Exploiting Broad-Spectrum Disease Resistance in Crops: From Molecular Dissection to Breeding

Article *in* Annual review of plant biology · April 2020

DOI: 10.1146/annurev-arplant-010720-022215

5 authors, including:

Yiwen Deng
Shanghai Institute of Plant Physiology and Ecology
17 PUBLICATIONS **608** CITATIONS
SEE PROFILE

Yuese Ning
Institute of Plant Protection, Chinese Academy of Agricultural Sciences
39 PUBLICATIONS **1,247** CITATIONS
SEE PROFILE

Zuhua He
Chinese Academy of Sciences
132 PUBLICATIONS **4,807** CITATIONS
SEE PROFILE

Annual Review of Plant Biology

Exploiting Broad-Spectrum Disease Resistance in Crops: From Molecular Dissection to Breeding

Wei Li,[1,2,*] Yiwen Deng,[3,*] Yuese Ning,[1,*] Zuhua He,[3] and Guo-Liang Wang[1,4]

[1]State Key Laboratory for Biology of Plant Diseases and Insect Pests, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China; email: wang.620@osu.edu

[2]Hunan Provincial Key Laboratory for Biology and Control of Plant Diseases and Insect Pests, College of Plant Protection, Hunan Agricultural University, Changsha 410128, China

[3]National Key Laboratory of Plant Molecular Genetics, CAS Center for Excellence in Molecular Plant Sciences, Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences, Shanghai 200032, China; email: zhhe@sibs.ac.cn

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

Annu. Rev. Plant Biol. 2020. 71:25.1–25.29

The *Annual Review of Plant Biology* is online at plant.annualreviews.org

https://doi.org/10.1146/annurev-arplant-010720-022215

*These authors contributed equally to this article

Keywords

broad-spectrum resistance, pattern recognition receptor, nucleotide-binding and leucine-rich repeat receptor, NLR, QTL, susceptibility gene, durable resistance, plant immunity, molecular breeding

Abstract

Plant diseases reduce crop yields and threaten global food security, making the selection of disease-resistant cultivars a major goal of crop breeding. Broad-spectrum resistance (BSR) is a desirable trait because it confers resistance against more than one pathogen species or against the majority of races or strains of the same pathogen. Many BSR genes have been cloned in plants and have been found to encode pattern recognition receptors, nucleotide-binding and leucine-rich repeat receptors, and defense-signaling and pathogenesis-related proteins. In addition, the BSR genes that underlie quantitative trait loci, loss of susceptibility and nonhost resistance have also been characterized. Here, we comprehensively review the advances made in the identification and characterization of BSR genes in various species and examine their application in crop breeding. We also discuss the challenges and their solutions for the use of BSR genes in the breeding of disease-resistant crops.

Contents

1. INTRODUCTION

1.1. Plant Diseases in Crop Production

Plant diseases caused by pathogenic fungi, oomycetes, bacteria, viruses, and nematodes cause huge yield losses annually. A recent survey showed that crop losses caused by pathogens and pests worldwide range from 10.1% to 28.1% in wheat (*Triticum aestivum*), 24.6% to 40.9% in rice (*Oryza sativa*), 19.5% to 41.1% in maize (*Zea mays*), 8.1% to 21.0% in potato (*Solanum tuberosum*), and 11.0% to 32.4% in soybean (*Glycine max*) (157, 160). In addition to reducing yields, plant diseases reduce crop quality and economic value and can cause food poisoning in humans and animals. The development of highly resistant cultivars is an economical and eco-friendly alternative to expensive and environmentally harmful chemical controls.

1.2. Use of BSR in Crop Production

Broad-spectrum resistance (BSR) refers to resistance against more than one pathogen species or against most races or strains of the same species (80). Plant breeders have relied on the use of single dominant or recessive resistance (R) genes because of their strong effects and ease of selection. Most *R* genes confer race-specific resistance against a single or few pathogen strains; however, mutations and virulence shifts in pathogen populations make the effectiveness of these race-specific *R* genes short-lived. In contrast to the high level of race-specific resistance conferred by *R* genes, the partial resistance controlled by quantitative trait loci (QTLs) is usually nonrace specific. This partial resistance is generally insufficient to defend against pathogen attack, especially in epidemic years. Although combining *R* genes and QTLs in the same genetic background is effective for disease control, integrating both types of resistance in an elite cultivar is technically challenging and time consuming. For these reasons, the selection of new cultivars with BSR, which is usually durable (195), has become an important crop breeding goal. In this review, we classify BSR into species-nonspecific (SNS) BSR, which confers resistance against two or more pathogen species, and race-nonspecific (RNS) BSR, which confers resistance against two or more races or strains of the same pathogen (195). **Supplemental Tables 1** and **2** list the SNS- and RNS-BSR plant genes that have been cloned to date.

1.3. Plant Immune System

Plants use a two-tiered innate immune system to defend against pathogen infection. The first layer of defense is triggered by the recognition of pathogen-associated molecular patterns (PAMPs) by membrane-associated pattern recognition receptors (PRRs), leading to PAMP-triggered immunity (PTI) (13). The second layer results from the recognition of pathogen avirulence (Avr) effectors by the nucleotide-binding and leucine-rich repeat receptors (NLRs) and other types of cytoplasmic proteins and often leads to the robust, race-specific effector-triggered immunity (ETI) (71). Although PTI is generally weaker than ETI, the opposite situation has been observed in some cases, while in others, it is not easy to clearly distinguish PTI from ETI (182).

R genes encode surface receptors [such as receptor-like kinases (RLKs)] or intracellular receptors (such as NLRs) that can detect cognate pathogen effectors directly or indirectly. Several genes encoding cell wall–associated kinases (WAKs) are also involved in pathogen detection. The PTI and ETI pathways involve numerous defense-signaling genes, such as those encoding receptor-like cytoplasmic kinases (RLCKs), mitogen-activated protein kinases (MAPKs), enzymes for epigenetic regulation and protein degradation, transcription factors (TFs), and other signaling molecules. In addition, pathogen infection induces the expression of many pathogenesis-related

Broad-spectrum resistance (BSR): plant disease resistance against at least two pathogen species or to multiple strains or races of one pathogen species

Resistance (R) genes: genes that confer disease resistance against pathogens and encode surface receptors (such as receptor-like kinases) or intracellular receptors (such as NLRs) that can detect cognate pathogen effectors directly or indirectly

Quantitative trait locus (QTL): a specific chromosomal region or genetic locus responsible for the variation of a quantitative trait in the phenotype of a population of organisms

Species-nonspecific broad-spectrum resistance (SNS BSR): plant disease resistance against more than one pathogen species

Race-nonspecific broad-spectrum resistance (RNS BSR): plant disease resistance against multiple races or strains of the same pathogen species

(PR) genes, resulting in the production of antimicrobial proteins such as defensins, proteases, protease inhibitors, or enzymes involved in the generation of reactive oxygen species (ROS) and the accumulation of secondary metabolites for cell wall cross-linking and the deposition of lignin and callose as well as phytoalexins (*6*). Furthermore, many genes underlying QTLs associated with susceptibility (*S*) and nonhost resistance (NHR) have recently been cloned and used in crop breeding (131). This review focuses on our current understanding of the structure and function of the BSR genes that have been cloned in plants, in addition to the strategies used to introduce these genes into crops.

Pathogen-associated molecular patterns (PAMPs): small molecular motifs conserved within a class of microbes and are recognized by cell surface pattern recognition receptors in both plants and animals

Pattern recognition receptors (PRR): receptor proteins capable of recognizing PAMPs or the damage-associated molecular patterns

Pathogen-associated molecular pattern-triggered immunity (PTI): a cascade of defense response via the recognition of the conserved PAMPs or microbe-associated molecular patterns by PRRs

Nucleotide-binding and leucine-rich repeat receptor (NLR) proteins: a class of cytoplasmic immune receptors in both plants and animals that contain the nucleotide-binding and leucine-rich repeat motifs

Effector-triggered immunity (ETI): a protective immune response in host initiated by the recognition of pathogenic effectors or toxins

2. STRUCTURE AND FUNCTION OF THE SPECIES-NONSPECIFIC BSR PROTEINS

2.1. Membrane-Associated Pattern Recognition Receptors

PAMPs are generally important for microbial survival or fitness and are therefore evolutionarily conserved. Plants perceive the PAMPs via cell surface PRRs that quickly activate immune responses. Plant PRRs are plasma membrane–localized RLKs or receptor-like proteins (RLPs) (71). Five PRRs from *Arabidopsis thaliana*, rice, and potato have been reported to confer SNS BSR (**Supplemental Table 1**). The first RLK-PRR to be characterized, FLAGELLIN SENSING 2 (FLS2) in *Arabidopsis*, confers SNS BSR against several genera of flagellated bacteria, including *Pseudomonas* (38), and heterologous expression of *FLS2* in other plant species enhances their resistance against many bacterial species (152). The bacterial PAMP elf18, a conserved N-terminal epitope of the elongation factor (EF) Tu, is recognized by the RLK-PRR EF-TU RECEPTOR (EFR), which functions as an SNS-BSR protein to regulate *Arabidopsis* resistance against different bacterial pathogens (84, 86). The transgenic expression of *Arabidopsis EFR* in *Nicotiana benthamiana*, tomato (*Solanum lycopersicum*), potato, rice and *Medicago truncatula* activates SNS BSR against several pathogenic bacteria (12, 86, 141, 161). *Xa21* was the first RLK-PRR *R* gene to be cloned in crops and confers resistance against multiple strains of the rice bacterial blight pathogen *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and partial resistance against multiple strains of the bacterial leaf streak pathogen *X. oryzae* pv. *oryzicola* (*Xoc*) (90, 191). Moreover, heterologous expression of *Xa21* in citrus (*Citrus* sp.), *Arabidopsis*, and banana (*Musa* sp.) conferred resistance against several bacterial pathogens (56, 137, 183). The Lysin motif-containing proteins LYP4 and LYP6 in rice are dual-role PRRs that sense bacterial peptidoglycan and fungal chitin, activating immunity against bacteria and fungi (100). In potato, the RLP-PRR elicitin response (ELR) recognizes extracellular elicitin, a conserved molecular pattern produced by *Phytophthora* species, and mediates SNS BSR against multiple species of this oomycete (34). In addition to ELR, the RLP-PRR RLP23 in *Arabidopsis* was reported to form a tripartite complex with the LRR receptor kinases Suppressor Of BIR1-1(SOBIR1) and BRI-associated kinase (BAK1) to regulate microbial protein Necrosis and ethylene-inducing peptide 1-like protein (NLP)-triggered immunity (4). The ectopic-expressed RLP23 in potato can recognize NLP and induce SNS BSR to oomycete *Phytophthora infestans* and fungus *Sclerotinia sclerotiorum*. These results demonstrate that PRRs that recognize widespread microbial patterns might be particularly suited for engineering immunity in crop plants (4).

2.2. Nucleotide-Binding and Leucine-Rich Repeat Receptor Proteins

The first identified SNS-BSR NLR proteins are the linked *Arabidopsis* RESISTANCE TO RALSTONIA SOLANACEARUM1 (RRS1) and RESISTANCE TO PSEUDOMONAS SYRINGAE4 (RPS4) that function cooperatively as a dual *R*-gene system against bacterial and

fungal pathogens (129). RPS4 works with RRS1 as a pair to trigger a hypersensitive reaction (HR) against *Pseudomonas syringae* containing AvrRps4. Apart from AvrRps4, RRS1/RPS4 also recognize the effector PopP2 from *Ralstonia solanacearum* (129). Moreover, both RRS1 and RPS4 are required for resistance against the fungal pathogen *Colletotrichum higginsianum*, probably through recognizing an unknown effector (10, 129). Recently, the NLR protein RECOGNITION OF XOPQ 1 (Roq1) in *N. benthamiana* was shown to recognize the effectors of two bacterial species. It physically interacts with HopQ1 from *Pseudomonas* as well as XopQ alleles from various *Xanthomonas* species in the presence of the resistance regulator Enhanced Disease Susceptibility 1 (EDS1) (160). N REQUIREMENT GENE 1 (NRG1) was recently found to be a key protein acting downstream of EDS1 to mediate various Toll/IL-1 receptor-NLR (TNL) signaling pathways, including those contributing to the *Roq1*-mediated resistance to *Xanthomonas* and *Pseudomonas* and to *XopQ*-regulated transcriptional changes in *N. benthamiana* (146). The mechanism of SNS BSR mediated by RRS1/RPS4 and Roq1 warrants further investigation.

2.3. Defense-Signaling Proteins

Following the perception of PAMPs or effectors, the PRRs or NLRs (or other R proteins) activate complex, interconnected signaling pathways that are involved in many biological processes, including protein–protein interactions, posttranslational modifications, epigenetic regulation, transcriptional regulation, and calcium ion signaling. The defense-signaling genes play positive or negative roles in these signaling processes. A total of 42 defense-signaling genes are known to be involved in SNS BSR (listed in **Supplemental Table 1**).

MAPKs are well-known defense-signaling proteins that transduce defense signals from the immune receptors to the downstream proteins; for example, OsMAPK5 negatively regulates rice resistance against both the bacterial pathogen *Burkholderia glumae* and the fungus *Magnaporthe oryzae* (198). Similarly, OsMPK15 negatively regulates *PR* gene expression and ROS accumulation, with the *osmpk15* knockout mutant having enhanced SNS BSR against *Xoo* and multiple *M. oryzae* strains (57). In addition, two MAPK cascade components in soybean, GmMPK4 and GmMEKK1, negatively regulate plant cell death, *PR* gene expression, the accumulation of salicylic acid (SA) and ROS, and resistance against multiple species of pathogens (105, 200).

In addition to the MAPKs, other types of kinases, such as the RLKs and RLCKs, also function as SNS-BSR proteins (**Supplemental Table 1**); for example, overexpression of the RLCK-like *BROAD-SPECTRUM RESISTANCE 1* (*BSR1*) gene confers BSR against at least two major bacterial species and two major fungal species in rice (115). Two rice WAKs, OsWAK25 and OsWAK91, are important for SNS BSR against *M. oryzae* and *Xoo* (3, 30, 49).

Protein ubiquitination-mediated degradation also plays an important role in SNS BSR (24). The rice U-box E3 gene *SPOTTED LEAF 11* (*Spl11*) encodes a negative regulator of cell death, and the *spl11* mutant has increased SNS BSR against *M. oryzae* and *Xoo* (212). The knockout of the gene encoding the SPL11-interacting Protein 6 (SPIN6) also increases plant resistance against these two pathogens (104). Another multisubunit E3 ubiquitin ligase, Cullin3a (OsCUL3a), negatively regulates rice cell death and SNR BSR against *M. oryzae* and *Xoo* by targeting and degrading NONEXPRESSER OF PATHOGENESIS-RELATED 1 (OsNPR1) (107). OsBAG4, the rice homolog of human BAG (Bcl2-associated athanogene), forms a module with the RING domain E3 ubiquitin ligase Enhanced Blight and blast Resistance 1 (EBR1) to control programmed cell death and SNS BSR against *M. oryzae* and *Xoo* (207).

