ETS) (Chisholm et al., 2006; Boller and He, 2009). To counter ETS, plants have evolved numerous intracellular immune receptors. These immune receptors directly or indirectly recognize microbial effectors, thereby triggering a rapid, robust defense response or ETI, which in turn typically induces the local hypersensitive response (HR) cell death to restrict pathogen growth and propagation (Dodds and Rathjen, 2010; Cui et al., 2015). Most intracellular receptors are NLRs, which are generally subdivided into TIR-NLRs (TNLs) with an N-terminal Toll-like/IL-1 receptor (TIR) domain, CC-NLRs (CNLs) with an N-terminal coiled-coil (CC) domain, and CC_R-NLRs with an N-terminal RPW8-like CC domain NLR (Baggs et al., 2017). Plant genomes encode hundreds of such NLR receptors, whose roles in immunity have functionally diversified during the co-evolution of plants and microbes (Chakraborty et al., 2018; Tamborski and Krasileva, 2020). Recently, the crystal structure of the NLR receptor ZAR1 was revealed with a wheel-like pentamer resistosome complex, associated with the cell membrane via the funnel structure formed by the CC domain oligomer to mediate ion influx across the membrane, which initiates cell death (Wang et al., 2019a, 2019b). The TIR domain of TNL acts as an NADase, which cleaves NAD^+ and NADP to activate immunity, including downstream response signaling and cell death upon recognition of pathogens (Horsefield et al., 2019; Wan et al., 2019). These studies revealed that the NLR receptors mediate plant immune responses using multiple different mechanisms. Therefore, structure studies of more NLRs from crop genomes may prove beneficial for understanding plant immune mechanisms, and in turn facilitate engineering of novel plant resistance proteins.

To date, more than 213 typical *R* genes conferring resistance to multiple types of pathogens have been functionally identified in rice, wheat, maize, barley, and other crop species (Table 1) (Kourelis and van der Hoorn, 2018; Li et al., 2020). In addition to NLRs, some typical race-specific *R* genes also encode PRRs, including RLKs, receptor-like proteins (RLPs), and cell wall-associated protein kinases (WAKs) (Zhong et al., 2017; Saintenac et al., 2018), indicating that some PRRs also recognize the specific pathogen patterns to trigger race-specific resistance in crops. This suggests that the demarcation of PRR-mediated PTI and NLR-mediated ETI is not always clear, as both immune pathways intertwine in crops. On the other hand, although PTI and ETI share downstream signaling pathways, such as those leading to production of reactive oxygen species, Ca^{2+} spikes, and MAPK activation, immune responses that occur during ETI are more prolonged and robust than those that occur during PTI (Tsuda and Katagiri, 2010; Yu et al., 2017). This is why *R* genes controlling ETI are major breeding targets for improving disease resistance in crops (Jones and Dangl, 2006; Dangl et al., 2013). Recently, two studies demonstrated that PTI is the primary source of plant innate immunity and ETI depends on PTI to inhibit pathogen growth, which, conversely, potentiates PTI response to halt pathogen spread (Ngou et al., 2020; Yuan et al., 2020). Therefore, pyramiding of multiple *NLR* genes in the same varieties also strengthens host PTI response, which should provide BSR and durable resistance to multiple adapted pathogens in crops.

Crop species	Total	NLR	RLK/RLP	Other
Rice	50	32	8	10
Wheat	39	24	10	5
Maize	17	4	3	10
Barley	15	13	1	1
Tomato	29	10	15	4
Potato	21	20	1	0
Other	42	29	3	10

Table 1. Various Type of Disease Resistance Genes Isolated from Major Crops and Related Wild Species.

Most cloned *R* genes encode intracellular NLR receptors. Some typical *R* genes also encode RLKs or RLPs, which act as PRRs. Other types of *R* genes encode immune signaling components in PTI or ETI.

In addition, numerous resistance QTLs were also identified in crops (St Clair, 2010; Niks et al., 2015; Cowger and Brown, 2019). Several QTLs, such as *Yr36*, *ZmWAK*, and *Htn1*, encode typical RLKs and WAKs, which act as PRRs in pathogen recognition early in defense responses (Fu et al., 2009; Hurni et al., 2015; Zuo et al., 2015). In some cases, QTLs encode atypical NLR receptor proteins, which play roles in delaying disease onset. This results in relatively low selection pressure on the pathogen, and leads to relatively durable resistance, as was observed with *Pi35* and *Pb1* in rice (Hayashi et al., 2010; Fukuoka et al., 2014). Additional resistance QTLs, such as *ZmFBL41*, *Fhb1*, and *Fhb7* act as defense signaling components to activate immune responses (Li et al., 2019a, 2019b; Su et al., 2019; Wang et al., 2020a). Interestingly, several resistance QTLs encode transporters or enzymes to produce metabolism components that lead to BSR to multiple diseases. For example, *Lr34* encodes an ATP-binding cassette transporter (Krattinger et al., 2009), which confers resistance to multiple wheat biotrophic pathogens, including stem rust, stripe rust, leaf rust, and powdery mildew; and *Lr67* encodes a hexose transporter that leads to reduced nutrient availability inside the host cell, conferring resistance to multiple rusts and powdery mildew (Moore et al., 2015). *ZmCCoAOMT2* encodes a caffeoyl-CoA O-methyltransferase associated with programmed cell death, conferring resistance to leaf blight and gray leaf spot in maize (Yang et al., 2017). Consequently, combining *R* genes with these QTLs usually achieves broad-spectrum and durable resistance (St Clair, 2010; Cowger and Brown, 2019).

PAMP-Triggered Immunity

Although several PRRs and their co-receptors have been well studied in the model plant *Arabidopsis*, only a few have been extensively studied in crops (Saijo et al., 2018). The well-studied PRR FLS2 is conserved in higher plants, which forms a heterodimer complex with BAK1 to activate immune signaling upon binding a 22-amino acid epitope (flg22) conserved in bacterial flagellins (Boller and Felix, 2009; Chinchilla et al., 2007; Gomez-Gomez and Boller, 2000; Hann and Rathjen, 2007; Robatzek et al., 2007; Takai et al., 2008; Trdá et al., 2014; Zipfel et al., 2004). Another well-known PRR is EFR, which recognizes the conserved 18-aa epitope (elf18) of PAMP EF-Tu in bacteria to trigger immunity in *Brassicaceae* (Boller and Felix, 2009; Zipfel et al., 2006). The rice cells can also recognize a bacterial EF-Tu fragment to activate immune response; however, the corresponding PRR is currently unknown (Furukawa et al., 2014). The introduction of *EFR* in other plants often confers bacterial resistance, as observed in transgenic wheat, rice, tobacco, and tomato (Lacombe et al., 2010; Schoonbeek et al., 2015; Schwessinger et al., 2015). Interestingly, evolutionary analysis suggests that *Arabidopsis* EFR and rice XA21 are phylogenetically related and may recruit similar signaling components to activate immunity (Holton et al., 2015; Schwessinger et al., 2015). XA21 isolated from wild rice *Oryza longistaminata* confers resistance to multiple strains of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) (Song et al., 1995). XA21 recognizes the PAMP RaxX, which is relatively conserved in *Xanthomonas* species, resulting in an ETI-like race-specific resistance (Pruitt et al., 2015) (Figure 1). XA21 can also confer disease resistance when expressed in phylogenetically diverse species (Mendes et al., 2010; Afroz et al., 2011; Tripathi et al., 2014). These findings demonstrate that the cross-species transfer of PRRs represents a promising approach for improving disease resistance in crops.

