REVIEW

Recent advances in developing disease resistance in plants

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Abstract

Approaches to manipulating disease resistance in plants is expanding exponentially due to advances in our understanding of plant defense mechanisms and new tools for manipulating the plant genome. The application of effective strategies is only limited now by adoption of rapid classical genetic techniques and the acceptance of genetically engineered traits for some problems. The use of genome editing and cis-genetics, where possible, may facilitate applications that otherwise require considerable time or genetic engineering, depending on settling legal definitions of the products. Nonetheless, the variety of approaches to developing disease resistance has never been greater.

Keywords

R genes, disease resistance, genome editing

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Genetic resistance represents the most economical approach to crop protection, and one goal of understanding plant/pathogen interactions at the molecular level is to facilitate disease resistance in crop species. Disease resistance is often the most dynamic component of the crop breeding process, requiring continual updating owing to pathogen adaptation to plant genotypes. An ancillary goal is to engineer resistance that is broad (effective against most or all genotypes of the pathogen) and durable (lasting through many cropping seasons). Research continues to unveil details and mechanisms that function to enable pathogens to parasitize plants and how plants defend themselves against parasitism. Increasingly, the knowledge is being implemented in strategies to enhance resistance to pathogens in crop species and to expedite resistance breeding in the field. Creative transgenic approaches continue to be explored, and the more recent genome editing tools have expanded the approaches to engineering resistance. Nonetheless, advances are needed in understanding how basic endogenous defense components work together and in generating novel resistances with components of the defense system.

Heterologous expression of pattern recognition receptors (PRRs), which recognize conserved molecules in pathogens or the products of pathogen-mediated degradation of host molecules and trigger immune responses to a wide range of pathogens, continues to be applied to a widening range of species, particularly those with recalcitrant disease issues¹. *Elongation Factor–Tu Receptor (EFR)* is a PRR that was identified in *Arabidopsis* and recognizes EF-Tu, a highly conserved abundant protein in prokaryotes². Many crop species apparently lack this specific or analogous receptor despite the conserved nature of EF-Tu. Transfer of *AtEFR* from *Arabidopsis* to tobacco and tomato, in particular, reduced disease severity in the field due to two bacterial pathogens with very different life styles, namely *Ralstonia solanacearum* and *Xanthomonas perforans*, the causal agents of bacterial southern wilt and bacterial spot, respectively^{3,4}. Similar results have been reported for potato⁵. *AtEFR* also triggered immunity in wheat upon challenge with *Pseudomonas syringae* pv. *oryzae*⁶. However, transfer of *AtEFR* to rice did not make the lines more resistant to the most prevalent pathogen, *Xanthomonas oryzae* pv. *oryzae* (Xoo), unless the elicitor portion of EF-TU was applied prior to infection^{7,8}. Transfer of another PRR, *Flagellin Sensitive 2 (FLS2)* from *Nicotiana*, to sweet orange reduced susceptibility to citrus canker⁹. Use of the PRR gene *Xa21* continues to be expanded. *Xa21* of rice produces a receptor kinase that recognizes a small sulfonated peptide (RaxX) synthesized by Xoo and some related species and confers resistance to bacterial blight of rice^{10,11}. The effectiveness of *Xa21* is limited to diseases caused by *Xanthomonas* species that produce RaxX¹⁰. Fortunately, transfer of *Xa21* to banana provides resistance to bacterial wilt, which is threatening banana and onset production in east Africa, because the pathogen, *Xanthomonas vasicola* pv. *musacearum*, also makes and processes RaxX¹².

The application of heterologous transfer of PRRs among species will be interesting. *EFR* and *FLS2* were originally identified by the response to the isolated elicitor and do not provide complete resistance to infection due to bacterial virulence

factors, which are capable of suppressing defense signaling by receptors¹³. Perhaps it is not surprising that the introduction of heterologous PRR genes corresponding to highly conserved elicitors does not always provide protection to crop species, as their pathogens may have already adapted to defense responses elicited by infection. On the other hand, it is striking, as noted above, that some bacterial pathogens do not suppress host immunity in the presence of the PRRs. Crop species, including tomato, may have lost some PRRs in the domestication and breeding process.