Proteins functioning in epigenetic modification appear to be key regulators of SNS BSR; for example, silencing *HISTONE H4 DEACETYLASE GENE 701* (*HDT701*) in rice enhanced resistance against *M. oryzae* and *Xoo* (33). These results demonstrate that genes involved in protein degradation or epigenetic modification make important contributions to SNS BSR.

Wall–associated kinases (WAKs): a class of plant receptor–like kinases which contain extracellular galacturonan-binding domain, transmembrane domain, and cytoplasmic serine threonine kinase domain

Defense-signaling genes: genes that function in signal transduction pathways that link pathogens recognition to defense activation

Pathogenesis-related (*PR*) genes: genes that are downstream components of defense response and responsible of production of antimicrobial agents

Nonhost resistance (NHR): plant disease resistance against all nonadapted pathogens; the most common form of disease resistance exhibited by plants against the majority of potentially pathogenic microorganisms

TFs are critical components of plant immune signaling and key regulators of defense-related gene expression. Several WRKY TFs are involved in SNS BSR in rice; for example, the overexpression of *OsWRKY45-1* or *OsWRKY45-2* activated the defense response against *M. oryzae* but suppressed the response against *Rhizoctonia solani* (163, 181). Furthermore, these two genes play opposite roles in rice–bacterium interactions: *OsWRKY45-1* negatively regulates rice resistance against *Xoo* and *Xoc*, but *OsWRKY45-2* positively regulates rice resistance against *Xoo* and *Xoc* (163, 181). In addition, *OsWRKY67*, *OsWRKY30*, *OsWRKY62*, and *OsWRKY76* function as SNS BSR genes in rice (102, 140, 186). In cucumber (*Cucumis sativus*), the ethylene response factor TF gene *CsERF004* positively regulates the expression of several *PR* genes, the levels of the defense hormones, and the levels of SA and ethylene, and the overexpression of this gene confers SNS BSR against *Corynespora cassiicola* and *Pseudoperonospora cubensis* (101).

As a central defense-signaling protein, NPR1 and its homologs NPR3 and NPR4 are SA receptors that activate SA-mediated systemic acquired resistance by transcriptionally activating defense genes in *Arabidopsis* (18, 41, 215). *NPR1* overexpression confers SNS BSR against the bacterial pathogen *P. syringae* and the oomycete pathogen *Phytophthora parasitica* in a dosage-dependent manner. The heterologous expression of *Arabidopsis NPR1* or its orthologs induces SNS BSR in many other plant species (165); for example, the expression of *NPR1* in rice increases resistance against *Xoo*, *M. oryzae*, *Fusarium verticillioides*, and *Erwinia chrysanthemi* (25, 150). However, it is worth noting that *NPR1* overexpression often leads to autoimmunity and pleiotropic phenotypes in transgenic plants.

2.4. Pathogenesis-Related Proteins

The dynamic and robust transduction of defense signaling during the early stages of infection by many different pathogens leads to the rapid production of defense enzymes, defensins, thaumatin-like proteins, and secondary metabolites including phytoalexins. It also leads to the generation of ROS, callose deposition and cell wall modifications, and/or the activation of programmed cell death in plants in an attempt to inhibit pathogen infection. The production of these antimicrobial agents is regulated by the *PR* genes, which are ubiquitous in plants and effective against a variety of pathogens. Three types of *PR* genes that contribute to SNS BSR are listed in **Supplemental Table 1**. SNS BSR of these *PR* genes is usually achieved by overexpressing them in transgenic plants. For example, the overexpression of the pepper gene *Capsicum annuum ANTIMICROBIAL PROTEIN1* (*CaAMP1*) in *Arabidopsis* increased resistance against various pathogens (89). Moreover, the overexpression of the motherwort (*Leonurus japonicus*) gene *LjAMP2*, encoding an antimicrobial protein, in white poplar (*Populus tomentosa*) conferred SNS BSR against multiple fungal pathogens (64).

Phytohormone synthesis–related proteins such as the rice ethylene biosynthesis enzyme 1-aminocyclopropane-1-carboxylic acid synthase 2 (OsACS2) also function in BSR. The overexpression of *OsACS2* enhances ethylene production, defense gene expression, and resistance to a field isolate of *R. solani* and multiple strains of *M. oryzae* (53). Interestingly, there is little or no difference between *OsACS2* overexpression plants and the wild-type plants in agronomic traits, which is ideal for rice resistance breeding. In addition, a rice homologue of mammalian selenium-binding proteins, *OsSBP*, also functions as a BSR PR gene (158). OsSBP positively regulates rice defense gene transcription and phytoalexin accumulation after *M. oryzae* infection and H_2O_2 accumulation after treatment by the protein phosphatase inhibitor calyculin A. As a result, overexpression of *OsSBP* activates rice disease resistance against *Xoo* and *M. oryzae* (158).

2.5. Susceptibility Proteins

Susceptibility (*S*) gene: any plant gene that facilitates the infection process or supports compatibility with a pathogen

Plant genes that facilitate pathogen infection and contribute to susceptibility are termed Susceptibility (*S*) genes (210). Loss-of-function mutations in *S* genes (recessive alleles) substantially reduce the compatibility between hosts and pathogens and thus result in resistance against a diverse array of pathogens. The *S* genes are usually targeted and induced by pathogens to negatively regulate host resistance. Over the past two decades, 11 *S* genes affecting SNS BSR have been identified in crops (**Supplemental Table 1**). For example, *Xa5*, encoding a γ-subunit of the TF IIA, was the first *S* gene to be identified in rice and was found to negatively regulate SNS BSR against multiple isolates of *Xoo* (66) and *Xoc* (209). *Xa13/OsSWEET11* encodes a sugar transporter that facilitates bacterial and fungal infections, and the loss of its function confers SNS BSR against *Xoo* and *R. solani*. A recent study reported that CRISPR/Cas9-mediated mutations in the promoters of *OsSWEET11* and its homologs *OsSWEET13* and *OsSWEET14* provide BSR to all tested *Xoo* strains collected in Asia and Africa (136). In addition, the team reported the development of a diagnostic kit, SWEET^{R} kit 1.0, to detect induction of *OsSWEET11*, *OsSWEET13* and *OsSWEET14* in the engineered reporter rice lines to visualize SWEET protein accumulation and identify suitable resistant lines for farmers (26, 36, 44).

Recently, *BROAD-SPECTRUM RESISTANCE KITAAKE-1* (*Bsr-k1*) was cloned in rice and was found to encode a tetratricopeptide repeat domain RNA-binding protein that negatively regulates SNS BSR. *Bsr-k1* knockout resulted in the upregulated expression of the rice phenylalanine ammonia lyase genes (*OsPALs*) and enhanced resistance against *M. oryzae* and *Xoo* (220). Similarly, the tomato *eukaryotic translation initiation factor* genes *eIF4E1* and *eIF4E2* function as *S* genes that negatively regulate SNS BSR (120). The knockdown of both genes activates tomato resistance against many potyviruses, including *Potato virus Y*, *Tobacco etch potyvirus*, *Pepper mottle virus*, *Ecuadorian rocoto virus*, and *Pepper severe mosaic virus* (120).

The *Arabidopsis* protein Downy Mildew Resistant 6 (DMR6) belongs to a superfamily of 2-oxoglutarate Fe(II)-dependent oxygenases, and its production is enhanced in response to pathogen infection (185). The knockout of *DMR6* enhances the expression of defense-related genes and increases SA levels, resulting in SNS BSR against many bacterial, fungal, and oomycete pathogens (135, 185, 211). Similarly, the knockout of the genes *SPOTTED LEAF 28* (*SPL28*, encoding a clathrin-associated adaptor protein), *ABSCISIC ACID2* (*OsABA2*, alcohol dehydrogenase), *OsPLDβ1* (phospholipase D), *Suppressor of Salicylate Insensitivity of npr1–5* (*OsSSI2*, stearoyl acyl carrier protein fatty acid desaturase), and *OsDRP1E* (dynamin-related protein) in rice resulted in SNS BSR against *M. oryzae* and *Xoo*, although all the mutants underwent cell death (65, 96, 97, 148, 201).

2.6. Quantitative Trait Loci

Compared with the major gene-mediated resistance, quantitative resistance controlled by QTLs is usually thought to be nonrace specific and more durable. To date, four QTLs contributing to SNS BSR have been cloned in wheat, maize, and cucumber (**Supplemental Table 1**). The genes *Lr67/Yr46* and *Lr34/Yr18/Pm38*, cloned in wheat, confer SNS BSR against important diseases. *Lr67/Yr46* encodes a hexose transporter that confers partial resistance against multiple pathogens, including pathogens that cause leaf rust, stripe rust, stem rust, and powdery mildew in wheat (54, 169). The transporter encoded by *Lr67/Yr46* is believed to modulate hexose transport in the infected leaves, thereby reducing the growth of multiple species of biotrophic pathogens. Similarly, *Lr34/Yr18/Pm38* encodes an ATP-binding cassette transporter that confers partial resistance against leaf rust, stripe rust, and powdery mildew in wheat (82, 87, 169).

The maize QTL *qMdr9.02* confers resistance against important diseases, including southern leaf blight, gray leaf spot, and northern leaf blight. Molecular cloning revealed that *ZmCCoAOMT2*, which encodes a caffeoyl-CoA *O*-methyltransferase, contributes to the *qMdr9.02*-mediated quantitative resistance against southern leaf blight and gray leaf spot (204), indicating that ZmCCoAOMT2 may control metabolite levels in the phenylpropanoid and lipoxygenase pathways associated with SNS BSR in maize.

The cucumber resistance QTL *STAYGREEN* (*CsSGR*), used for over 50 years to confer SNS BSR against oomycete downy mildew, bacterial angular leaf spot, and fungal anthracnose pathogens, was recently cloned (192). A single-nucleotide polymorphism was found to cause an amino acid substitution in CsSGR, resulting in the inhibition of chlorophyll degradation (and thus a stay-green phenotype) upon pathogen infection, which may inhibit the overaccumulation of ROS and phytotoxic catabolites in the plants. *SGR* is highly conserved in plants; however, its resistance function has not previously been reported in other species.

2.7. Nonhost-Resistance Proteins

NHR is the most common form of disease resistance exhibited by plants against the majority of potentially pathogenic microorganisms (128). It is believed to confer long-lasting BSR and helps ensure plant survival (52). The first *NHR* gene to be isolated was *NONHOST 1* (*NHO1*) in *Arabidopsis*, which positively regulates SNS BSR against several nonhost pathogens, such as the bacteria *P. syringae pv. tabaci*, *P. syringae pv. phaseolicola*, and *Pseudomonas fluorescens* and the fungus *Botrytis cinerea* (72, 113). Three *NHR* genes related to pathogen penetration were isolated in genetic screens of *Arabidopsis*. *PENETRATION1* (*PEN1*) encodes a syntaxin that localizes to the plasma membrane, and its role in vesicle trafficking and exocytosis appears to confer NHR to the powdery mildew pathogens *Blumeria graminis* f. sp. *hordei* (*Bgh*) and *Erysiphe pisi* (8, 27, 99). *PEN2*, which encodes a glycosyl hydrolase that localizes to peroxisomes, positively regulating BSR against the host-specific pathogen *Erysiphe cichoracearum* and the nonhost-specific pathogens *Bgh* and *E. pisi* (99, 171). *PEN3* is a plasma membrane–localized putative ATP-binding cassette transporter that not only positively regulates plant resistance against many nonhost-specific pathogens but also negatively regulates host resistance against *E. cichoracearum* in an SA-dependent manner (111, 171).

3. STRUCTURE AND FUNCTION OF RACE-NONSPECIFIC BSR PROTEINS

3.1. Cytoplasmic Nucleotide-Binding and Leucine-Rich Repeat Receptors and Other Types of Resistance Genes

Nearly all cloned NLR *R* genes in plants confer resistance against a single pathogen; however, as indicated in **Supplemental Table 2**, 36 NLR *R* genes confer RNS BSR in rice, wheat, potato, tomato, pepper, and roses (*Rosa* sp., multiple cultivars). Among the cloned rice blast *R* genes, 12 were reported to confer RNS BSR, and all these except *Ptr* encode NLR proteins (**Supplemental Table 2**). The *Pi2/Pi9* locus on rice chromosome 6 contains several RNS-BSR genes, including *Pi2*, *Pi9*, *Pi50*, *Piz-t*, and *Pigm* (109). The *Pigm* locus is unique in that it encodes a pair of antagonistic NLRs, Pigm Resistant (PigmR) and Pigm Susceptible (PigmS) (31); PigmR confers BSR, while PigmS competitively forms heterodimers with PigmR to inhibit its function in immunity. However, *PigmS* expression is tightly controlled by epigenetic regulation, resulting in strong and durable blast resistance without a yield penalty. *Pi2*, *Pi9*, *Pi50*, *Piz-t*, and *Pigm* have been widely used in the breeding of blast-resistant rice. In wheat, three leaf rust *R* genes (*Lr1*, *Lr10*, and *Lr21*),

five stem rust *R* genes (*Sr33*, *Sr35*, *Sr22*, *Sr45*, and *Sr50*), one yellow rust *R* gene (*Yr5/Yr7*), and one powdery mildew *R* gene (*Pm21*) confer RNS BSR, and all these genes encode NLR proteins (**Supplemental Table 2**).

Nine RNS-BSR *R* genes encode non-NLR proteins (**Supplemental Table 2**); for example, the rice gene *Xa4* encodes a WAK protein and confers durable RNS BSR against *Xoo* without compromising grain yield (58). In noninoculated plants, XA4 activates the transcription of the cellulose synthase gene *CesA* to facilitate cellulose biosynthesis and inhibits *Expansin* expression, increasing the mechanical strength of the plant cell wall and suppressing *Xoo* infection (58). The rice genes *Xa10*, *Xa23*, and *Xa27* encode executor R proteins and confer durable RNS BSR at the seedling and adult stages (110, 177, 213). In addition, the yellow rust *R* genes *Yr15* and *Yr36* in wheat encode a tandem kinase and a START kinase, respectively (40, 77).