Another type of PRRs identified in tomato and *Arabidopsis* are RLPs, which lack kinase motifs and form heteromeric complexes with different co-receptors, such as BAK1 or SOBIR1, in a ligand-independent manner to trigger an immune response (Boutrot and Zipfel, 2017; Saijo et al., 2018). In tomato, EIX1/Eix2 and Ve1 recognize fungal xylanase and the Ave1 peptide, respectively (Ron and Avni, 2004; Bar et al., 2010; de Jonge et al., 2012). Transfer of tomato *Ve1* into other crop species also confers resistance against *Verticillium* wilt in an Ave1-dependent manner (Song et al., 2018). Necrosis and ethylene-inducing peptide-like proteins (NLPs) are widespread from oomycetes to fungi and bacteria, and can be recognized by an RLP23-SOBIR1-BAK1 complex to trigger immune responses (Albert et al., 2015). The interfamily transfer of RLP23 to solanaceous plants also enhances resistance to oomycete and fungal pathogens in potato (Albert et al., 2015). Although most PRRs can directly perceive their cognate PAMPs, indirect PAMP recognition by PRRs also occurs. For example, the tomato PRR Cf-2 recognizes the conserved *Cladosporium fulvum* effector protein Avr2 through the host target Rcr3 to elicit immune responses (Dixon et al., 1996; Rooney et al., 2005), indicating that there exist diverse recognition mechanisms across PRRs and PAMPs.

Increasing evidence shows that WAKs are a key kinase family for disease resistance in crops (Kanneganti and Gupta, 2008; Zuo et al., 2015; Saintenac et al., 2018). WAK1 recognizes oligogalacturonides to activate defense in *Arabidopsis* and tobacco (Brutus et al., 2010). The wheat *R* gene *Stb6* encodes a WAK that recognizes fungal secreted effectors in the plant apoplastic space and interacts with the accessory RLKs to activate defense (Zhong et al., 2017; Saintenac et al., 2018). Similarly, the rice WAK XA4 confers durable resistance to several *Xoo* strains by strengthening cell wall-based defense responses (Hu et al., 2017). Two maize WAKs, qHSR1 and Htn1, contribute to quantitative disease resistance (Hurni et al., 2015; Zuo et al., 2015). Another WAK, the wheat susceptibility protein Snn1, binds to the pathogen virulence factor SnTox1 to induce

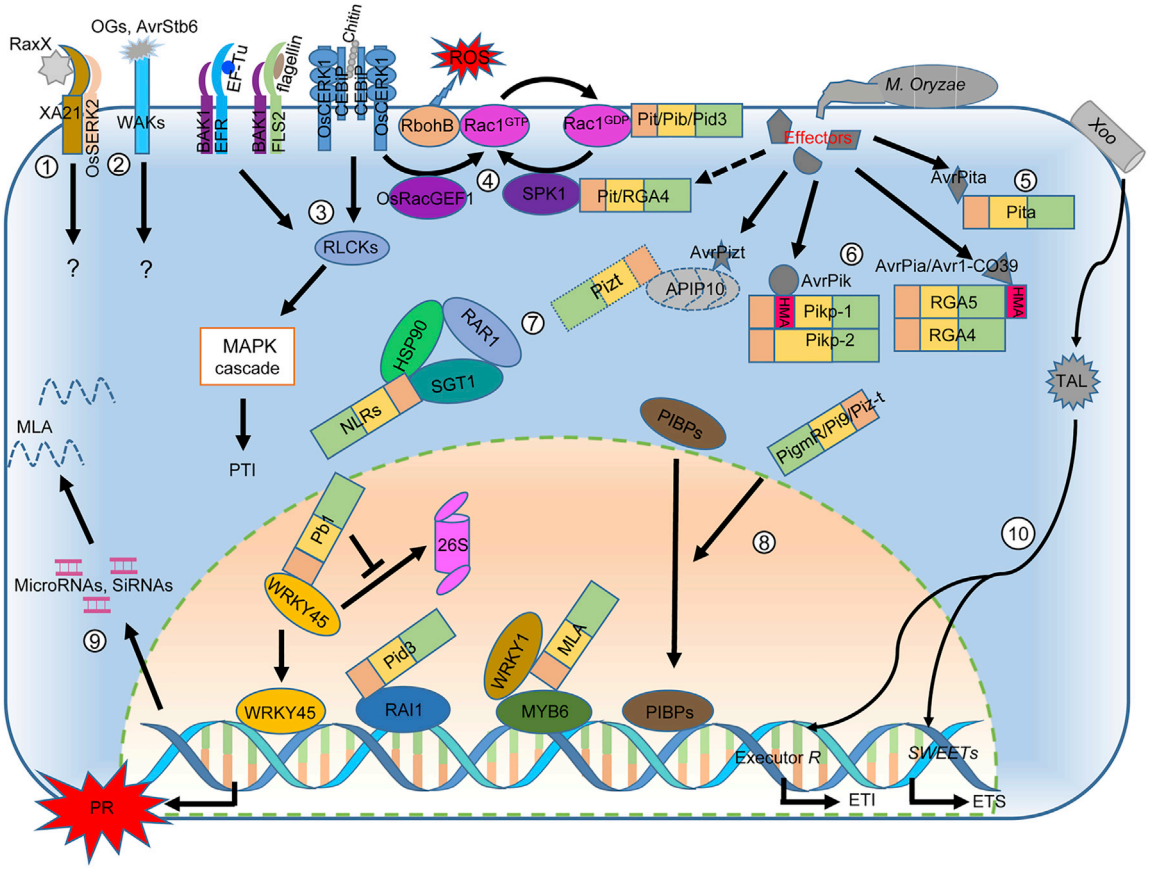

Figure 1. Schematic Diagrams Showing How PTI and ETI Occur in Crops.

(1) Binding of the sulfated RaxX to the rice XA21 LRR domain induces downstream immune signaling. (2) WAKs recognize OG PAMPs or apoplast effectors AvrStb6 to trigger defense response. (3) The PRRs FLS2, EFR, and OsCEiBP interact with a co-receptor form complex to activate the immune response upon perception of pathogen PAMPs. (4) The OsRac1 GTPase is required for the NLR-mediated ETI. NLR activates OsRac1 through a GDP (guanosine diphosphate) bound to a GTP (guanosine triphosphate) bound state transformation by the interaction with SPK, a guanine nucleotide exchange factor. (5) The direct interaction between AvrPita and Pi-ta triggers ETI in rice to *Magnaporthe oryzae*. (6) The ID of NLR is critical for effector detection and immune activation. (7) NLR protein stability is regulated by the molecular chaperone complex. (8) NLR proteins activate defense responses through TFs. (9) miRNAs and siRNAs modulate plant immunity by regulating *NLR* expression. (10) *Xoo* TALEs induce ETI through targeting the promoters of executor *R* genes or induce ETS through binding to the promoters of *SWEET* genes.

tissue necrosis, thereby enhancing host susceptibility (Shi et al., 2016). The *Arabidopsis* genome encodes only 26 WAK-like proteins; in contrast, more than 125 WAK-like proteins are encoded in the rice, wheat, and maize genomes (Kanneganti and Gupta, 2008; Zuo et al., 2015; Saintenac et al., 2018). Therefore, the WAK family has likely expanded during cereal evolution and domestication, and plays important role in base defense in these crops (Delteil et al., 2016).

As an important group of PRRs, lysine motif receptor kinases (LysM-RKs), perceive fungal cell wall oligosaccharide components, such as chitin (Kaku et al., 2006; Miya et al., 2007) (Figure 1). In *Arabidopsis*, the LysM-RLK, CERK1/RLK1/LYK1, directly binds the oligomers of fungal chitin using the three extracellular LysM domains, leading to the formation of an active homodimer complex to initiate chitin-induced immune responses (Miya et al., 2007; Wan et al., 2008; Liu et al., 2012). However, OsCERK1 alone does not bind chitin. Instead, the LysM-RLP, CEBiP, the major chitin-binding protein in rice, cooperates with OsCERK1 to form a plasma membrane receptor complex to trigger immunity (Kaku et al., 2006; Shimizu et al., 2010; Shinya et al., 2012). Although the chitin perception mechanism is different in rice and *Arabidopsis*, the downstream chitin-induced immune signaling through the MAPK cascade is likely conserved in rice and *Arabidopsis* (Kawasaki et al., 2017; Wang et al., 2017; Yamada et al., 2017). Similarly, CEBiP and CERK1 also function in chitin recognition and fungal resistance in wheat and barley (Tanaka et al., 2010; Lee et al., 2014), suggesting a promising strategy to improve fungal resistance in crops. However, how these kinase-mediated PTI pathways coordinately function during pathogen infection remains elusive.

PTI usually acts to confer only partial (quantitative) disease resistance to pathogens, except that several PRRs from crops, such as XA21, Cf-2, and Stb6, confer complete resistance similar to the classical gene-for-gene resistance. Therefore, the emerging strategy of interfamily transfer of PTI-triggering genes to confer BSR is needed in crop breeding. With this scenario, more novel PPRs should be explored in crops.

Effector-Triggered Immunity

ETI is activated by intracellular receptors, usually NLRs, upon recognition of pathogen effectors, which leads to strong and robust resistance. Therefore, ETI has been widely used for disease control during crop production (Dangl et al., 2013; Nelson et al., 2018; Li et al., 2020). Nevertheless, isolation of new *NLR* genes and elucidation of the molecular mechanisms underlying *NLR*-mediated resistance certainly provide valuable genetic resources and knowledge to facilitate crop breeding to improve disease resistance.

R Protein Diversity and Structures in Crops

Among the 213 *R* genes cloned in crops, 50 were from rice (Table 1) (Kourelis and van der Hoorn, 2018), of which, 37 *R* genes confer resistance to the rice blast fungus *Magnaporthe oryzae* (Zhang et al., 2019a). Most of the rice blast *R* genes encode NLR proteins, except for *Pi-d2* (which encodes a β-lectin receptor kinase) (Chen et al., 2006) and *Ptr* (which encodes an ARM repeat domain protein) (Zhao et al., 2018). These blast *R* genes are mainly located in several gene clusters. Clustered distributions of *NLR*s were also observed in other plant genomes (Smith et al., 2004; Baggs et al., 2017; Keller et al., 2018). It appears that *NLR* clustering is beneficial for the rapid evolution of new *R* genes via homologous recombination and facilitates the selection of novel *R* genes.

In addition to the canonical motif, a few NLRs also contain integrated domains (IDs) that resemble effector targets. For example, RGA5 and Pikp-1 contain a heavy metal-associated binding (HMA) domain (Cesari et al., 2014a; Maqbool et al., 2015), and Pi5-2/Pii-2 contains a nitrate-induced domain (Lee et al., 2009; Fujisaki et al., 2017). In wheat, *Yr5*, *Yr7*, and *YrSP* encode proteins with a non-canonical N-terminal zinc-finger BED domain (Marchal et al., 2018), and *YrU1* encodes a protein containing N-terminal ankyrin-repeat and C-terminal WRKY domains, representing a unique NLR structure in plants (Wang et al., 2020b). Additional IDs were also found in the potato NLRs R3 and R1 (Kroj et al., 2016). It has been well recognized that targeting of IDs by pathogen effectors is essential for immune activation. Therefore, the discovery of new IDs and underlying mechanisms of effectors will shed new light on ETI activation as well as *R* gene deployment in crop breeding.

In contrast to NLR-triggered disease resistance, the recognition of bacterial transcription activator-like effectors (TALEs) presents a distinct mechanism of plant immunity. TALEs with a C-terminal acidic activation domain and a central repeat domain that directly binds to the promoter *cis*-elements (effector-binding elements [EBEs]), can manipulate host gene expression in a sequence-specific manner. Several executor *R* genes that carry EBEs embedded in their promoters are recognized by TALEs, which triggers resistance to *Xanthomonas* in rice, pepper, and tomato (Gu et al., 2005; Tian et al., 2014; Wang et al., 2015). Many *R* genes or susceptibility (*S*) genes to *Xanthomonas* are targets of TALE effectors, highlighting the diverse mechanisms of *R*-mediated resistance or *S*-mediated susceptibility in crops. It is also notable that the *R* gene *STV11*, conferring resistance against rice stripe virus, encodes a sulfotransferase (Wang et al., 2014b), supporting the notion that different defense strategies have been evolved against diverse pathogens in crops.