3.2. Defense-Signaling Proteins

The ubiquitination-mediated pathway plays important roles in RNS BSR by activating the NLRs and downstream immune signaling (24). Three defense-signaling genes encode E3 ligases in rice and potato (**Supplemental Table 2**). The rice RING finger E3 ubiquitin ligase BLAST AND BTH-INDUCED 1 (OsBBI1) was reported to regulate RNS BSR against *M. oryzae* by modifying the host cell wall (93). The overexpression of *OsBBI1* increased rice resistance against multiple strains of *M. oryzae* and enhanced accumulation of defense-associated H_2O_2 and other ROS. The rice U-box/ARM E3 ubiquitin ligase OsPUB15 interacts with the rice blast R protein Pid2 to positively regulate plant cell death and the basal defense response, thereby conferring RNS BSR against *M. oryzae* (189). The RING-H2 Finger Protein 1 (StRFP1) is a potato E3 ubiquitin ligase that positively regulates RNS BSR against multiple strains of *Phytophthora infestans* in potato and in transgenic *N. benthamiana* via an E3 ligase activity-dependent pathway (133, 218).

Protein kinase genes are also involved in RNS BSR in crops (**Supplemental Table 2**). The rice RLK Blast Resistance-Related 1 (OsBRR1) positively regulates resistance against *M. oryzae*, with *OsBRR1*-overexpressing plants exhibiting enhanced resistance against virulent *M. oryzae* isolates without showing obvious developmental changes (139). The L-type lectin receptor kinase V (LecRK-V) was cloned from the diploid wheat relative *Haynaldia villosa*, and its transgenic expression in wheat enhances powdery mildew resistance at the seedling and adult stages (194). *Stpk-V*, a serine threonine protein kinase gene also from *H. villosa*, confers BSR against wheat powdery mildew (147). Most recently, we discovered a novel plant RNA recognition motif domain–containing TF family that physically interacts with rice NLRs to trigger RNS-BSR blast resistance, which directly activates rice defense genes including *OsWAK14* and *OsPAL1*, establishing a direct link between transcriptional activation of immune responses with NLR-mediated pathogen perception (214).

3.3. Susceptibility Proteins

To date, five *S* genes have been reported to confer RNS BSR (**Supplemental Table 2**). *Mildew Resistance Locus O* (*Mlo*) was the first *S* gene to be identified in barley (*Hordeum vulgare*), but it has also been found in almost all higher plants (17). The EMS, X-rays, or ɣ-rays induced recessive *mlo* loss-of-function alleles of barley confer durable RNS BSR to all known isolates of *Bgh* (17). MLO localizes to the plasma membrane and contains seven conserved transmembrane domains and a calmodulin-binding domain in its C terminus (75). In wild-type barley, MLO suppresses the hydrogen peroxide burst in the epidermal cell wall at the *Bgh* penetration site, thus inhibiting disease resistance by suppressing plant cell death and a second oxidative burst (142). The

effectiveness and durability of the barley *mlo* gene to powdery mildew led to the identification and functional characterization of many *MLO* orthologs in other plant species, such as *Arabidopsis AtMLO2*, *AtMLO6*, and *AtMLO12*; tomato *SlMLO1*; pea *Er1/PsMLO1*; grapevine *VvMLO3* and *VvMLO4*; tobacco *NtMLO1*; pepper *CaMLO2*; cucumber *CsaMLO8*; *Lotus japonicus LjMLO1*; barrel clover *MtMLO1*; rice *OsMLO3*; and wheat *TaMLO-A1*, *TaMLO-B1*, and *TaMLO-D1* (217). The functions of these orthologous genes in disease resistance remain to be elucidated.

Pyramiding: a process of combining two or more genes by genetic strategies to develop elite lines or varieties

Marker-assisted selection (MAS): a complementary tool for traditional breeding in which the selection of individuals depends on the link between the polymorphic molecular marker and trait

The rice *S* gene *Pi21* (also referred to as a QTL) encodes a proline-rich protein with a putative heavy metal–binding domain and a protein–protein interaction domain (42). The *pi21* recessive allele containing mutations in its proline-rich motif confers durable RNS BSR against many *M. oryzae* strains and has been used in rice breeding in Japan for many years (42). Another rice blast RNS-BSR *S* gene, *Broad-spectrum resistance Digu 1 (Bsr-d1)*, was recently cloned and reported to encode a C2H2-type TF (94, 220). A single-nucleotide change in the promoter of *Bsr-d1* enhances the binding of the MYB TF MYBS1, which suppresses *Bsr-d1* expression and enhances resistance against multiple strains of *M. oryzae* (94). Several *S* genes also function in the rice-*Xoo* pathosystem, including *Xa25/OsSWEET13* and *Xa41(t)/OsSWEET14*, which encode sugar transporters that facilitate bacterial infection, reducing RNS BSR against *Xoo* (62, 219).

3.4. Quantitative Trait Loci

Three RNS-BSR QTLs have been cloned in wheat, maize, and potato (**Supplemental Table 2**). Recently, the long-sought wheat QTL *Fhb1*, which confers durable RNS BSR against *Fusarium* head blight, was cloned and characterized by three independent research groups and was found to likely encode a putative histidine-rich calcium-binding protein (5, 91, 174) or a chimeric lectin with agglutinin domains and a pore-forming toxin-like domain (151). Because *Fhb1* is highly conserved in the genomes of grass species, the identification of *Fhb1* is significant for the breeding of cereal crops resistant to *Fusarium* species. The maize RNS-BSR gene *Helminthosporium turcicum resistance N1* (*Htn1*) protects against northern corn leaf blight and was found to encode a WAK (ZmWAK-RLK) with a highly diverse extracellular domain in different maize genotypes (60). The potato QTL *R8* encodes an NLR, which contributes to providing durable BSR against late blight (70). The further characterization of these genes will elucidate the molecular mechanisms underlying QTL-mediated resistance.

4. PLANT BREEDING STRATEGIES FOR ACHIEVING BSR IN CROPS

4.1. Pyramiding Multiple Resistance Genes

Breeding resistant cultivars using *R* genes is currently the most effective and economical strategy for controlling crop diseases (126); however, the frequent loss of *R* gene–mediated resistance in the field limits the widespread and long-lasting use of single *R* genes in breeding programs. Pyramiding multiple *R* genes, especially BSR genes, with different resistance spectra against a single pathogen or multiple pathogens in the same genetic background has proved to be an effective strategy for achieving BSR. With the use of marker-assisted selection (MAS), multiple *R* genes have been successfully pyramided into recipient cultivars of various crops to generate new varieties with resistance against several major diseases, including rice blast, rice bacterial blight, wheat rust, wheat powdery mildew, and soybean cyst nematodes.

Rice blast and bacterial blight are the two most important diseases of rice (109). Rice lines containing multiple pyramided *R* genes usually have broader resistance than lines containing single *R* genes; for example, the resistance spectra and levels in lines containing *Pi2/Pi1*, *Pigm/Pi54*,

Pi2/Pi54, and *Piz-t/Pi54* pairs were significantly better than the monogenic lines containing individual *R* genes (67, 196, 197). Similarly, elite rice varieties with pyramided *Xa4*, *Xa21*, *Xa7*, *Xa23*, and *Xa27* genes obtained using MAS have broader resistance spectra and higher resistance levels than lines containing only a single gene (114, 176, 202). Efforts to integrate multiple *R* genes that confer BSR against different pathogens in elite rice cultivars have recently been increased, as exemplified by the development of lines containing *Pi9* and *Xa23*, *Pi2* and *Xa23*, or *Xa21* and *Pi54* (68, 132, 178).

Durable resistance: resistance that remains effective for long periods when widely exposed to the pathogen under the prevailing growing conditions

Wheat fungal diseases cause annual yield losses of 15–20% (2, 39). Over 187 *R* genes in wheat have been found to confer resistance against various rust diseases, and many have been used in breeding for rust resistance. The *R* genes *Sr22*, *Sr23*, *Sr25*, *Sr33*, *Sr35*, *Sr45*, and *Sr50* are considered to be the most valuable for pyramiding to protect against the newly evolved races of stem rust, including the aggressive race Ug99 (35, 166). Pyramiding of two single dominant yellow rust genes, *Yr5* and *Yr15* or *Yr64* and *Yr15*, in common wheat resulted in complete resistance against all tested stripe rust races (77, 149). In addition, different combinations of the powdery mildew *R* genes *Pm2*, *Pm4a*, and *Pm21* were successfully integrated into the elite wheat cultivar Yang 158, resulting in broad-spectrum powdery mildew resistance (103).

The soybean cyst nematode (*Heterodera glycines*) has a major effect on soybean production (108). *Resistance to Heterodera glycines 1* (*Rhg1*), which encodes a serine hydroxymethyltransferase, is located in a cluster with genes encoding an amino acid transporter, an α-soluble NSF (N-ethylmaleimide-sensitive factor) attachment protein, and a wound-inducible domain protein 12 (WI12), each of which contributes to providing resistance against the cyst nematode (28, 108). A strong epistatic interaction occurs between *Rhg1* and *Rhg4* in the Peking background, which provides the only known instance of full resistance against the pathogenic nematode (122); therefore, lines containing these two genes have a broader spectrum of resistance against the cyst nematode (208). Similarly, potato plants containing stacks of two or three of the *R* genes *Rpi-vnt1*, *Rpi-sto1*, *Rpi-vnt1.1*, and *Rpi-blb3* exhibit BSR against the late blight *P. infestans* in the field (51, 221).

As mentioned above, the pyramiding of *R* genes with complementary resistance spectra or modes of action can produce additive and synergistic effects on resistance levels and spectrum. In a few cases, however, the pyramiding of *R* genes can reduce resistance to levels lower than what could be obtained with individual *R* genes. In the case of blast disease in rice, for example, the resistance level of plants containing *Piz-5* and *Pita* is lower than the level observed in the monogenic lines expressing *Piz-5* alone (55). Similar phenotypes were also observed in the pyramiding lines containing *Piz* and *Pi54* (196); therefore, different *R* gene combinations should be tested for their compatibility in different genetic backgrounds before they are used in breeding programs.

4.2. Combining Resistance Genes with Quantitative Trait Loci

It has been well documented that a combination of *R* genes and QTLs or partial resistance genes confers durable resistance (127, 131). Plant breeders have pyramided *R* genes with multiple QTLs to achieve broad-spectrum and durable resistance and to reduce the selection of resistance-breaking pathogen genotypes (88, 170). In wheat, the best-known QTL genes are *Sr2*, *Lr34*, *Lr46*, and *Lr67*; these genes have provided partial resistance in mature plants for many years over large areas, despite high and prolonged disease pressure in the field (35). Combining *Lr34* and *Lr67* with various dominant race-specific *Lr* genes enhanced the resistance of wheat plants against leaf rust in multiyear, multilocation field trials (29, 46, 184). The pyramiding of *R* genes with QTLs, such as the combination of *Sr2*, *Lr34/Yr18/Pm38*, and *Lr46/Yr29/Pm39*, has proved effective for the control of stripe rust and powdery mildew in the CIMMYT spring wheat breeding programs (98, 167). The QTL *Fhb1* has been widely deployed to improve *Fusarium* head blight resistance

in different cultivated wheat varieties (91, 151, 174, 205), and the pyramiding of *Fhb1* with the leaf rust *R* gene *Lr21* in elite spring wheat greatly improved its BSR against various pathogens (168).

Several maize disease QTLs have been cloned, including *qHSR1*, *Htn1*, *qMdr9.02*, and *ZmTrxh* (203, 204). Resistance alleles from multiple QTLs have been stacked into a single line using MAS, resulting in BSR against multiple pathogens (7, 216). The pyramiding of the *R* genes *Ht1* and *Ht2* with a head smut QTL provided a higher level of disease resistance against northern leaf blight and head smut than was observed in the parental lines (69). In addition, two studies showed that rice lines with multiple blast-resistance QTLs, including *pi21*, *qBR4-2*, *Pi34*, *qBR12-1*, and *Pi35*, had a strong, nonrace-specific, environmentally stable resistance against *M. oryzae* (43, 206). Integration of these resistance QTL alleles into elite cultivars with major *R* genes will likely lead to the development of durable BSR rice lines.

4.3. Modifying Immune Receptor Expression and Structure

Plant *R* gene expression is typically strictly controlled to avoid autoimmunity when plants are not under pathogen attack (95); however, the overexpression of a few *R* genes can activate immune responses and generate BSR against multiple pathogens without inducing high levels of cell death. For example, increasing expression of the rice *R* gene *Xa3/Xa26* using different promoters, including the native, *WRKY13*, and maize *Ubiquitin* promoters, can increase the spectrum of *Xoo* resistance (19). In addition, overexpression of the rice PRRs *OsLYP4* and *OsLYP6* conferred BSR against *Xoo* and *M. oryzae* (100). Similarly, overexpression of the *Pto* gene in tomato conferred resistance against *P. syringae* pv. *tomato*, *Xanthomonas campestris* pv. *vesicatoria*, and *Cladosporium fulvum* (180).

Modification of the transcription activator-like effector (TALE)-binding sites in *R* genes can generate broad, durable resistance against important *Xanthomonas* diseases (59, 153). The introduction of multiple TALE-binding elements into the promoter of the *R* gene *Xa27* activates its expression and expands resistance against *Xoo* and *Xoc* (59, 153). The designer TALEs strategy uses the scaffold of the TALE AvrBs3 and modified repeat-variable diresidues that match the tomato *Bacterial spot resistance 4* (*Bs4*), *Arabidopsis ENHANCER OF GLABRA3* (*EGL3*), or the *Arabidopsis KNOTTED-LIKE 1*(*KNAT1*) promoters to transcriptionally activate them in a sequence-specific manner (124). Engineering synthetic TALEs to induce the transcription of these immune receptor–encoding *R* genes can therefore trigger BSR against various pathogens.

Recently, significant progress has been made in engineering sensitized NLR variants with a lower activation threshold, which recognize a wider spectrum of effectors. Mutations in the conserved coiled-coil and nucleotide-binding domains of the NLR receptors expanded their response spectra to include more effector variants (21, 50, 162, 173). Another study (47) reported that the engineered tomato immune receptor I2 (I141N) confers partial resistance against *P. infestans* and has an expanded response spectrum to the fungus *Fusarium oxysporum* f. sp. *lycopersici*, suggesting that synthetic immune receptors can be engineered to confer resistance against phylogenetically divergent pathogens. Mutations in the LRR domain and near the nucleotide-binding pocket structure of the NLR receptors Rx and R3a may increase the resistance spectrum (37, 50, 162). These studies illustrate that immune receptors can be modified to improve the NLR resistance spectra. It remains to be determined how base-editing technologies could be used to generate point mutations at conserved NLR nucleotides to obtain new BSR genes (45).