Molecular Mechanisms of Effector Recognition by R Proteins

Since the cloning of the first *R* gene, *Hm1*, from maize (Johal and Briggs, 1992), many *R* genes were determined to confer resistance to different pathogens in crops and their corresponding Avr effectors in pathogens have been identified. Three models have been proposed based on R-Avr interactions: the direct interaction model, the guard/decoy model, and the integrated decoy model (van der Hoorn and Kamoun, 2008; Cesari et al., 2014a; Jones et al., 2016) (Figure 1).

The Direct Interaction Model. The first example of the direct interaction between R and Avr reported in crops was the case study of rice blast resistance NLR Pi-ta and its cognate Avr effector Avr-Pita (Jia et al., 2000). Subsequent studies suggested that the dynamic co-evolution of *Avr-Pita* and *Pi-ta* alleles occurred under field conditions (Jia et al., 2016). The direct recognition and dynamic co-evolution of *Avr* and *R* genes in crops was also reported for the flax-*Melampsora lini* pathosystem (Dodds et al., 2006). Notably, the allelic NLRs MLA7, MLA9, and MLA10 from barley directly bind to the *Blumeria graminis* effectors AVR_{a7}, AVR_{a9}, and AVR_{a10}, which are sequence-unrelated, indicating that different MLA receptors even when they are allelic can perceive dissimilar fungal effectors (Saur et al., 2019). However, despite that direct NLR-Avr interactions have been reported in crops, little is known about how this direct recognition triggers downstream signaling of immunity in these pathosystems.

The Guard/Decoy Model. In most cases, pathogen effectors do not directly bind to their cognate NLR receptors (Jones et al., 2016; Sun et al., 2020). Instead, the NLR receptors indirectly perceive the effectors via their associations with effector-targeted proteins, which are generally referred to as guardees or decoys; these interactions are thus described by the guard and decoy models, respectively. The only difference between these two models is that the guardee usually has another independent function in host defense, while the decoy itself has no role in the compatible reaction (van der Hoorn and Kamoun, 2008; Jones et al., 2016).

The well-studied examples of the guard model involve the interaction of the *Arabidopsis* NLR, RPM1, RPM1-INTERACTING PROTEIN 4 (RIN4), and *Pseudomonas syringae* effectors AvrRpm1 and AvrB (Mackey et al., 2002). Similarly, the soybean RIN4 homolog GmRIN4b also acts as the guardee for the soybean R protein RPG1-B and recognizes the *P. syringae* effector AvrB (Selote and Kachroo, 2010). Therefore, RIN4 likely uses a conserved regulatory mechanism in plant immunity.

The best example of the decoy model in crops is the interaction of the tomato R protein Prf, protein kinase Pto, and *P. syringae* AvrPto (van der Hoorn and Kamoun, 2008; Jones et al., 2016). The protein kinase Pto was initially reported to physically interact with the Avr protein AvrPto to trigger plant immunity (Scofield et al., 1996; Tang et al., 1996). Subsequently, Prf was reported to act as the guard and Pto as its guardee (Dangl and Jones, 2001). Strikingly, another study proposed that some PRRs, such as LeFLS2, might function as the virulence targets of AvrPto and that Pto is a mimic receptor kinase that attracts AvrPto and triggers ETI as a decoy (van der Hoorn and Kamoun, 2008; Zhou and Chai, 2008).

As exemplified above, it is difficult to simply determine whether an effector target is a guardee or a decoy when the function of the target in defense has not been clearly revealed (Jones et al., 2016). As more effector targets are being identified in crops, it now appears that many effectors might have multiple targets involved in ETI and/or PTI (Jones et al., 2016; Kourelis and van der Hoorn, 2018); therefore, the guardee and decoy models may not easily differentiate in these complicated R-Avr interactions.

The Integrated Decoy Model. It has been widely recognized that many NLRs interact with other NLRs to form heterodimers (pairs) that either activate or suppress ETI in the absence of the pathogen. A more evolutionary elaboration model with paired NLRs is that one NLR (sensor) possesses an ID as decoy for sensing the presence of effectors, and the another NLR with canonical domains act as a helper in ETI activation (Jones et al., 2016; Adachi et al., 2019).

The well-studied NLR pairs that fit the integrated decoy model include RRS1/RPS4 in *Arabidopsis* and RGA4/RGA5 in rice (Cesari et al., 2014a; Le Roux et al., 2015; Sarris et al., 2015; Baggs et al., 2017). One of these NLR proteins targeted by the cognate effector contains a conserved ID as a decoy for effector binding (Cesari et al., 2014a). Pioneering research on the integrated decoy model in crops was performed on the rice NLRs RGA4 and RGA5 and their cognate *Magnaporthe oryzae* effectors AVR1-CO39 and AVR-Pia (Cesari et al., 2013; Cesari et al., 2014a; Cesari et al., 2014b; Kourelis and van der Hoorn, 2018). The interaction of RGA5 with AVR-Pia triggers an RGA4-dependent defense response (Cesari et al., 2014b). The ID HMA in RGA5 is important for AVR-Pia detection and RGA4-mediated immune activation (Cesari et al., 2014a). Because the ID in NLRs is essential for effector recognition (Cesari et al., 2014a; Baggs et al., 2017), use of the ID to extend effector recognition has been proposed as a method for engineering BSR in crops (Grund et al., 2019). Approximately 3.5%–5.0% of NLRs in plant genomes analyzed contained IDs (Kroj et al., 2016; Sarris et al., 2016), suggesting that NLRs with IDs are widespread in plants. A genome-wide NLR pair identification study also predicted that approximately 20% of NLRs are paired in the rice genome (Wang et al., 2019c). However, how many NLR pairs that contain IDs remains to be determined. For example, Pizh-1 and Pizh-2 are predicted to be paired NLRs that lack IDs in rice. Pizh-2 might act as a helper NLR involved in Pizh-1-mediated BSR to *Magnaporthe oryzae* (Xie et al., 2019). These findings suggest that paired NLRs lacking IDs might evolve different immune activation mechanisms.

NLR-Mediated Resistance Signaling Mechanisms in Crops

Despite many *R* genes identified in crops, the molecular mechanisms underlying *R*-mediated immune activation and signaling have only recently been elucidated using genetic, biochemical, and multi-omics approaches (Sun et al., 2020; van Wersch et al., 2020).

Posttranscriptional Regulation of NLRs. Because disease resistance often affects plant growth, *NLR* gene expression or ETI activation must be under strict control to limit fitness cost. One such regulatory mechanism is posttranscriptional regulation, which includes alternative splicing, alternative polyadenylation, and microRNA (miRNA)- and small interfering RNA (siRNA)-mediated suppression (Shivaprasad et al., 2012; Deng et al., 2017; Lai and Eulgem, 2018). Several miRNAs have been identified that regulate *NLR* expression in crops. For example, the miRNAs nta-miR6019 and nta-miR6020 target the *tobacco N* gene and guide the cleavage of *N* transcripts. Overexpressing *nta-miR6019* and *nta-miR6020* impairs *N*-mediated resistance to tobacco mosaic virus (Li et al., 2012). In addition, miR9863a and miR9863b are involved in cleaving *Mla1* in barley. Silencing of *miR9863* leads to induction of *Mla1* expression, whereas overexpressing *miR9863a* and *miR9863b* attenuates *Mla1*-mediated resistance and HR (Liu et al., 2014). The siRNA-mediated epigenetic regulation of *NLR* expression also plays a critical role in disease resistance. For example, *PigmR*-mediated resistance is subject to tight epigenetic regulation via RNA-directed DNA methylation, which balances rice blast resistance and yields (Deng et al., 2017).

Posttranslational Regulation of NLRs. NLR protein homeostasis must be strictly controlled to avoid autoimmunity cell death in plants (Li et al., 2015). The roles of the RAR1-SGT1-HSP90 chaperone complex and ubiquitin E3 ligases in controlling R protein degradation and dynamics during immune activation are well established (Sun et al., 2020; van Wersch et al., 2020) (Figure 1). In tobacco, the NLR protein, N, directly associates with HSP90, whose suppression impairs *N*-mediated resistance to tobacco mosaic virus (Liu et al., 2004). The UBR-box ubiquitin E3 ligase NbUBR7 interacts with and promotes degradation of the N protein. *NbUBR7* silencing significantly enhances virus resistance (Zhang et al., 2019b). Therefore, homeostasis of N protein levels is controlled by both the chaperone complex and ubiquitin E3 ligase. Similarly, the NLR MLA1 associates with both HvSGT1 and HvHSP90 in barley (Bieri et al., 2004). Moreover, the RING-type E3 ligase MIR1 mediates the ubiquitination-triggered degradation of MLA1, and overexpressing *MIR1* impairs *MLA1*-mediated disease resistance (Wang et al., 2016b). The RING-type E3 ligase APIP10 mediates degradation of the NLR protein Piz-t in rice; suppressing *APIP10* expression leads to the accumulation of Piz-t and autoimmunity cell death (Park et al., 2016). However, APIP10 does not interact with Piz-t, implying that an unknown component interacts with APIP10 to mediate the ubiquitination-based degradation of Piz-t. Whether other types of posttranslational modification also play important roles in NLR protein homeostasis and function require further investigation.

Key Components of NLR Signaling in Crops. Upon the perception of effectors by crop NLRs, a cascade of downstream immune signaling events is rapidly reprogrammed at the transcriptional level to inhibit pathogen invasion, in a process that includes the activity of many transcription factors (TFs) (Sun et al., 2020) (Figure 1). For example, the rice NLR Piz-t directly interacts with the bZIP-type TF APIP5 and positively regulates its accumulation and, in turn, APIP5 is required for the accumulation of Piz-t (Wang et al., 2016a). The plant-specific RRM domain-containing TF family member PIBP1 and its homologs interact with the CC domains of the NLR proteins Pigm, Piz-t, and Pi9, and are translocated into the nucleus to activate defense gene expression; mutations in these TF genes greatly impair NLR-mediated blast resistance in rice (Zhai et al., 2019). The NLR protein Pb1 interacts with WRKY45 through its CC domain, which prevents the ubiquitination-mediated degradation of this TF by the 26S proteasome, leading to the accumulation of WRKY45 to activate defense responses (Inoue et al., 2013; Matsushita et al., 2013). In barley, MLA10 interacts with the

TFs, WRKY1 and MYB6, which act as a repressor and an activator, respectively. MLA10 interacts with WRKY1 to release MYB6, thereby initiating immunity signaling (Chang et al., 2013). Thus, direct interactions with NLRs modulate the accumulation, subcellular localization, and transcriptional activity of TFs, which leads to the transcriptional reprogramming of defense responses (Figure 1). Manipulating these TF genes might provide BSR against different pathogens in crops.

The small GTPase OsRac1 and associated proteins form a well-known immune complex that functions downstream of R proteins in rice (Kawano et al., 2014) (Figure 1). OsRac1 is required for *Pit*- and *Pia*-mediated resistance (Chen et al., 2010b; Kawano et al., 2010). The guanine nucleotide exchange factor OsSPK1 interacts with Pit and RGA4 and acts as an activator of OsRac1 (Wang et al., 2018b). OsRac1 also interacts with PID3 and is essential for *PID3*-mediated blast resistance (Zhou et al., 2019). Notably, overexpressing the dominant negative form of *OsRac1* in tobacco compromised the *N*-mediated HR (Moeder et al., 2005), suggesting that this small GTPase plays conserved roles in *R* gene-mediated resistance in crop plants.

Crop Susceptibility Genes

Plant genes that are beneficial for pathogen infection and suppress host immune responses are generally referred as susceptibility (*S*) genes (van Schie and Takken, 2014). *S* genes are negative regulators of defense signaling and are usually targeted by pathogen effectors. Importantly, *S* genes also often function in plant growth; therefore, disease resistance tends to be associated with altered growth phenotypes and yield penalty (Langner et al., 2018; Zaidi et al., 2018). Several important *S* genes have been extensively studied in crops. For example, *mildew resistance locus O* (*Mlo*) was the first *S* gene identified in barley. The mutation of *Mlo* orthologs confers strong powdery mildew resistance in many other crops (Consonni et al., 2006; Bai et al., 2008; Humphry et al., 2011; Kim and Hwang, 2012; Wang et al., 2014c), suggesting that *Mlo* is a good candidate for powdery mildew resistance engineering.