Another significant breakthrough was made in modifying a decoy to engineer novel pathogen recognition specificities (81). The *Arabidopsis* NLR receptor RESISTANCE TO PSEUDOMONAS SYRINGAE5 (RPS5) guards the host kinase AVRPPHB SUSCEPTIBLE1 (PBS1) against cleavage by the bacterial effector AvrPphB, a protease that cleaves PBS1 at a defined

region to produce a conformational change. The engineered modification of the AvrPphB cleavage site within PBS1 to resemble that of a bacterial or viral protease enabled RPS5 to recognize these proteases upon infection (76). This study indicates that decoys can be used to expand the recognition specificity of a plant NLR, an approach with potential use in the rational engineering of disease resistance in crop plants.

4.4. Inducible Expression of Pathogen Elicitor and Avirulence Genes in Plants

Some pathogen elicitor or *Avr* genes trigger a strong HR when expressed in transgenic plants; therefore, researchers investigated the possibility of using a pathogen-inducible promoter to drive an elicitor/*Avr* gene to activate BSR. Keller et al. (74) generated transgenic tobacco plants harboring a fusion between the pathogen-inducible tobacco *hsr203J* gene promoter and a *Phytophthora cryptogea* gene encoding the elicitor cryptogein. After *P. cryptogea* inoculation, the induced production of cryptogein resulted in a localized HR that restricted further growth of the oomycete *Phytophthora* and unrelated fungal pathogens (74). BSR was also obtained through the expression of both *R* and *Avr* genes in transgenic rice plants (61). These plants expressed the *Avr1-CO39* effector gene from *M. oryzae*, under the control of an inducible promoter, and were challenged with *Xoo* and *Xoc* strains carrying a TALE designed to transactivate the inducible promoter. The recognition of the corresponding NLR receptor *Pi-CO39* by the induced *Avr1-CO39* triggered resistance against the bacterial diseases (61). Such an approach, which is based on synthetic promoter traps, expands the panel of genes that can be exploited to engineer resistance in plants against infections by TALE-injecting pathogens. This strategy has not yet been tested in the control of crop diseases caused by pathogens that lack TALEs.

4.5. Altered Expression of Defense-Signaling and Pathogenesis-Related Genes

Engineering BSR is possible using both defense signaling and *PR* genes because they usually function downstream of the immune receptors. For example, silencing soybean *GmMPK4*s caused spontaneous cell death in the leaves and stems and enhanced resistance against downy mildew and the soybean mosaic virus (105). Defense signaling and *PR* genes are conserved in different plant species, allowing BSR to be achieved in many crops by expressing the *Arabidopsis* defense master regulator *NPR1* (116, 119, 164, 165, 188). The *NPR1* orthologs cloned from other plants also function as BSR regulators in their native species and when expressed in other species; for example, *NPR1* cloned from *Malus pumila* (*MpNPR1*) or *Malus hupehensis* (*MhNPR1*) can activate BSR in apple (*Malus* × *domestica*), protecting against fire blight, apple scab, and cedar apple rust (23, 117, 118). Similarly, the transgenic expression of *StoNPR1* from *Solanum torvum* (a wild eggplant highly resistant to *Verticillium dahliae*) in potato enhances its resistance against *V. dahliae* (32).

Some *PR* genes are involved in strengthening cell walls, generating an oxidative burst, and producing antimicrobial compounds in the host plants. The overexpression of *PR* genes, such as those encoding defensins, enhanced plant resistance to multiple pathogens (138, 156). In another example, the expression of *CaAMP1*, which encodes an antimicrobial protein, led to BSR against biotrophic, hemibiotrophic, and necrotrophic pathogens in pepper (89).

Transgenic plants with alterations in their expression of a single defense signaling or *PR* gene usually have relatively low levels of resistance against pathogens; however, stacking these transgenes may increase their resistance. If a strong HR occurs in the transgenic plants, an inducible expression system should be used to alleviate the cell death phenotypes. Another approach is to screen germplasm for new alleles with high expression levels but a minimal yield penalty.

4.6. Genome Editing of Susceptibility Genes

Gene editing: a group of genetic technologies in which DNA is highly specific inserted, deleted, modified or replaced in the genome of a living organism

Recent advances in genome editing technologies have enabled the targeted mutagenesis of *S* genes in several important crops, with the goal of generating BSR against multiple pathogens. TALEN and CRISPR/Cas9 technologies were used to target the *Mlo* loci in wheat and thereby obtain plants resistant to powdery mildew (193). In tomato, knocking out the *Mlo* ortholog *SlMlo1* using CRISPR/Cas9 resulted in plants fully resistant to the powdery mildew fungus *Oidium neolycopersici* (130). Moreover, in rice, CRISPR/Cas9-induced mutations in the proline-rich motif of *Pi21* provided RNS BSR against *M. oryzae* (42, 92), and promoter editing of three *SWEET* genes led to the development of BSR transgenic lines in all tested *Xoo* strains in two mega rice varieties (136). Another example involves eIF4E, which is essential for the cellular infection cycle of potyviruses (155). Two independent studies recently showed that disruption of *eIF4E*s using CRISPR/Cas9 led to resistance against ipomoviruses and potyviruses in *Arabidopsis* and cucumber (20, 145). These results clearly show that manipulation of *S* genes is a powerful approach for generating resistance in economically important crops.

4.7. Using the Multiline Strategy to Confer BSR

A multiline cultivar is a mixture of pure lines that are agronomically similar but differ in a single trait, such as an *R* gene (125). Relative to single-component cultivars, multiline barley cultivars have up to 80% less disease, while wheat multilines show a 60% disease reduction (143). In rice, mixed plantings of disease-resistant and susceptible varieties grown in multiple locations for two years can greatly reduce the severity of rice blast infections in both varieties (222). Blast-resistant multilines composed of near-isogenic lines with different *R* genes had lower levels of blast disease than their corresponding single-component cultivars (63, 78, 85). Generating uniform sets of near-isogenic lines in the same genetic background is time consuming; therefore, multilines composed of transgenic wheat lines overexpressing *Pm3a*, *Pm3c*, *Pm3d*, *Pm3f*, or *Pm3g* in the Bobwhite cultivar background were developed. Field tests showed that all transgenic lines were more resistant to powdery mildew than the respective control lines, with substantially greater resistance in the multilines containing all four pyramided alleles (15, 79). This demonstrated that a difference in a single *R* gene is sufficient to cause host-diversity effects, and that the development of multilines represents a promising strategy for the effective and sustainable use of *R* alleles. Gene editing techniques are rapidly being improved, meaning breeders will soon be able to engineer crop multilines containing both SNS- and RNS-BSR genes.

5. POTENTIAL CHALLENGES AND POSSIBLE SOLUTIONS

As discussed above and shown in **Figure 1**, significant progress has been made in the identification of BSR genes and in our understanding of the molecular basis of BSR. In addition, several breeding strategies have been employed to select BSR cultivars (**Figure 2**). However, many challenges remain regarding the application of BSR in crop breeding. These challenges and their possible solutions are discussed in the following sections.

5.1. Identifying Novel Genes that Balance BSR and Yield

The molecular mechanisms underlying the trade-off between resistance and crop yield are largely unknown (134); however, several recent studies have described new approaches for minimizing the fitness cost of disease tolerance in rice. The *Pigm* locus in rice encodes a pair of antagonistic NLR receptors, PigmR and PigmS (31), which decrease and enhance yields, respectively. The transfer

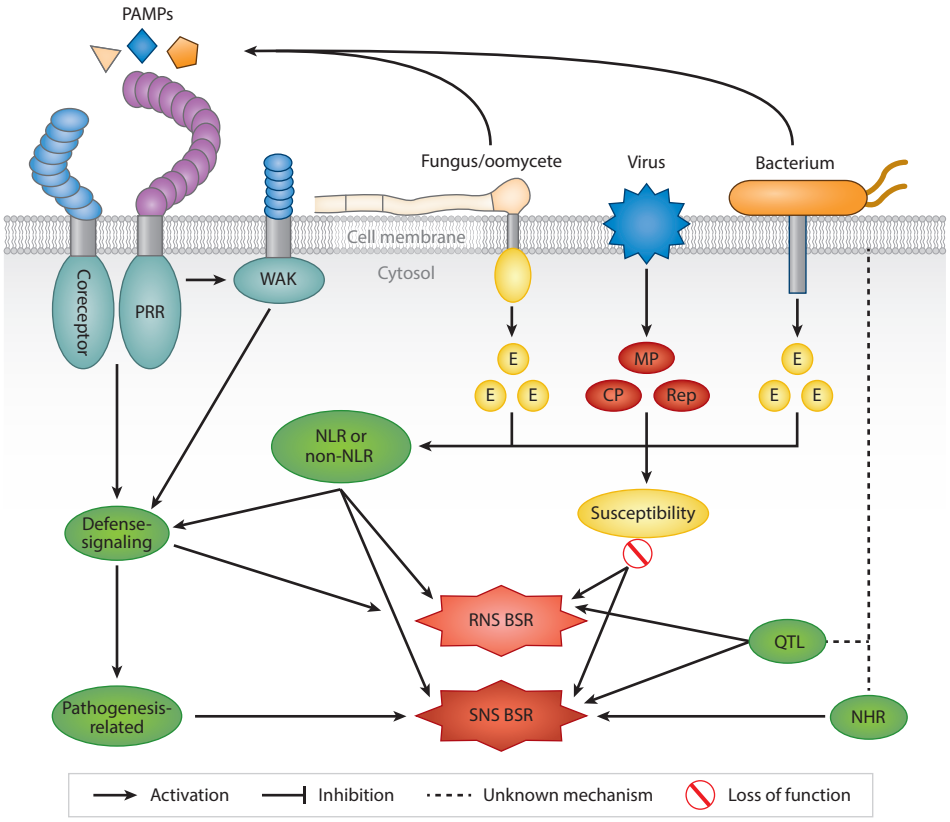

Figure 1

Mechanism of BSR in plants. PAMPs from bacteria, fungi, oomycetes, and other pathogens are perceived by membrane-associated PRRs and coreceptors. WAKs can also recognize pathogen effectors or plant signals, such as damage-associated molecular patterns, and can be activated by PRRs (16). Meanwhile, intracellular resistance proteins such as NLRs or non-NLRs can recognize pathogen-secreted Es or viral proteins such as CP, Rep, and MP. These specific recognitions activate various immune signaling cascades mediated by defense-signaling proteins that lead to the synthesis of numerous pathogenesis-related proteins to confer RNS BSR, SNS BSR, or both. By contrast, loss of function of susceptibility genes targeted by pathogen effectors or viral proteins, expression of QTLs, and *NHR* genes can initiate RNS BSR and SNS BSR to pathogens in plants. Abbreviations: BSR, broad-spectrum resistance; CP, capsid protein; E, effector; MP, movement protein; NHR, nonhost resistance; NLR, nucleotide-binding and leucine-rich repeat receptor; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; QTL, quantitative trait locus; Rep, replicase; RNS, race-nonspecific; SNS, species-nonspecific; WAK, cell wall–associated kinase.

of both receptors into a susceptible line ensures a good balance between yield and immunity, and the entire *Pigm* locus has been introduced into elite cultivars using traditional breeding. Another study demonstrates that the substitution of a single nucleotide in the promoter of the *Bsr-d1* gene enhances disease resistance without reducing yields (94). Two recent studies showed that the TF-encoding gene *Ideal Plant Architecture1* (*IPA1*) promotes high yields while contributing to rice immunity against *M. oryzae* and *Xoo* (106, 190). The use of genetic and genomic approaches to identify additional *Pigm*-, *Bsr-d1*-, and *IPA1*-like alleles in rice and other crops will provide new germplasm materials for the breeding of new cultivars with both high pathogen resistance and high yields.

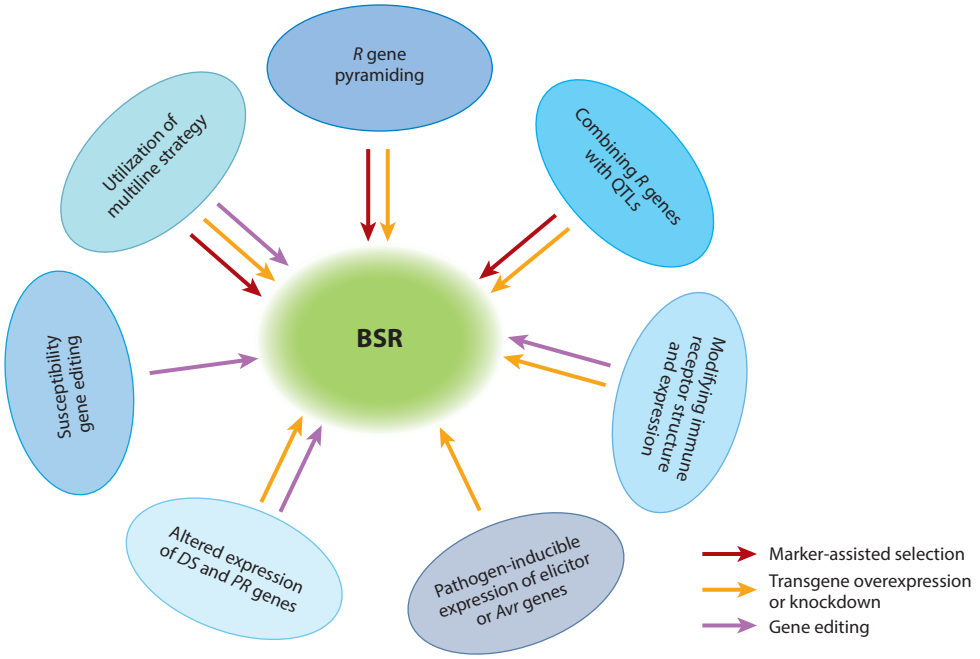

Figure 2

Multiple strategies for breeding BSR in crops. The proposed strategies can be used separately or in combinations dependent on the availability of BSR genes and technologies for the crop. Abbreviations: Avr, avirulence; BSR, broad-spectrum resistance; DS, defense-signaling; PR, pathogen-related; R, resistance; QTL, quantitative trait locus.

5.2. Eliminating the Negative Effects of Defense Proteins on Plant Growth Using Upstream Open Reading Frames

The overexpression of immune receptor–encoding, defense signaling, *PR*, and *NHR* genes often leads to cell death and dwarf phenotypes (134). Upstream open reading frames (uORFs), located in the 5′ untranslated regions, are potent *cis*-acting regulators of translation and mRNA turnover and are abundant in angiosperm genomes (187). In *Arabidopsis*, the TF TL1-binding factor 1 (TBF1) is involved in the switch from growth to defense that occurs upon induction of the immune response. The TBF1 cassette consists of the *TBF1* promoter and the 5′ untranslated region, which contains two pathogen-inducible uORFs. A recent study used $uORFs_{TBF1}$-mediated translational control to minimize the fitness cost of BSR in *Arabidopsis* and rice (199). The authors found that the *TBF1p:uORFs-NPR1* and *TBF1p:uORFs-SNC1* transgenic plants displayed BSR against three rice pathogens without suffering any fitness cost. This strategy provides a way of minimizing the negative effects of the overexpression of BSR genes in crops. The search for additional TBF1-like TFs in plant genomes may lead to the development of crop plants with BSR but without the associated reductions in growth and yield.

5.3. Reducing the Selection Pressure on Pathogens When Growing BSR Cultivars

The widespread and long-term planting of BSR cultivars will likely increase the selection pressure on pathogens and increase the appearance of resistance-breaking populations (121). In theory,

BSR cultivars should provide durable resistance because overcoming their resistance mechanisms would require the accumulation of mutations in multiple pathogen effectors. The durability of BSR cultivars mainly depends on the evolutionary potential of the pathogens, however, which can be considerable for species with complex populations, mixed reproductive systems, and substantial gene flow (121). Researchers have proposed that multivirulent pathogen populations develop in a step-by-step manner (14); therefore, a complete survey of the frequency of virulent strains in the field is essential for the correct deployment of BSR genes or combinations of *R* genes and QTLs in crop production. In addition, the establishment of natural disease nurseries used for the evaluation of the resistance capabilities of different BSR cultivars will also be helpful for testing the effectiveness of the BSR genes.

5.4. Identifying and Using Nonhost Resistance Genes in Crop Breeding

Although the molecular mechanism underlying NHR in plant defense is still not clear, the use of NHR in crops is a promising approach for breeding BRS cultivars. The wheat *Lr34* gene is a good example because the transfer of this gene to other cereal species, such as barley, rice, and maize, confers resistance against multiple species-specific pathogens of these crops (11, 83, 175). Another promising *NHR* gene is the *Cajanus cajan Resistance against Phakopsora pachyrhizi 1* (*CcRpp1*), an NLR-encoding gene from pigeonpea (*C. cajan*) that confers resistance against the fungal pathogen *P. pachyrhizi* in soybean (73). Nevertheless, the number of *Lr34*- and *CcRpp1*-like genes in crops is limited, and new methods for rapidly isolating such genes are required. Although the expression of *NHR* genes across phylogenetically distant species may lead to the development of BSR in economically important crops, some crop plants currently remain untransformable, which limits the application of the *NHR* genes. The development of new transformation techniques in these crops will facilitate the use of *NHR* genes for the engineering of additional BSR crops.

5.5. Optimizing Strategies for Intra- and Interspecies Transfer of Immune Receptors

Crop breeders have introgressed *R* genes from wild relatives into elite cultivars (9, 60). The maize *R* gene *Htn1*, encoding a putative WAK that confers quantitative resistance against most isolates of northern corn leaf blight, was introduced from a Mexican landrace into modern maize breeding lines in the 1970s (60). In apple, the susceptible cultivar Gala showed enhanced scab resistance against multiple strains of *Venturia inaequalis* after being transformed with the *R* gene *HcrVf2* from the wild species *Malus floribunda* (9). One challenge for transferring new *R* genes from wild relatives into cultivated lines is how to rapidly identify and clone the R alleles that confer BSR. Recently, multiple strategies have been used to clone new *R* genes from the wild relatives of wheat, barley, and potato, including MutRenSeq, MutChromseq, dRenSeq, and RenSeq (22, 154, 172). These low-cost mapping strategies can be adapted for use with other crop plants.

The interspecies transfer of PRR genes was recently reported; for example, the *Arabidopsis EFR* gene was introduced into tomato (86), rice (112, 161), potato (12), *Medicago* (141) and wheat (159), and the resulting transgenic plants displayed resistance to the pathogens adapted to each of these crops. Similarly, the transformation of *Xa21* into tomato (1), sweet orange (*Citrus aurantium*) (123), and banana (*Musa acuminata*) (183) increased resistance to *Xanthomonas axonopodis* pv. *citri*, *R. solanacearum*, and *X. campestris* pv. *musacearum*, respectively. Although PRRs have been transferred between species, the resistance levels of the transgenic lines, such as the *Arabidopsis EFR* gene in rice, to their species-specific pathogens have usually been relatively low (161); however, combining

PRR genes with NLRs or QTLs in the recipient species could enhance the resistance levels and spectra of the transgenic plants.

5.6 Choosing the Right BSR Gene Combinations and Pyramids

Previous research suggests that, in a pyramid, one *R* gene may mask the effects of the others, such that some *R* gene combinations provide less disease resistance than other combinations (127). For example, rice plants containing both *Piz-5* and *Pita* had lower blast resistance than plants containing *Piz-5* alone (55). Similar results were reported in the pyramided lines containing *Piz* and *Pi54* (196). In addition, the genetic background of the recipient cultivars may affect the resistance phenotype; the resistance conferred by a combination of *Xa5*, *Xa13*, and *Xa21* differed substantially among five rice cultivars, indicating the possible presence of resistance suppressors in some of the host plants (144). The effects of specific combinations of different BSR genes or pyramids of *R* genes and QTLs are therefore not predicable and should be tested in different genetic backgrounds before being used in crop breeding programs. Further investigation of the mechanisms underlying the synergistic or antagonistic effects of different BSR gene combinations or genetic backgrounds will provide essential new information for BSR breeding.

5.7. Screening for Genes that Provide BSR Against Both Necrotrophic and Biotrophic Pathogens in Crops

Biotrophic and necrotrophic pathogens use different strategies: Necrotrophic pathogens kill host tissues because they colonize and thrive on the contents of dead or dying cells, whereas biotrophs depend on living host cells to complete their life cycle (48). In many cases, plants with resistance against biotrophic pathogens are susceptible to necrotrophic pathogens, and vice versa (179); however, transgenic carrots (*Daucus carota*) expressing *NPR1* had BSR against both necrotrophic and biotrophic pathogens (188). The two transgenic carrot lines in that study exhibited a 35–50% reduction in disease symptoms on their foliage and roots when exposed to three necrotrophic pathogens and an 80–90% reduction in disease development in response to two biotrophic pathogens. It is therefore critical for breeders to identify new BSR genes that confer resistance against both necrotrophic and biotrophic pathogens in crops.

SUMMARY POINTS

1. Selection of new cultivars with broad-spectrum resistance (BSR) is an important goal in crop breeding programs.
2. BSR genes encode pattern recognition receptors (PRRs), nucleotide-binding and leucine-rich repeat receptors (NLRs), and other defense-related proteins.
3. Genes underlying quantitative trait loci (QTLs), loss of susceptibility and nonhost resistance (NHR) are also involved in BSR.
4. Durable BSR can be achieved with different breeding strategies in crops.
5. Low-cost mapping strategies such as RenSeq can be adapted for rapid isolation of BSR genes in wild species.
6. Genome-editing technologies such as CRISPR/Cas9 will play a vital role in engineering BSR crops.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank many colleagues who have contributed to broad-spectrum disease resistance research in plants and apologize to those whose work was not cited owing to space limitations. This work was supported by grants from the National Key Research and Development Program of China, Ministry of Science and Technology of China (2016YFD0100600 to Z.H.), and the National Natural Science Foundation of China (31300250 to W.L., 31720103913 to Z.H., 31772149 to Y.D., and 31822041 to Y.N.).

LITERATURE CITED

1. Afroz A, Chaudhry Z, Rashid U, Ali GM, Nazir F, et al. 2011. Enhanced resistance against bacterial wilt in transgenic tomato (*Lycopersicon esculentum*) lines expressing the *Xa21* gene. *Plant Cell Tissue Organ Cult*. 104:227–37
2. Aktar-Uz-Zaman M, Tuhina-Khatun M, Hanafi MM, Sahebi M. 2017. Genetic analysis of rust resistance genes in global wheat cultivars: an overview. *Biotechnol. Biotechnol. Equip.* 31:431–45
3. Al-Bader N, Meier A, Geniza M, Gongora YS, Oard J, Jaiswal P. 2019. Loss of premature stop codon in the *Wall-Associated Kinase 91* (*OsWAK91*) gene confers sheath blight disease resistance in rice. bioRxiv 625509. **https://doi.org/10.1101/625509**
4. Albert I, Böhm H, Albert M, Feiler CE, Imkampe J, et al. 2015. An RLP23-SOBIR1-BAK1 complex mediates NLP-triggered immunity. *Nat. Plants* 1:15140
5. Ali F, Yan J. 2012. Disease resistance in maize and the role of molecular breeding in defending against global threat. *J. Integr. Plant Biol.* 54:134–51
6. Andersen EJ, Ali S, Byamukama E, Yen Y, Nepal MP. 2018. Disease resistance mechanisms in plants. *Genes* 9:339
7. Asea G, Vivek BS, Lipps PE, Pratt RC. 2012. Genetic gain and cost efficiency of marker-assisted selection of maize for improved resistance to multiple foliar pathogens. *Mol. Breed.* 29:515–27
8. Assaad FF, Qiu J, Youngs H, Ehrhardt D, Zimmerli L, et al. 2004. The PEN1 syntaxin defines a novel cellular compartment upon fungal attack and is required for the timely assembly of papillae. *Mol. Biol. Cell* 15:5118–29
9. Belfanti E, Silfverberg-Dilworth E, Tartarini S, Patocchi A, Barbieri M, et al. 2004. The *HcrVf2* gene from a wild apple confers scab resistance to a transgenic cultivated variety. *PNAS* 101:886–90
10. Birker D, Heidrich K, Takahara H, Narusaka M, Deslandes L, et al. 2009. A locus conferring resistance to *Colletotrichum higginsianum* is shared by four geographically distinct Arabidopsis accessions. *Plant J.* 60:602–13
11. Boni R, Chauhan H, Hensel G, Roulin A, Sucher J, et al. 2018. Pathogen-inducible *Ta-Lr34res* expression in heterologous barley confers disease resistance without negative pleiotropic effects. *Plant Biotechnol. J.* 16:245–53
12. Boschi F, Schvartzman C, Murchio S, Ferreira V, Siri MI, et al. 2017. Enhanced bacterial wilt resistance in potato through expression of *Arabidopsis* EFR and introgression of quantitative resistance from *Solanum commersonii*. *Front. Plant Sci*. 8:1642
13. Boutrot F, Zipfel C. 2017. Function, discovery, and exploitation of plant pattern recognition receptors for broad-spectrum disease resistance. *Annu. Rev. Phytopathol.* 55:257–86
14. Brown JKM. 2015. Durable resistance of crops to disease: a Darwinian perspective. *Annu. Rev. Phytopathol.* 53:513–39
15. Brunner S, Stirnweis D, Diaz Quijano C, Buesing G, Herren G, et al. 2012. Transgenic *Pm3* multilines of wheat show increased powdery mildew resistance in the field. *Plant Biotechnol. J.* 10:398–409

16. Brutus A, Sicilia F, Macone A, Cervone F, De Lorenzo G. 2010. A domain swap approach reveals a role of the plant wall-associated kinase 1 (WAK1) as a receptor of oligogalacturonides. *PNAS* 107:9452–57
17. Büschges R, Hollricher K, Panstruga R, Simons G, Wolter M, et al. 1997. The barley *Mlo* gene: a novel control element of plant pathogen resistance. *Cell* 88:695–705
18. Cao H, Li X, Dong X. 1998. Generation of broad-spectrum disease resistance by overexpression of an essential regulatory gene in systemic acquired resistance. *PNAS* 95:6531–36
19. Cao Y, Ding X, Cai M, Zhao J, Lin Y, et al. 2007. The expression pattern of a rice disease resistance gene *Xa3/Xa26* is differentially regulated by the genetic backgrounds and developmental stages that influence its function. *Genetics* 177:523–33
20. Chandrasekaran J, Brumin M, Wolf D, Leibman D, Klap C, et al. 2016. Development of broad virus resistance in non-transgenic cucumber using CRISPR/Cas9 technology. *Mol. Plant Pathol.* 17:1140–53
21. Chapman S, Stevens LJ, Boevink PC, Engelhardt S, Alexander CJ, et al. 2014. Detection of the virulent form of AVR3a from *Phytophthora infestans* following artificial evolution of potato resistance gene *R3a*. *PLOS ONE* 9:e110158
22. Chen X, Lewandowska D, Armstrong MR, Baker K, Lim T, et al. 2018. Identification and rapid mapping of a gene conferring broad-spectrum late blight resistance in the diploid potato species *Solanum verrucosum* through DNA capture technologies. *Theor. Appl. Genet.* 131:1287–97
23. Chen XK, Zhang JY, Zhang Z, Du XL, Du BB, Qu SC. 2012. Overexpressing *MhNPR1* in transgenic Fuji apples enhances resistance to apple powdery mildew. *Mol. Biol. Rep.* 39:8083–89
24. Cheng YT, Li X. 2012. Ubiquitination in NB-LRR-mediated immunity. *Curr. Opin. Plant Biol.* 15:392–99
25. Chern MS, Fitzgerald HA, Yadav RC, Canlas PE, Dong X, Ronald PC. 2001. Evidence for a disease-resistance pathway in rice similar to the *NPR1*-mediated signaling pathway in *Arabidopsis*. *Plant J.* 27:101–13
26. Chu Z, Fu B, Yang H, Xu C, Li Z, et al. 2006. Targeting *xa13*, a recessive gene for bacterial blight resistance in rice. *Theor. Appl. Genet.* 112:455–61
27. Collins NC, Thordal-Christensen H, Lipka V, Bau S, Kombrink E, et al. 2003. SNARE-protein-mediated disease resistance at the plant cell wall. *Nature* 425:973–77
28. Cook DE, Lee TG, Guo X, Melito S, Wang K, et al. 2012. Copy number variation of multiple genes at *Rhg1* mediates nematode resistance in soybean. *Science* 338:1206–9
29. Dakouri A, McCallum BD, Radovanovic N, Cloutier S. 2013. Molecular and phenotypic characterization of seedling and adult plant leaf rust resistance in a world wheat collection. *Mol. Breed.* 32:663–77
30. Delteil A, Gobbato E, Cayrol B, Estevan J, Michel-Romiti C, et al. 2016. Several wall-associated kinases participate positively and negatively in basal defense against rice blast fungus. *BMC Plant Biol.* 16:17
31. Deng Y, Zhai K, Xie Z, Yang D, Zhu X, et al. 2017. Epigenetic regulation of antagonistic receptors confers rice blast resistance with yield balance. *Science* 355:962–65
32. Deng-wei J, Min C, Qing Y. 2014. Cloning and characterization of a *Solanum torvum NPR1* gene involved in regulating plant resistance to *Verticillium dahliae*. *Acta Physiol. Plant.* 36:2999–3011
33. Ding B, Bellizzi MR, Ning Y, Meyers BC, Wang GL. 2012. HDT701, a histone H4 deacetylase, negatively regulates plant innate immunity by modulating histone H4 acetylation of defense-related genes in rice. *Plant Cell* 24:3783–94
34. Du J, Verzaux E, Chaparro-Garcia A, Bijsterbosch G, Keizer LC, et al. 2015. Elicitin recognition confers enhanced resistance to *Phytophthora infestans* in potato. *Nat. Plants* 1:15034
35. Ellis JG, Lagudah ES, Spielmeyer W, Dodds PN. 2014. The past, present and future of breeding rust resistant wheat. *Front. Plant Sci.* 5:641
36. Eom J-S, Luo D, Atienza-Grande G, Yang J, Ji C, et al. 2019. Diagnostic kit for rice blight resistance. *Nat. Biotechnol.* 37:1372–79
37. Farnham G, Baulcombe DC. 2006. Artificial evolution extends the spectrum of viruses that are targeted by a disease-resistance gene from potato. *PNAS* 103:18828–33
38. Felix G, Duran JD, Volko S, Boller T. 1999. Plants have a sensitive perception system for the most conserved domain of bacterial flagellin. *Plant J.* 18:265–76