Interestingly, many sugar transporter (*SWEET*) genes function as *S* genes (Langner et al., 2018). In rice, *OsSWEET11*, *OsSWEET13*, and *OsSWEET14* are hijacked by *Xoo* TALEs to supply sugar for the invading bacteria (Chen et al., 2010a) (Figure 1). Consequently, the recessive *xa13* (*Ossweet11*) and *xa25* (*Ossweet13*) alleles confer resistance against *Xoo* strains containing the cognate TALEs PthXo1 and PthXo2, respectively (Chu et al., 2006; Yang et al., 2006; Chen et al., 2010a; Antony et al., 2010). The rice plants, which contain mutations in the TALEs EBEs in the promoters of *OsSWEET11*, *OsSWEET13*, and *OsSWEET14*, were created by gene editing, and exhibited BSR against all *Xoo* strains tested with no obvious effects on other agronomic traits (Oliva et al., 2019; Xu et al., 2019), indicating their great potential for improving rice *Xoo* resistance. Therefore, *S* gene mutation-based resistance is likely to be more durable than *R* gene-mediated resistance in crops (van Schie and Takken, 2014), such as *pi21* (Fukuoka et al., 2009). Next, it is urgent to identify additional *S* genes and dissect novel susceptibility mechanisms to generate BSR for molecular breeding in crops.

Balancing Crop Disease Resistance and Yield

Disease resistance, particularly when it is associated with high levels of *R* gene expression and resistance, often results in fitness costs due to the tradeoff between defense and growth (Bergelson and Purrington, 1996; van Schie and Takken, 2014; Li et al., 2020). Therefore, understanding the molecular mechanisms underlying the growth/defense tradeoff is essential for designing breeding strategies to achieve both high yields and disease resistance (Brown, 2002; Deng et al., 2017; Karasov et al., 2017; Ning et al., 2017). The tradeoff between defense and plant growth is largely attributed to complex crosstalk among phytohormones, including salicylic acid, jasmonic acid, and ethylene for defense and gibberellins, auxin, and brassinosteroids (BRs) for growth (Spoel and Dong, 2008; Pieterse et al., 2012; Yang et al., 2012, 2013; Karasov et al., 2017; Bürger and Chory, 2019), and also to autoimmunity cell death and accumulation of reactive oxygen species (You et al., 2016; Gao et al., 2017; Li et al., 2017; Yin et al., 2018; Zhou et al., 2018).

In the model plant *Arabidopsis*, several studies reported that effective fine-tuning of the tradeoff between immunity and growth results from coordination between FLS2-mediated PTI signaling and BRI1-mediated BR signaling in a timely and cost-efficient manner (Lozano-Durán and Zipfel, 2015). The balance between defense and growth can be fine-tuned by altering the activity of key regulatory hubs. Rice plants harboring the TF gene *IDEAL PLANT ARCHITECTURE 1* (*IPA1*) have high yields (Jiao et al., 2010; Zhang et al., 2017). IPA1 fine-tunes the balance between disease resistance and growth via the differential activation of defense- and growth-related genes and directly interacts with SLR1 to regulate the gibberellin pathway (Wang et al., 2018a; Liu et al., 2019). NPR1 is a master regulator of plant immunity (Fu and Dong, 2013). Overexpressing *NPR1* enhances resistance against a variety of pathogens, but the transgenic plants show fitness costs in *Arabidopsis* and rice (Cao et al., 1998; Heidel et al., 2004; Yuan et al., 2007; Li et al., 2016). Notably, uORFs-mediated translational control of *Arabidopsis NPR1* generated BSR without the NPR1-induced growth penalty in transgenic rice (Xu et al., 2017). Therefore, it is possible that the expression patterns of *BSR* genes and other key defense regulators could be modulated to improve the balance between disease resistance and yield.

Elevated or reduced expression of *NLR* genes often results in growth inhibition and yield loss in plants (Tian et al., 2003; Chae et al., 2014; Sicard et al., 2015). The rice blast *R* locus *Pigm*, which was likely subjected to domestication selection, encodes the NLRs PigmR and PigmS. *PigmR*, which is constitutively expressed in all rice tissues, confers broad-spectrum blast resistance but has a negative effect on grain yield. PigmS physically associates with PigmR and dampens its effect on broad-spectrum blast resistance. *PigmS* is silenced by RNA-directed DNA methylation and is only expressed in pollen and not in leaves (the site of pathogen infection and PigmR activity). PigmS increases grain yield by promoting seed setting, thereby alleviating the yield penalty and maintaining both yield and strong disease resistance (Deng et al., 2017) (Figure 2). Therefore, evolution and domestication selection have shaped the defense/growth tradeoff and generated elite *NLR* loci with

Figure 2. High-Throughput Identification of Resistance Genes in Natural Blast Nursery.
Highly effective field evaluation of blast resistance can be performed from rice seedling **(A)** to mature heading stage **(E)** in the blast nursery. The blast fungal pathogen infects all plant tissues, mainly causing leaf blast and panicle blast **(B and C)**. Improvement of blast resistance using the broad-spectrum *Pi* genes, such as *Pigm* to provide efficient protection. The susceptible hybrid rice parent 9311 **(D)** was introduced with a *BSR* gene to develop the new elite variety 9311-R **(E)**, which exerts high level of resistance during the blast nursery trail, and has been widely used in rice production.

strong disease resistance and yield balance. However, more studies are needed to explore these types of elite loci in crop germplasm and the molecular mechanisms underlying domestication selection and the evolution of complex *NLR* loci in crops.

Breeding Strategies for Improving Disease Resistance in Crops

Exploiting Disease-Resistant Germplasm to Increase Crop Diversity

The declining genetic diversity of crops, mainly due to the continuous pursuit of high yield and monoculture, has placed modern crops at risk for disease epidemics (Reif et al., 2005). Wild species and landraces represent valuable resources for new *R* genes that might be effective against predominant races of pathogens (Figure 3A). Indeed, many *R* genes that are widely used in crop production were originally introgressed from wild species or landraces, such as *Yr36*, *Fhb7*, *Xa21*, *Xa23*, *Xa27*, and *CcRpp1* (Song et al., 1995; Gu et al., 2005; Fu et al., 2009; Wang et al., 2015, 2020a; Kawashima et al., 2016). *CcRpp1*, which was retrieved from a wild pigeon pea relative, confers full resistance to soybean rust (Kawashima et al., 2016); and *Fhb7*, which was introgressed from a wild wheat relative confers strong resistance to *Fusarium* head blight (Wang et al., 2020a). Therefore, landraces and wild relatives are often exploited to identify new *R* genes for improving modern cultivars (Feuillet et al., 2008; Dwivedi et al., 2016).

To identify effective *R* genes or elite alleles for breeding programs, it is essential to utilize an efficient field trial platform for resistance evaluation. Natural nursery-based selection for most pandemic pathogens should be established for large-scale screening of resistant germplasm resources, particularly those with BSR (Figure 3B). With high-pressure selection of natural nurseries, plants are subject to continuous and mixed infection by various types of pathogens in whole growth stage, thus, novel resistance genes, including those unique PRRs and NLRs conferring BSR resistance will be identified more efficiently with great potential of breeding application. For example, *Pigm*-mediated BSR was evaluated using a blast nursery test over multiple years and locations in combination with inoculation with hundreds of isolates in the laboratory to ensure its resistance and potential for rice breeding (Deng et al., 2006, 2017) (Figure 2).