39. Figueroa M, Hammond Kosack KE, Solomon PS. 2018. A review of wheat diseases—a field perspective. *Mol. Plant Pathol.* 19:1523–36
40. Fu D, Uauy C, Distelfeld A, Blechl A, Epstein L, et al. 2009. A kinase-START gene confers temperature-dependent resistance to wheat stripe rust. *Science* 323:1357–60
41. Fu ZQ, Yan S, Saleh A, Wang W, Ruble J, et al. 2012. NPR3 and NPR4 are receptors for the immune signal salicylic acid in plants. *Nature* 486:228–32
42. Fukuoka S, Saka N, Koga H, Ono K, Shimizu T, et al. 2009. Loss of function of a proline-containing protein confers durable disease resistance in rice. *Science* 325:998–1001
43. Fukuoka S, Saka N, Mizukami Y, Koga H, Yamanouchi U, et al. 2015. Gene pyramiding enhances durable blast disease resistance in rice. *Sci. Rep.* 5:7773
44. Gao Y, Zhang C, Han X, Wang Z, Ma L, et al. 2018. Inhibition of *OsSWEET11* function in mesophyll cells improves resistance of rice to sheath blight disease. *Mol. Plant Pathol.* 19:2149–61
45. Gaudelli NM, Komor AC, Rees HA, Packer MS, Badran AH, et al. 2017. Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. *Nature* 551:464–71
46. German SE, Kolmer JA. 1992. Effect of gene *Lr34* in the enhancement of resistance to leaf rust of wheat. *Theor. Appl. Genet.* 84:97–105
47. Giannakopoulou A, Steele JFC, Segretin ME, Bozkurt TO, Zhou J, et al. 2015. Tomato 12 immune receptor can be engineered to confer partial resistance to the oomycete *Phytophthora infestans* in addition to the fungus *Fusarium oxysporum*. *Mol. Plant-Microbe Interact.* 28:1316–29
48. Glazebrook J. 2005. Contrasting mechanisms of defense against biotrophic and necrotrophic pathogens. *Annu. Rev. Phytopathol.* 43:205–27
49. Harkenrider M, Sharma R, De Vleesschauwer D, Tsao L, Zhang X, et al. 2016. Overexpression of rice wall-associated kinase 25 (OsWAK25) alters resistance to bacterial and fungal pathogens. *PLOS ONE* 11:e0147310
50. Harris CJ, Slootweg EJ, Goverse A, Baulcombe DC. 2013. Stepwise artificial evolution of a plant disease resistance gene. *PNAS* 110:21189–94
51. Haverkort AJ, Boonekamp PM, Hutten R, Jacobsen E, Lotz LAP, et al. 2016. Durable late blight resistance in potato through dynamic varieties obtained by cisgenesis: scientific and societal advances in the DuRPh project. *Potato Res.* 59:35–66
52. Heath MC. 2000. Nonhost resistance and nonspecific plant defenses. *Curr. Opin. Plant Biol.* 3:315–19
53. Helliwell EE, Wang Q, Yang Y. 2013. Transgenic rice with inducible ethylene production exhibits broad-spectrum disease resistance to the fungal pathogens *Magnaporthe oryzae* and *Rhizoctonia solani*. *Plant Biotechnol. J.* 11:33–42
54. Herrera-Foessel SA, Singh RP, Lillemo M, Huerta-Espino J, Bhavani S, et al. 2014. *Lr67/Yr46* confers adult plant resistance to stem rust and powdery mildew in wheat. *Theor. Appl. Genet.* 127:781–89
55. Hittalmani S, Parco A, Mew TV, Zeigler RS, Huang N. 2000. Fine mapping and DNA marker-assisted pyramiding of the three major genes for blast resistance in rice. *Theor. Appl. Genet.* 100:1121–28
56. Holton N, Nekrasov V, Ronald PC, Zipfel C. 2015. The phylogenetically-related pattern recognition receptors EFR and XA21 recruit similar immune signaling components in monocots and dicots. *PLOS Pathog.* 11:e1004602
57. Hong Y, Liu Q, Cao Y, Zhang Y, Chen D, et al. 2019. The *OsMPK15* negatively regulates *Magnaporthe oryza* and *Xoo* disease resistance via SA and JA signaling pathway in rice. *Front. Plant Sci.* 10:752
58. Hu K, Cao J, Zhang J, Xia F, Ke Y, et al. 2017. Improvement of multiple agronomic traits by a disease resistance gene via cell wall reinforcement. *Nat. Plants* 3:17009
59. Hummel AW, Doyle EL, Bogdanove AJ. 2012. Addition of transcription activator-like effector binding sites to a pathogen strain-specific rice bacterial blight resistance gene makes it effective against additional strains and against bacterial leaf streak. *New Phytol.* 195:883–93
60. Hurni S, Scheuermann D, Krattinger SG, Kessel B, Wicker T, et al. 2015. The maize disease resistance gene *Htn1* against northern corn leaf blight encodes a wall-associated receptor-like kinase. *PNAS* 112:8780–85
61. Hutin M, Césari S, Chalvon V, Michel C, Tran TT, et al. 2016. Ectopic activation of the rice NLR heteropair RGA4/RGA5 confers resistance to bacterial blight and bacterial leaf streak diseases. *Plant J.* 88:43–55

62. Hutin M, Sabot F, Ghesquière A, Koebnik R, Szurek B. 2015. A knowledge-based molecular screen uncovers a broad-spectrum *OsSWEET14* resistance allele to bacterial blight from wild rice. *Plant J.* 84:694–703
63. Ishizaki K, Hoshi T, Abe S, Sasaki Y, Kobayashi K, et al. 2005. Breeding of blast resistant isogenic lines in rice variety "Koshihikari" and evaluation of their characters. *Breed. Sci.* 55:371–77
64. Jia Z, Gou J, Sun Y, Yuan L, Tang Q, et al. 2010. Enhanced resistance to fungal pathogens in transgenic *Populus tomentosa* Carr. by overexpression of an nsLTP-like antimicrobial protein gene from motherwort (*Leonurus japonicus*). *Tree Physiol.* 30:1599–605
65. Jiang CJ, Shimono M, Maeda S, Inoue H, Mori M, et al. 2009. Suppression of the rice fatty-acid desaturase gene *OsSSI2* enhances resistance to blast and leaf blight diseases in rice. *Mol. Plant-Microbe Interact.* 22:820–29
66. Jiang GH, Xia ZH, Zhou YL, Wan J, Li DY, et al. 2006. Testifying the rice bacterial blight resistance gene *xa5* by genetic complementation and further analyzing *xa5* (*Xa5*) in comparison with its homolog *TFIIAγ 1*. *Mol. Genet. Genom.* 275:354–66
67. Jiang H, Feng Y, Bao L, Li X, Gao G, et al. 2012. Improving blast resistance of Jin 23B and its hybrid rice by marker-assisted gene pyramiding. *Mol. Breed.* 30:1679–88
68. Jiang JF, Yang DB, Ali J, Mou TM. 2015. Molecular marker-assisted pyramiding of broad-spectrum disease resistance genes, *Pi2* and *Xa23*, into GZ63-4S, an elite thermo-sensitive genic male-sterile line in rice. *Mol. Breed.* 35:83
69. Jiang M, Zhang CY, Khalid H, Li N, Sun Q, et al. 2012. Pyramiding resistance genes to northern leaf blight and head smut in maize. *Int. J. Agric. Biol.* 14:430–44
70. Jiang R, Li J, Tian Z, Du J, Armstrong M, et al. 2018. Potato late blight field resistance from QTL *dPI09c* is conferred by the NB-LRR gene *R8*. *J. Exp. Bot.* 69:1545–55
71. Jones JD, Dangl JL. 2006. The plant immune system. *Nature* 444:323–29
72. Kang L, Li J, Zhao T, Xiao F, Tang X, et al. 2003. Interplay of the *Arabidopsis* nonhost resistance gene *oNHO1* with bacterial virulence. *PNAS* 100:3519–24
73. Kawashima CG, Guimaraes GA, Nogueira SR, MacLean D, Cook DR, et al. 2016. A pigeonpea gene confers resistance to Asian soybean rust in soybean. *Nat. Biotechnol.* 34:661–65
74. Keller H, Pamboukdjian N, Ponchet M, Poupet A, Delon R, et al. 1999. Pathogen-induced elicitin production in transgenic tobacco generates a hypersensitive response and nonspecific disease resistance. *Plant Cell* 11:223–35
75. Kim MC, Panstruga R, Elliott C, Muller J, Devoto A, et al. 2002. Calmodulin interacts with MLO protein to regulate defence against mildew in barley. *Nature* 416:447–51
76. Kim SH, Qi D, Ashfield T, Helm M, Innes RW. 2016. Using decoys to expand the recognition specificity of a plant disease resistance protein. *Science* 351:684–87
77. Klymiuk V, Yaniv E, Huang L, Raats D, Fatiukha A, et al. 2018. Cloning of the wheat *Yr15* resistance gene sheds light on the plant tandem kinase-pseudokinase family. *Nat. Commun.* 9:3735
78. Koizumi S. 2010. Ecological and genetic studies on durable use of blast resistance in rice. *J. Gen. Plant Pathol.* 76:406–10
79. Koller T, Brunner S, Herren G, Hurni S, Keller B. 2018. Pyramiding of transgenic *Pm3* alleles in wheat results in improved powdery mildew resistance in the field. *Theor. Appl. Genet.* 131:861–71
80. Kou Y, Wang S. 2010. Broad-spectrum and durability: understanding of quantitative disease resistance. *Curr. Opin. Plant Biol.* 13:181–85
81. Kourelis J, van der Hoorn RAL, Sueldo DJ. 2016. Decoy engineering: the next step in resistance breeding. *Trends Plant Sci.* 21:371–73
82. Krattinger SG, Lagudah ES, Spielmeyer W, Singh R, Huerta-Espino J, et al. 2009. A putative ABC transporter confers durable resistance to multiple fungal pathogens in wheat. *Science* 323:1360–63
83. Krattinger SG, Sucher J, Selter LL, Chauhan H, Zhou B, et al. 2016. The wheat durable, multipathogen resistance gene *Lr34* confers partial blast resistance in rice. *Plant Biotechnol. J.* 14:1261–68
84. Kunze G, Zipfel C, Robatzek S, Niehaus K, Boller T, Felix G. 2004. The N terminus of bacterial elongation factor Tu elicits innate immunity in Arabidopsis plants. *Plant Cell* 16:3496–507

85. Kwon SW, Cho YC, Kim YG, Suh JP, Jeung JU, et al. 2008. Development of near-isogenic *Japonica* rice lines with enhanced resistance to *Magnaporthe grisea*. *Mol. Cell* 25:407–16
86. Lacombe S, Rougon-Cardoso A, Sherwood E, Peeters N, Dahlbeck D, et al. 2010. Interfamily transfer of a plant pattern-recognition receptor confers broad-spectrum bacterial resistance. *Nat. Biotechnol.* 28:365–69
87. Lagudah ES, Krattinger SG, Herrera-Foessel SA, Singh RP, Huerta-Espino J, et al. 2009. Gene-specific markers for the wheat gene *Lr34/Yr18/Pm38* which confers resistance to multiple fungal pathogens. *Theor. Appl. Genet.* 119:889–98
88. Leach JE, Cruz CMV, Bai JF, Leung H. 2001. Pathogen fitness penalty as a predictor of durability of disease resistance genes. *Annu. Rev. Phytopathol.* 39:187–224
89. Lee SC, Hwang IS, Choi HW, Hwang BK. 2008. Involvement of the pepper antimicrobial protein CaAMP1 gene in broad spectrum disease resistance. *Plant Physiol.* 148:1004–20
90. Lee SW, Han SW, Sririyanum M, Park CJ, Seo YS, Ronald C. 2009. A type I–secreted, sulfated peptide triggers XA21-mediated innate immunity. *Science* 326:850–53
91. Li G, Zhou J, Jia H, Gao Z, Fan M, et al. 2019. Mutation of a histidine-rich calcium-binding-protein gene in wheat confers resistance to Fusarium head blight. *Nat. Genet.* 51:1106–12
92. Li S, Shen L, Hu P, Liu Q, Zhu X, et al. 2019. Developing disease-resistant thermosensitive male sterile rice by multiplex gene editing. *J. Integr. Plant Biol.* 61:1201–5
93. Li W, Zhong S, Li G, Li Q, Mao B, et al. 2011. Rice RING protein OsBBI1 with E3 ligase activity confers broad-spectrum resistance against *Magnaporthe oryzae* by modifying the cell wall defence. *Cell Res.* 21:835–48
94. Li W, Zhu Z, Chern M, Yin J, Yang C, et al. 2017. A natural allele of a transcription factor in rice confers broad-spectrum blast resistance. *Cell* 170:114–26
95. Li X, Kapos P, Zhang Y. 2015. NLRs in Plants. *Curr. Opin. Immunol.* 32:114–21
96. Li Z, Ding B, Zhou X, Wang GL. 2017. The rice dynamin-related protein OsDRP1E negatively regulates programmed cell death by controlling the release of cytochrome *c* from mitochondria. *PLOS Pathog.* 13:e1006157
97. Liao Y, Bai Q, Xu P, Wu T, Guo D, et al. 2018. Mutation in rice *Abscisic Acid2* results in cell death, enhanced disease-resistance, altered seed dormancy and development. *Front. Plant Sci.* 9:405
98. Lillemo M, Asalf B, Singh RP, Huerta-Espino J, Chen XM, et al. 2008. The adult plant rust resistance loci *Lr34/Yr18* and *Lr46/Yr29* are important determinants of partial resistance to powdery mildew in bread wheat line Saar. *Theor. Appl. Genet.* 116:1155–66
99. Lipka V, Dittgen J, Bednarek P, Bhat R, Wiermer M, et al. 2005. Pre- and postinvasion defenses both contribute to nonhost resistance in *Arabidopsis*. *Science* 310:1180–83
100. Liu B, Li JF, Ao Y, Qu J, Li Z, et al. 2012. Lysin motif-containing proteins LYP4 and LYP6 play dual roles in peptidoglycan and chitin perception in rice innate immunity. *Plant Cell* 24:3406–19
101. Liu D, Xin M, Zhou X, Wang C, Zhang Y, Qin Z. 2017. Expression and functional analysis of the transcription factor-encoding gene *CsERF004* in cucumber during *Pseudoperonospora cubensis* and *Corynespora cassiicola* infection. *BMC Plant Biol.* 17:96
102. Liu J, Chen X, Liang X, Zhou X, Yang F, et al. 2016. Alternative splicing of rice *WRKY62* and *WRKY76* transcription factor genes in pathogen defense. *Plant Physiol.* 171:1427–42
103. Liu J, Liu D, Tao W, Li W, Wang S, et al. 2000. Molecular marker-facilitated pyramiding of different genes for powdery mildew resistance in wheat. *Plant Breed* 119:21–24
104. Liu J, Park CH, He F, Nagano M, Wang M, et al. 2015. The RhoGAP SPIN6 associates with SPL11 and OsRac1 and negatively regulates programmed cell death and innate immunity in rice. *PLOS Pathog.* 11:e1004629
105. Liu JZ, Horstman HD, Braun E, Graham MA, Zhang C, et al. 2011. Soybean homologs of MPK4 negatively regulate defense responses and positively regulate growth and development. *Plant Physiol.* 157:1363–78
106. Liu M, Shi Z, Zhang X, Wang M, Zhang L, et al. 2019. Inducible overexpression of *Ideal Plant Architecture1* improves both yield and disease resistance in rice. *Nat. Plants* 5:389–400