High-Throughput Genomic Approaches for Identifying New R Genes

In recent years, rapid advancements in genome sequencing and bioinformatics have led to the development of novel strategies to accelerate *R* gene cloning (Wulff and Moscou, 2014) (Figure 3C). Mapping-by-sequencing is a powerful tool for mapping and cloning important genes in plants (Austin et al., 2011; Abe et al., 2012; Mascher et al., 2014). Genome-wide association studies have been widely used to identify genes and the genetic architecture of many agronomic traits in crops (Huang et al., 2010, 2011; Samayoa et al., 2015; Li et al., 2019b). Several new blast resistance genes have been mapped via genome-wide association studies of large rice germplasm collections (Wang et al., 2014a; Kang et al., 2016), leading to the identification of the *R* gene *LABR_64* (Kang et al., 2016) and the partial resistance gene *PiPR1* (Liu et al., 2020).

Another powerful method for *R* gene identification is resistance gene enrichment sequencing (RenSeq), which can be used to isolate new *NLR*-like genes from wild species or landraces (Jupe et al., 2013). MutRenSeq, a technique that combines RenSeq and EMS mutagenesis to identify *NLR* genes, was used to rapidly isolate two wheat stem rust resistance genes: *Sr22* and *Sr45* (Steuernage et al., 2016). In addition, the TACCA method was successfully used to isolate the *R* gene *Lr22a* from polyploid wheat genomes (Thind et al., 2017). MutChromSeq, combining EMS mutagenesis, chromosome flow sorting, and high-throughput sequencing, was used to identify the gene *Pm2* (Sánchez-Martín et al., 2016). Finally, AgRenSeq, which combines association genetics with the RenSeq strategy to exploit pan-genome variations, is suitable for cloning *R* genes in crops with diverse germplasm panels, with case studies on

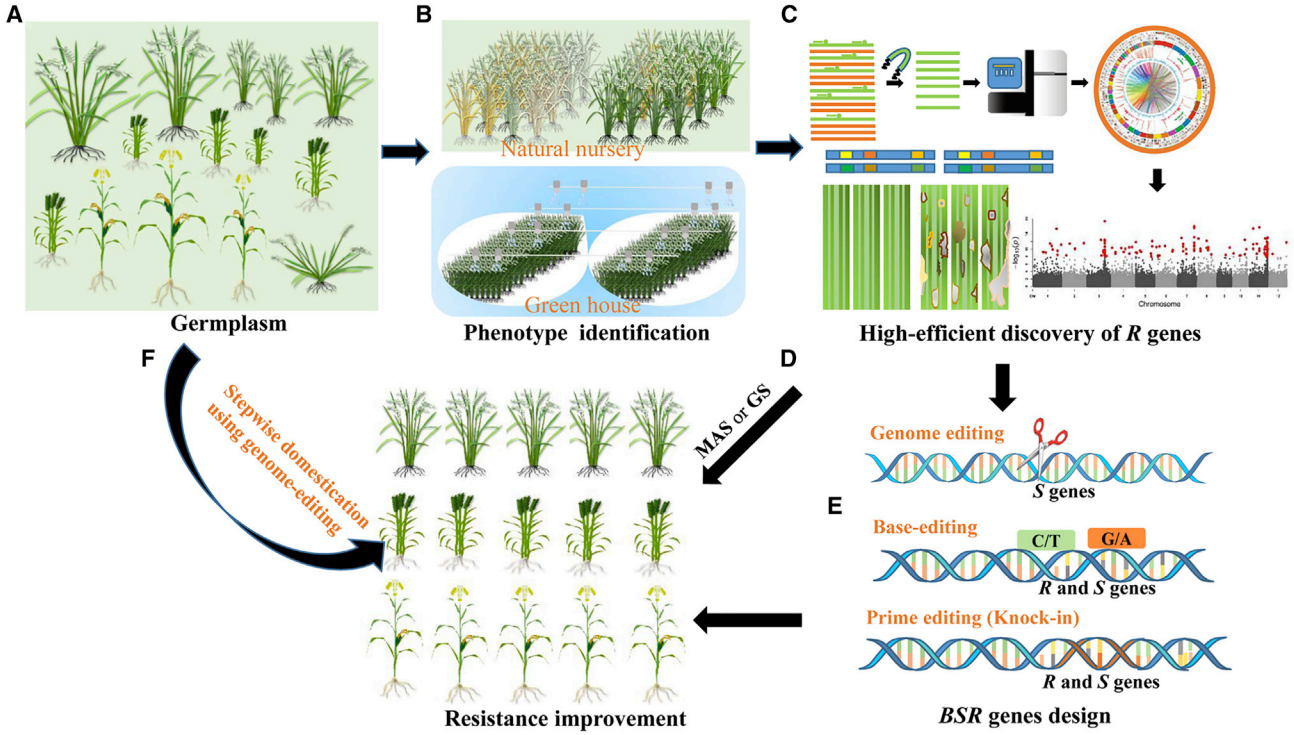

Figure 3. Breeding Strategies for Improving Disease Resistance in Crops.

(A) Large collections of germplasm are available for major crops.

(B) Disease resistance can be screened in a natural disease nursery in combination with high-throughput inoculation screening in the greenhouse.

(C) High efficient mapping-by-sequencing strategies can be used for rapid discovery of new *R* genes.

(D) The cloned *R* genes can be directly utilized in crop breeding for disease resistance by markers-aid-selection (MAS), genome selection (GS), or a transformation approach.

(E) The new genome-editing technique can be applied to create elite *BSR* genes by modifying *S* and *R* genes.

(F) A stepwise *de novo* domestication strategy can be adopted to improve crop resistance against multiple pathogens.

Sr33, *Sr45*, *Sr46*, and *SrTA1662* in wheat (Arora et al., 2019). Therefore, combining mapping-by-sequencing and mutagenesis is an efficient strategy for identifying new *R* genes in cultivars and wild species.

Allele mining is a simple, effective approach for identifying elite alleles of *R* genes from landraces and wild relatives (Kumar et al., 2010; Ashkani et al., 2015). To date, this approach has been used to identify novel alleles of many major blast *R* genes from different cultivated rice varieties and wild species, such as the *Pi54*, *Pid3*, and *Pi-ta* loci (Huang et al., 2008; Lv et al., 2013; Devanna et al., 2014; Vasudevan et al., 2015).