107. Liu Q, Ning Y, Zhang Y, Yu N, Zhao C, et al. 2017. OsCUL3a negatively regulates cell death and immunity by degrading OsNPR1 in rice. *Plant Cell* 29:345–59
108. Liu S, Kandoth PK, Warren SD, Yeckel G, Heinz R, et al. 2012. A soybean cyst nematode resistance gene points to a new mechanism of plant resistance to pathogens. *Nature* 492:256–60
109. Liu W, Liu J, Triplett L, Leach JE, Wang GL. 2014. Novel insights into rice innate immunity against bacterial and fungal pathogens. *Annu. Rev. Phytopathol.* 52:213–41
110. Liu Y, Cao Y, Zhang Q, Li X, Wang S. 2018. A cytosolic triosephosphate isomerase is a key component in XA3/XA26-mediated resistance. *Plant Physiol.* 178:923–35
111. Loehrer M, Langenbach C, Goellner K, Conrath U, Schaffrath U. 2008. Characterization of nonhost resistance of *Arabidopsis* to the Asian soybean rust. *Mol. Plant-Microbe Interact.* 21:1421–30
112. Lu F, Wang H, Wang S, Jiang W, Shan C, et al. 2015. Enhancement of innate immune system in monocot rice by transferring the dicotyledonous elongation factor Tu receptor EFR. *J. Integr. Plant Biol.* 57:641–52
113. Lu M, Tang X, Zhou JM. 2001. Arabidopsis *NHO1* is required for general resistance against *Pseudomonas* bacteria. *Plant Cell* 13:437–47
114. Luo Y, Ma T, Zhang AF, Ong K, Luo Z, et al. 2017. Marker-assisted breeding of Chinese elite rice cultivar 9311 for disease resistance to rice blast and bacterial blight and tolerance to submergence. *Mol. Breed.* 37:106
115. Maeda S, Hayashi N, Sasaya T, Mori M. 2016. Overexpression of *BSR1* confers broad-spectrum resistance against two bacterial diseases and two major fungal diseases in rice. *Breed. Sci.* 66:396–406
116. Makandar R, Essig JS, Schapaugh MA, Trick HN, Shah J. 2006. Genetically engineered resistance to fusarium head blight in wheat by expression of *Arabidopsis NPR1*. *Mol. Plant-Microbe Interact.* 19:123–29
117. Malnoy M, Borejsza-Wysocka MM, Aldwinckle HS, Jin QL, He SY. 2006. Transgenic apple lines overexpressing the apple gene *MpNPR1* have increased resistance to fire blight. *Acta Hortic.* 704:521–26
118. Malnoy M, Jin Q, Borejsza-Wysocka EE, He SY, Aldwinckle HS. 2007. Overexpression of the apple *MpNPR1* gene confers increased disease resistance in *Malus* × *domestica*. *Mol. Plant-Microbe Interact.* 20:1568–80
119. Matthews BF, Beard H, Brewer E, Kabir S, MacDonald MH, Youssef RM. 2014. *Arabidopsis* genes, *AtNPR1*, *AtTGA2* and *AtPR-5*, confer partial resistance to soybean cyst nematode (*Heterodera glycines*) when overexpressed in transgenic soybean roots. *BMC Plant Biol.* 14:96
120. Mazier M, Flamain F, Nicolaï M, Sarnette V, Caranta C. 2011. Knock-down of both *eIF4E1* and *eIF4E2* genes confers broad-spectrum resistance against potyviruses in tomato. *PLOS ONE* 6:e2959
121. McDonald BA, Linde C. 2002. Pathogen population genetics, evolutionary potential, and durable resistance. *Annu. Rev. Phytopathol.* 40:349–79
122. Meksem K, Pantazopoulos P, Njiti VN, Hyten LD, Arelli PR, Lightfoot DA. 2001. 'Forrest' resistance to the soybean cyst nematode is bigenic: saturation mapping of the *Rhg*1and *Rhg*4 loci. *Theor. Appl. Genet.* 103:710–17
123. Mendes BMJ, Cardoso SC, Boscariol-Camargo RL, Cruz RB, Mourão-Filho FAA, Bergamin Filho A. 2010. Reduction in susceptibility to *Xanthomonas axonopodis* pv. *citri* in transgenic *Citrus sinensis* expressing the rice *Xa21* gene. *Plant Pathol.* 59:68–75
124. Morbitzer R, Römer P, Boch J, Lahaye T. 2010. Regulation of selected genome loci using de novo-engineered transcription activator-like effector (TALE)-type transcription factors. *PNAS* 107:21617–22
125. Mundt CC. 2002. Use of multiline cultivars and cultivar mixtures for disease management. *Annu. Rev. Phytopathol.* 40:381–410
126. Mundt CC. 2014. Durable resistance: a key to sustainable management of pathogens and pests. *Infect. Genet. Evol.* 27:446–55
127. Mundt CC. 2018. Pyramiding for resistance durability: theory and practice. *Phytopathology* 108:792–802
128. Mysore KS, Ryu CM. 2004. Nonhost resistance: How much do we know? *Trends Plant Sci.* 9:97–104
129. Narusaka M, Shirasu K, Noutoshi Y, Kubo Y, Shiraishi T, et al. 2009. *RRS1* and *RPS4* provide a dual *Resistance*-gene system against fungal and bacterial pathogens. *Plant J.* 60:218–26
130. Nekrasov V, Wang CM, Win J, Lanz C, Weigel D, Kamoun S. 2017. Rapid generation of a transgene-free powdery mildew resistant tomato by genome deletion. *Sci. Rep.* 7:6

131. Nelson R, Wiesner-Hanks T, Wisser R, Balint-Kurti P. 2018. Navigating complexity to breed disease-resistant crops. *Nat. Rev. Genet.* 19:21–33
132. Ni DH, Song FS, Ni JL, Zhang AF, Wang CL, et al. 2015. Marker-assisted selection of two-line hybrid rice for disease resistance to rice blast and bacterial blight. *Field Crop. Res.* 184:1–8
133. Ni X, Tian Z, Liu J, Song B, Xie C. 2010. Cloning and molecular characterization of the potato RING finger protein gene *StRFP1* and its function in potato broad-spectrum resistance against Phytophthora infestans. *J. Plant Physiol.* 167:488–96
134. Ning Y, Liu W, Wang GL. 2017. Balancing immunity and yield in crop plants. *Trends Plant Sci*. 22:1069–79
135. O'Connell RJ, Panstruga R. 2006. Tête à tête inside a plant cell: establishing compatibility between plants and biotrophic fungi and oomycetes. *New Phytol*. 171:699–718
136. Oliva R, Ji C, Atienza-Grande G, Huguet-Tapia JC, Perez-Quintero A, et al. 2019. Broad-spectrum resistance to bacterial blight in rice using genome editing. *Nat. Biotechnol.* 37:1344–50
137. Omar AA, Murata MM, El-Shamy HA, Graham JH, Grosser JW. 2018. Enhanced resistance to citrus canker in transgenic mandarin expressing Xa21 from rice. *Transgenic Res*. 27:179–91
138. Parisi K, Shafee TMA, Quimbar P, van der Weerden NL, Bleackley MR, Anderson MA. 2019. The evolution, function and mechanisms of action for plant defensins. *Semin. Cell Dev. Biol.* 88:107–18
139. Peng H, Zhang Q, Li Y, Lei C, Zhai Y, et al. 2009. A putative leucine-rich repeat receptor kinase, OsBRR1, is involved in rice blast resistance. *Planta* 230:377–85
140. Peng X, Hu Y, Tang X, Zhou P, Deng X, et al. 2012. Constitutive expression of rice *WRKY30* gene increases the endogenous jasmonic acid accumulation, *PR* gene expression and resistance to fungal pathogens in rice. *Planta* 236:1485–98
141. Pfeilmeier S, George J, Morel A, Roy S, Smoker M. et al. 2019. Expression of the *Arabidopsis thaliana* immune receptor *EFR* in *Medicago truncatula* reduces infection by a root pathogenic bacterium, but not nitrogen-fixing rhizobial symbiosis. *Plant Biotechnol. J.* 17:569–79
142. Piffanelli P, Zhou F, Casais C, Orme J, Jarosch B, et al. 2002. The barley MLO modulator of defense and cell death is responsive to biotic and abiotic stress stimuli. *Plant Physiol.* 129:1076–85
143. Pink DAC. 2002. Strategies using genes for non-durable disease resistance. *Euphytica* 124:227–36
144. Pradhan SK, Nayak DK, Mohanty S, Behera L, Barik SR, et al. 2015. Pyramiding of three bacterial blight resistance genes for broad-spectrum resistance in deepwater rice variety, Jalmagna. *Rice* 8:51
145. Pyott DE, Sheehan E, Molnar A. 2016. Engineering of CRISPR/Cas9-mediated potyvirus resistance in transgene-free *Arabidopsis* plants. *Mol. Plant Pathol.* 17:1276–88
146. Qi T, Seong K, Thomazella DPT, Kim JR, Pham J, et al. 2018. NRG1 functions downstream of EDS1 to regulate TIR-NLR-mediated plant immunity in *Nicotiana benthamiana*. *PNAS* 115:10979–87
147. Qian C, Cui C, Wang X, Zhou C, Hu P, et al. 2017. Molecular characterisation of the broad-spectrum resistance to powdery mildew conferred by the *Stpk-V* gene from the wild species *Haynaldia villosa*. *Plant Biol*. 19:875–85
148. Qiao Y, Jiang W, Lee J, Park B, Choi MS, et al. 2010. *SPL28* encodes a clathrin-associated adaptor protein complex 1, medium subunit μ1 (AP1M1) and is responsible for spotted leaf and early senescence in rice (*Oryza sativa*). *New Phytol*. 185:258–74
149. Qie Y, Liu Y, Wang M, Li X, See DR, et al. 2019. Development, validation, and re-selection of wheat lines with pyramided genes *Yr64* and *Yr15* linked on the short arm of chromosome 1B for resistance to stripe rust. *Plant Dis*. 103:51–58
150. Quilis J, Peñas G, Messeguer J, Brugidou C, San Segundo B. 2008. The *Arabidopsis AtNPR1* inversely modulates defense responses against fungal, bacterial, or viral pathogens while conferring hypersensitivity to abiotic stresses in transgenic rice. *Mol. Plant-Microbe Interact.* 21:1215–31
151. Rawat N, Pumphrey MO, Liu S, Zhang X, Tiwari VK, et al. 2016. Wheat *Fhb1* encodes a chimeric lectin with agglutinin domains and a pore-forming toxin-like domain conferring resistance to Fusarium head blight. *Nat. Genet.* 48:1576–80
152. Robatzek S, Bittel P, Chinchilla D, Köchner P, Felix G, et al. 2007. Molecular identification and characterization of the tomato flagellin receptor LeFLS2, an orthologue of *Arabidopsis* FLS2 exhibiting characteristically different perception specificities. *Plant Mol. Biol.* 64:539–47