Engineering BSR Genes by Expanding NLR Recognition Specificity

R gene-mediated resistance tends to be short-lived because of changes in pathogen virulence (McDonald and Linde, 2002). Genetic engineering of NLR variants might provide a solution to this bottleneck, given that engineered NLRs can recognize a broader range of pathogen effectors. Different conserved motifs or IDs of NLRs can be modified to acquire new capacity to improve disease resistance to different strains or even different pathogens (Segretin et al., 2014). Considering that only a few nucleotide differences between the coding regions of resistance alleles, CRISPR-mediated homology-directed repair and prime genome-editing technology can be used to generate new *R* alleles with an expanding resistance spectrum (Chen et al., 2019; Lin et al., 2020) (Figure 3E). For example, the blast resistance NLRs, Pi2 and Piz-t, differ by only eight amino acids in the LRR region (Zhou et al., 2006), which could be edited or inter-replaced to change or expand resistance spectrum. Similarly, SNP differences exist in many resistant and susceptible alleles, and single base-pair editing technology could be used to generate the resistance allele in a high-yielding susceptible variety, such as for the blast *R* genes *Pi-ta*, *Pid2*, and *Pid3* (Bryan et al., 2000; Chen et al., 2006; Shang et al., 2009). Moreover, the IDs or decoys of NLRs could be modified to expand the effector recognition specificity and resistance spectrum (Maqbool et al., 2015; Kim et al., 2016). Thus, diverse *R* variants can be generated by CRISPR-Cas9-based technology for selection of desired BSR in crops. In addition, genome editing could also be used to develop *NLR* gene pyramids rapidly via *in situ* gene editing in the same *NLR* cluster in which some NLRs have lost function, and to engineer chimeric immune receptors that could be activated upon different ligands binding in transgenic plants (He et al., 2000; Brutus et al., 2010; Kishimoto et al., 2010; Mueller et al., 2012), providing a paradigm for new immune receptor design in crops.

Interestingly, the genome-editing approach was used to modify the domestication-related genes to accelerate the transfer of biotic and abiotic stress tolerance from wild species or

landrace to modern varieties (Li et al., 2018). Therefore, a stepwise *de novo* domestication strategy can be adopted to improve crop resistance against multiple pathogens (Fernie and Yan, 2019; Li et al., 2018) (Figure 3F). In addition, recently developed CRISPR-mediated base editors were used to create novel genetic variations in the rice OsALS1 protein to develop elite varieties with tolerance to herbicide (Kuang et al., 2020). This technology can be easily adopted to create new elite *R* alleles for breeding crop varieties with BSR and without yield penalties.

Genome Editing of Executor Genes in Crops

The function of executor *R* genes is dependent on the direct binding of TALEs secreted from pathogens to specific EBEs in their promoters for defense activation (Zhang et al., 2015). Five executor *R* genes and their cognate TAL effector genes have been cloned in rice and pepper, including *Xa27*, *Bs3*, *Bs4C-R*, *Xa10*, and *Xa23* (Gu et al., 2005; Romer et al., 2007; Strauss et al., 2012; Tian et al., 2014; Wang et al., 2015; Zhang et al., 2015). These executor *R* genes are good candidates for engineering BSR to bacterial pathogens that contain cognate TALEs by editing the promoter regions of susceptible alleles of these genes to create *in situ* executor *R* genes (Figure 3E). In susceptible cultivars lacking executor *R* genes, TALEs-binding elements can be inserted in the promoters of BSR genes, such as *NPR1* to create a binding "trap" thereby activating defense responses to a broad range of pathogens and avoid of defense cost in crops.

Genome Editing of S Genes in Crops

Several *S* genes have been successfully edited by CRISPR-Cas9 to create rice and wheat plants with BSR (Wang et al., 2014c; Zaidi et al., 2018; Eom et al., 2019; Oliva et al., 2019; Xu et al., 2019). As most *S* genes are involved in regulating the growth, development, or metabolic processes of plants, mutating *S* genes usually creates BSR with fitness costs (Li et al., 2020). Hence, CRISPR-mediated base genome editing could be used to create artificial mutations of *S* genes, which generate new elite alleles conferring BSR but decreasing, or without, defense costs, as recently reported for the editing of rice *SWEET* genes (Oliva et al., 2019; Xu et al., 2019) (Figure 3E). In addition, key virulence targets, which are usually beneficial for pathogen infection and nutrition acquisition, may be important targets using CRISPR-Cas9 technology to enhance plant disease resistance in crops.

CONCLUDING REMARKS

Crop improvement for disease resistances requires new *R* genes and knowledge of disease resistance. Most *R* genes encode NLRs that recognize pathogen effectors to trigger defense responses, but less is known about the mechanisms underlying NLR-mediated resistance, particularly the downstream signaling of ETI in crops. Therefore, further studies are needed to dissect NLR-Avr interactions and immune signaling in crops. In particular, the immune machinery in crops is likely somehow different from that in the model plant *Arabidopsis* owing to extensive domestication and breeding selection (Soltis et al., 2018); the *NLR* genes especially have been positively selected in rice (Huang et al., 2010). The WAK family in crops is more than fourfold expanded in crops compared that in *Arabidopsis*, and the TALEs-executor *R* genes are absent in *Arabidopsis* (Kanneganti and Gupta, 2008; Zhang et al., 2015; Zuo et al., 2015; Saintenac et al., 2018). The diversity and functionality of *NLR*s might have been shaped by their original agro-ecological conditions. A recent pan-NLRome study in *Arabidopsis* suggested that many *NLR* genes are also under strong diversifying selection, resulting in the arms race between the host and pathogen (Van de Weyer et al., 2019). Therefore, it is worth investigating how evolution and domestication drive *NLR* selection in crops. In the context of this scenario, it is important to understand how NLRs dominate the arms race with pathogen effectors to ensure efficient disease resistance in crops when they are exposed to frequently changing pathogen populations in the field.

Recent advances on genome sequencing and bioinformatic technologies have led to the discovery of new *R* genes/alleles via high-throughput, large-scale analyses, which will facilitate further improvement of disease resistance in crops, including disease resistance against important recalcitrant diseases, such as rice false smut caused by *Ustilaginoidea oryzae*, sheath blight caused by *Rhizoctonia solani*, and emerging rice spikelet rot caused by mixed infection of *Fusarium* and *Alternaria*. In modern crop design, on the one hand, the balance between disease resistance and yield should be considered. On the other hand, the integration of pathogen/pest resistance with abiotic stress tolerance into a crop variety is also desirable, because the regulation of these processes in many cases is linked via recruiting common hormone signaling pathways, which may affect both traits simultaneously. The development of new breeding approaches, such as *R* gene engineering and editing, will be an important theme in future crop breeding toward improved disease resistance.

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