153. Römer P, Strauss T, Hahn S, Scholze H, Morbitzer R, et al. 2009. Recognition of AvrBs3-like proteins is mediated by specific binding to promoters of matching pepper *Bs3* alleles. *Plant Physiol*. 150:1697–712
154. Sánchez-Martín J, Steuernagel B, Ghosh S, Herren G, Hurni S, et al. 2016. Rapid gene isolation in barley and wheat by mutant chromosome sequencing. *Genome Biol*. 17:221
155. Sanfaçon H. 2015. Plant translation factors and virus resistance. *Viruses* 7:3392–419
156. Sathoff AE, Velivelli S, Shah DM, Samac DA. 2019. Plant defensin peptides have antifungal and antibacterial activity against human and plant pathogens. *Phytopathology* 109:402–8
157. Savary S, Willocquet L, Pethybridge SJ, Esker P, McRoberts N, Nelson A. 2019. The global burden of pathogens and pests on major food crops. *Nat. Ecol. Evol.* 3:430–39
158. Sawada K, Hasegawa M, Tokuda L, Kameyama J, Kodama O, et al. 2004. Enhanced resistance to blast fungus and bacterial blight in transgenic rice constitutively expressing *OsSBP*, a rice homologue of mammalian selenium-binding proteins. *Biosci. Biotechnol. Biochem*. 68:873–80
159. Schoonbeek HJ, Wang HH, Stefanato FL, Craze M, Bowden S, et al. 2015. Arabidopsis EF-Tu receptor enhances bacterial disease resistance in transgenic wheat. *New Phytol*. 206:606–13
160. Schultink A, Qi T, Lee A, Steinbrenner AD, Staskawicz B. 2017. Roq1 mediates recognition of the Xanthomonas and Pseudomonas effector proteins XopQ and HopQ1. *Plant J*. 92:787–95
161. Schwessinger B, Bahar O, Thomas N, Holton N, Nekrasov V, et al. 2015. Transgenic expression of the dicotyledonous pattern recognition receptor EFR in rice leads to ligand-dependent activation of defense responses. *PLOS Pathog*. 11:e1004809
162. Segretin ME, Pais M, Franceschetti M, Chaparro-Garcia A, Bos JIB, et al. 2014. Single amino acid mutations in the potato immune receptor R3a expand response to *Phytophthora* effectors. *Mol. Plant-Microbe Interact.* 27:624–37
163. Shimono M, Koga H, Akagi A, Hayashi N, Goto S, et al. 2012. Rice WRKY45 plays important roles in fungal and bacterial disease resistance. *Mol. Plant Pathol.* 13:83–94
164. Silva KJP, Brunings A, Peres NA, Mou Z, Folta KM. 2015. The *Arabidopsis NPR1* gene confers broad-spectrum disease resistance in strawberry. *Transgenic Res*. 24:693–704
165. Silva KJP, Mahna N, Mou Z, Folta KM. 2018. *NPR1* as a transgenic crop protection strategy in horticultural species. *Hortic Res*. 5:15
166. Singh RP, Hodson DP, Jin Y, Lagudah ES, Ayliffe MA, et al. 2015. Emergence and spread of new races of wheat stem rust fungus: continued threat to food security and prospects of genetic control. *Phytopathology* 105:872–84
167. Singh RP, Huerta-Espino J, Bhavani S, Herrera-Foessel SA, Singh D, et al. 2011. Race non-specific resistance to rust diseases in CIMMYT spring wheats. *Euphytica* 179:175–86
168. Somers DJ, Thomas J, DePauw R, Fox S, Humphreys G, Fedak G. 2005. Assembling complex genotypes to resist *Fusarium* in wheat (*Triticum aestivum* L.). *Theor. Appl. Genet.* 111:1623–31
169. Spielmeyer W, Mago R, Wellings C, Ayliffe M. 2013. *Lr67* and *Lr34* rust resistance genes have much in common – they confer broad spectrum resistance to multiple pathogens in wheat. *BMC Plant Biol*. 13:96
170. St. Clair DA. 2010. Quantitative disease resistance and quantitative resistance loci in breeding. *Annu. Rev. Phytopathol*. 48:247–68
171. Stein M, Dittgen J, Sánchez-Rodríguez C, Hou BH, Molina A, et al. 2006. *Arabidopsis* PEN3/PDR8, an ATP binding cassette transporter, contributes to nonhost resistance to inappropriate pathogens that enter by direct penetration. *Plant Cell* 18:731–46
172. Steuernagel B, Periyannan SK, Hernández-Pinzón I, Witek K, Rouse MN, et al. 2016. Rapid cloning of disease-resistance genes in plants using mutagenesis and sequence capture. *Nat. Biotechnol.* 34:652–55
173. Stirnweis D, Milani SD, Jordan T, Keller B, Brunner S. 2014. Substitutions of two amino acids in the nucleotide-binding site domain of a resistance protein enhance the hypersensitive response and enlarge the PM3F resistance spectrum in wheat. *Mol. Plant-Microbe Interact.* 27:265–76
174. Su Z, Bernardo A, Tian B, Chen H, Wang S, et al. 2019. A deletion mutation in *TaHRC* confers *Fhb1* resistance to Fusarium head blight in wheat. *Nat. Genet.* 51:1099–105
175. Sucher J, Boni R, Yang P, Rogowsky P, Buchner H, et al. 2017. The durable wheat disease resistance gene *Lr34* confers common rust and northern corn leaf blight resistance in maize. *Plant Biotechnol. J.* 15:489–96

176. Suh JP, Jeung JU, Noh TH, Cho YC, Park SH, et al. 2013. Development of breeding lines with three pyramided resistance genes that confer broad-spectrum bacterial blight resistance and their molecular analysis in rice. *Rice* 6:5
177. Sun X, Cao Y, Yang Z, Xu C, Li X, et al. 2004. *Xa26*, a gene conferring resistance to *Xanthomonas oryzae* pv. *oryzae* in rice, encodes an LRR receptor kinase-like protein. *Plant J.* 37:517–27
178. Swathi G, Rani CVD, Md J, Madhav MS, Vanisree S, et al. 2019. Marker-assisted introgression of the major bacterial blight resistance genes, *Xa21* and *xa13*, and blast resistance gene, *Pi54*, into the popular rice variety, JGL1798. *Mol. Breed.* 39:58
179. Tang D, Simonich MT, Innes RW. 2007. Mutations in *LACS2*, a long-chain acyl-coenzyme A synthetase, enhance susceptibility to avirulent *Pseudomonas syringae* but confer resistance to *Botrytis cinerea* in Arabidopsis. *Plant Physiol.* 144:1093–103
180. Tang X, Xie M, Kim YJ, Zhou J, Klessig DF, Martin GB. 1999. Overexpression of *Pto* activates defense responses and confers broad resistance. *Plant Cell* 11:15–29
181. Tao Z, Liu H, Qiu D, Hou Y, Li X, et al. 2009. A pair of allelic WRKY genes play opposite roles in rice-bacteria interactions. *Plant Physiol.* 151:936–48
182. Thomma BP, Nurnberger T, Joosten MH. 2011. Of PAMPs and effectors: the blurred PTI-ETI dichotomy. *Plant Cell* 23:4–15
183. Tripathi JN, Lorenzen J, Bahar O, Ronald P, Tripathi L. 2014. Transgenic expression of the rice *Xa21* pattern-recognition receptor in banana (*Musa* sp.) confers resistance to *Xanthomonas campestris* pv. *musacearum*. *Plant Biotechnol. J.* 12:663–73
184. Tsilo TJ, Kolmer JA, Anderson JA. 2014. Molecular mapping and improvement of leaf rust resistance in wheat breeding lines. *Phytopathology* 104:865–70
185. Van Damme M, Huibers RP, Elberse J, Van den Ackerveken G. 2008. Arabidopsis *DMR6* encodes a putative 2OG-Fe(II) oxygenase that is defense-associated but required for susceptibility to downy mildew. *Plant J.* 54:785–93
186. Vo KTX, Kim CY, Hoang TV, Lee SK, Shirsekar G, et al. 2018. OsWRKY67 plays a positive role in basal and XA21-mediated resistance in rice. *Front. Plant Sci.* 8:2220
187. von Arnim AG, Jia Q, Vaughn JN. 2014. Regulation of plant translation by upstream open reading frames. *Plant Sci.* 214:1–12
188. Wally O, Jayaraj J, Punja ZK. 2009. Broad-spectrum disease resistance to necrotrophic and biotrophic pathogens in transgenic carrots (*Daucus carota* L.) expressing an Arabidopsis *NPR1* gene. *Planta* 231:131–41
189. Wang J, Qu B, Dou S, Li L, Yin D, et al. 2015. The E3 ligase OsPUB15 interacts with the receptor-like kinase PID2 and regulates plant cell death and innate immunity. *BMC Plant Biol.* 15:49
190. Wang J, Zhou L, Shi H, Chern M, Yu H, et al. 2018. A single transcription factor promotes both yield and immunity in rice. *Science* 361:1026–28
191. Wang L, Jiang W, Zhang Y, Wang S, Ma R, Sun W. 2013. Ax21-triggered immunity plays a significant role in rice defense against *Xanthomonas oryzae* pv. oryzicola. *Phytopathology*. In press. DOI:10.1094/PHYTO-12-12-0333-R
192. Wang Y, Tan J, Wu Z, VandenLangenberg K, Wehner TC, et al. 2019. STAYGREEN, STAY HEALTHY: A loss-of-susceptibility mutation in the *STAYGREEN* gene provides durable, broad-spectrum disease resistances for over 50 years of US cucumber production. *New Phytol.* 221:415–30
193. Wang YP, Cheng X, Shan QW, Zhang Y, Liu JX, et al. 2014. Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew. *Nat. Biotechnol.* 32:947–51
194. Wang Z, Cheng J, Fan A, Zhao J, Yu Z, et al. 2018. *LecRK-V*, an L-type lectin receptor kinase in *Haynaldia villosa*, plays positive role in resistance to wheat powdery mildew. *Plant Biotechnol. J.* 16:50–62
195. Wisser RJ, Sun Q, Hulbert SH, Kresovich S, Nelson RJ. 2005. Identification and characterization of regions of the rice genome associated with broad-spectrum, quantitative disease resistance. *Genetics* 169:2277–93
196. Wu Y, Xiao N, Chen Y, Yu L, Pan C, et al. 2019. Comprehensive evaluation of resistance effects of pyramiding lines with different broad-spectrum resistance genes against *Magnaporthe oryzae* in rice (*Oryza sativa* L.). *Rice* 12:11

197. Xiao N, Wu YY, Pan CH, Yu L, Chen Y, et al. 2017. Improving of rice blast resistances in *Japonica* by pyramiding major R genes. *Front. Plant Sci.* 7:1918
198. Xiong L, Yang Y. 2003. Disease resistance and abiotic stress tolerance in rice are inversely modulated by an abscisic acid–inducible mitogen-activated protein kinase. *Plant Cell* 15:745–59
199. Xu G, Yuan M, Ai C, Liu L, Zhuang E, et al. 2017. uORF-mediated translation allows engineered plant disease resistance without fitness costs. *Nature* 545:491–94
200. Xu HY, Zhang C, Li ZC, Wang ZR, Jiang XX, et al. 2018. The MAPK kinase kinase GmMEKK1 regulates cell death and defense responses. *Plant Physiol.* 178:907–22
201. Yamaguchi T, Kuroda M, Yamakawa H, Ashizawa T, Hirayae K, et al. 2009. Suppression of a phospholipase D gene, *OsPLDβ1*, activates defense responses and increases disease resistance in rice. *Plant Physiol.* 150:308–19
202. Yan C, Liu Y, Mou T. 2013. Improvement of rice bacterial blight resistance of hybrid rice Jinyou 207 by molecular marker-assisted selection. *Chin. J. Rice Sci.* 27:365–72
203. Yang Q, Balint-Kurti P, Xu M. 2017. Quantitative disease resistance: dissection and adoption in maize. *Mol. Plant* 10:402–13
204. Yang Q, He Y, Kabahuma M, Chaya T, Kelly A, et al. 2017. A gene encoding maize caffeoyl-CoA *O*-methyltransferase confers quantitative resistance to multiple pathogens. *Nat. Genet.* 49:1364–72
205. Yang ZP, Gilbert J, Somers DJ, Fedak G, Procunier JD, McKenzie IH. 2003. Marker assisted selection of Fusarium head blight resistance genes in two doubled haploid populations of wheat. *Mol. Breed.* 12:309–17
206. Yasuda N, Mitsunaga T, Hayashi K, Koizumi S, Fujita Y. 2015. Effects of pyramiding quantitative resistance genes *pi21*, *Pi34*, and *Pi35* on rice leaf blast disease. *Plant Dis.* 99:904–9
207. You Q, Zhai K, Yang D, Yang W, Wu J, et al. 2016. An E3 ubiquitin ligase-BAG protein module controls plant innate immunity and broad-spectrum disease resistance. *Cell Host Microbe* 20:758–69
208. Yu N, Lee TG, Rosa DP, Hudson M, Diers BW. 2016. Impact of *Rhg1* copy number, type, and interaction with *Rhg4* on resistance to *Heterodera glycines* in soybean. *Theor. Appl. Genet.* 129:2403–12
209. Yuan M, Ke Y, Huang R, Ma L, Yang Z, et al. 2016. A host basal transcription factor is a key component for infection of rice by TALE-carrying bacteria. *eLife* 5:e19605
210. Zaidi SS, Mukhtar MS, Mansoor S. 2018. Genome editing: targeting susceptibility genes for plant disease resistance. *Trends Biotechnol.* 36:898–906
211. Zeilmaker T, Ludwig N, Elberse J, Seidl MF, Berke L, et al. 2015. DOWNY MILDEW RESISTANT 6 and DMR6-LIKE OXYGENASE 1 are partially redundant but distinct suppressors of immunity in Arabidopsis. *Plant J.* 81:210–22
212. Zeng LR, Qu S, Bordeos A, Yang C, Baraoidan M, et al. 2004. *Spotted leaf11*, a negative regulator of plant cell death and defense, encodes a U-box/armadillo repeat protein endowed with E3 ubiquitin ligase activity. *Plant Cell* 16:2795–808
213. Zeng X, Tian D, Gu K, Zhou Z, Yang X, et al. 2015. Genetic engineering of the *Xa10* promoter for broad-spectrum and durable resistance to *Xanthomonas oryzae* pv. *oryzae*. *Plant Biotechnol. J.* 13:993–1001
214. Zhai K, Deng Y, Liang D, Tang J, Liu J, et al. 2019. RRM transcription factors interact with NLRs and regulate broad-spectrum blast resistance in rice. *Mol. Cell* 74:996–1009
215. Zhang Y, Cheng YT, Qu N, Zhao Q, Bi D, Li X. 2006. Negative regulation of defense responses in Arabidopsis by two *NPR1* paralogs. *Plant J.* 48:647–56
216. Zhao X, Tan G, Xing Y, Wei L, Chao Q, et al. 2012. Marker-assisted introgression of *qHSR1* to improve maize resistance to head smut. *Mol. Breed.* 30:1077–88
217. Zheng Z, Appiano M, Pavan S, Bracuto V, Ricciardi L, et al. 2016. Genome-wide study of the tomato *SlMLO* gene family and its functional characterization in response to the powdery mildew fungus *Oidium neolycopersici*. *Front. Plant Sci.* 7:380
218. Zhong C, Ren Y, Qi Y, Yu X, Wu X, Tian Z. 2018. PAMP-responsive ATL gene *StRFP1* and its orthologue *NbATL60* positively regulate *Phytophthora infestans* resistance in potato and *Nicotiana benthamiana*. *Plant Sci.* 270:47–57
219. Zhou J, Peng Z, Long J, Sosso D, Liu B, et al. 2015. Gene targeting by the TAL effector PthXo2 reveals cryptic resistance gene for bacterial blight of rice. *Plant J.* 82:632–43

220. Zhou X, Liao H, Chern M, Yin J, Chen Y, et al. 2018. Loss of function of a rice TPR-domain RNA-binding protein confers broad-spectrum disease resistance. *PNAS* 115:3174–79
221. Zhu S, Li Y, Vossen JH, Visser RG, Jacobsen E. 2012. Functional stacking of three resistance genes against *Phytophthora infestans* in potato. *Transgenic Res.* 21:89–99
222. Zhu Y, Chen H, Fan J, Wang Y, Li Y, et al. 2000. Genetic diversity and disease control in rice. *Nature* 406:718–22