The largest family of resistance (R) genes encode the nucleotide binding site and leucine-rich repeat (NBS-LRR or NLR for short) proteins. Owing to their conservation and ease of identification, NLRs are closest to what might be called industrial-scale application, and NLR mining could potentially replace R-gene introgression from related but poorer quality germplasm and crosses with related species (wide crosses). NLR members (and the associated components, which often provide the pathogen recognition function) generally provide resistance against a specific subset of pathogens, or races, that express specific effector proteins, and the NLR complex often acts in a gene-for-gene manner. More problematic is that the genes tend to function only within closely related species, possibly because of the adaptation to other components of the specific NLR complex. An early example was the transfer of the *Bs2* gene for resistance to bacterial spot disease in pepper to tomato, which suffers disease from related pathogens^{4,14}. The NLR gene *RG2* for resistance to *Fusarium* was transferred from a resistant diploid banana species to Cavendish banana¹⁵. Another example is the transfer of an NLR from pigeon pea to soybean for resistance to soybean rust¹⁶. The success of transferring NLR genes between species has led to more extensive efforts of extracting NLR homologs (often referred to as R gene analogs or RGAs) from resistant species. R gene enrichment sequencing, or RenSeq, is a sequence capture technique for the enrichment of NLR sequences¹⁷. The underlying goal is to recover NLR family members from plants with known resistance and transfer candidates to the desired variety. Several variations of this method have been reported, including chemical mutagenesis of a line followed by sequence capture and association genetics of wild populations followed by sequence capture^{18,19}. NLR capture from related species will facilitate the stacking of R genes against common core effectors of all extant pathogen genotypes and, consequentially, provide broad resistance. For example, the *Bs2* gene, which targets the ubiquitous AvrBs2 effector of *Xanthomonas*, can be combined with *Roq1*, a new R gene from *Nicotiana* directed at the common effector XopQ, and other as-yet-unidentified NLRs directed toward other conserved effectors as identified in sequencing of large strain collections from infected plants^{20,21}. Advances in NLR gene mining and gene transfer may have come none too soon and can be applied to wheat blast outbreaks²². Advancements in NLR applications will come from new methods to identify novel R genes in existing NLR libraries.

Research is also providing clues that promise to broaden the application of NLR resistance strategies and even the promise of generating NLR libraries with novel pathogen recognition

properties *de novo*. Single NLR-related R gene transfer between distantly related species often fails, and broader application of NLRs will come from a greater understanding of NLR function. NLR-like R genes are simply the variable genetic component of NLR signaling complexes, which occur in a variety of forms. The complex can include a guarded protein, alternatively called guardee or sensor, and the sensor may be an integrated domain of the NLR²³. The guardee may be a defense signaling protein or other component that is targeted by pathogens to enhance susceptibility. In some cases, the guardee has no apparent function other than to recognize the effector or effector activity of the pathogen. In the latter case, the guardee is referred to as a decoy. In a variety of cases, the components consist of a pair of NLR or NLR-like genes²⁴. The NLRs *RPS4* and *RRS1*, for example, are R genes from *Arabidopsis* and provide resistance against the bacteria *Pseudomonas syringae* and *Ralstonia solanacearum*, respectively. The *RPS4/RRS1* pair is a remarkable case where the variation between resistance and susceptibility toward each of the two pathogens was based on separate components. However, both genes are, in fact, required for the resistance to each pathogen²⁵. Furthermore, tomato plants expressing both *RPS4* and *RRS1* were resistant to both bacteria, and similar results were obtained for transgenic cucumber expressing *RPS4/RRS1* against anthracnose²⁶. Manipulation of the complexes may also allow changing the complex to recognize other pathogens. In the *Arabidopsis*–*P. syringae* system, the R gene *PBS1* product is perceived as a decoy working in concert with the NLR *RPS5* and cleaved by the secreted bacterial protease effector AvrPphB. The cleavage of *PBS1* is recognized by R-gene *RPS5*, resulting in the detection of bacteria and a resistance reaction²⁷. A novel *PBS1* gene was created by substituting the cleavage site with cleavage site sequences that are recognized by other viral and secreted bacterial proteases²⁸. When expressed together, the modified *PBS1* genes conferred *RPS5*-mediated resistance to new pathogens. Changes in the integrated sensor domain of the Pik group of NLRs directed at the rice blast pathogen effectors indicate that manipulation of the domain could produce new recognition motifs²⁹. In the potato–*Phytophthora infestans* system, the resistance gene *R3a* is activated by the RXLR effector, AVR3a^{KI}, but not by the allelic product AVR3a^{EM}, and, through random mutagenesis, a mutant version of *R3a* was identified that recognized AVR3a^{EM}³⁰. Interestingly, mutation in the same position in the *I2* gene, a homologue of the *R3a* gene in tomato, made the gene more responsive to AVR3a and conferred partial resistance to *P. infestans* and expanded the gene's effectiveness to an additional fungal pathogen³¹. Recent studies of the structural changes that the NLR proteins themselves undergo upon elicitation may also provide insight for improved manipulation of this effector class^{32,33}. Further utility of the NLR class will come from improved structural models and associated components and induced variation by gene targeting strategies²³.

Ectopic expression of defense-related, toxin, and other miscellaneous genes has always been a major part of the toolbox in engineering resistance. The approaches have been applied to recalcitrant disease problems and, in a variety of cases, have reached or completed confined field trial stage³⁴. Secreted

anti-microbial peptides (AMPs) are used in a variety of crop species³⁵. Cecropin is an AMP naturally produced by a moth, *Hyalophora cecropia*, that confers a broad spectrum of protection against a wide range of pathogens. Rice seed expressing cecropin A from endosperm-specific promoter exhibited resistance to infection by *Fusarium verticillioides* and *Dickeya dadantii*³⁶. A synthetic version of cecropin expressed in citrus was reported to be effective against the bacterium *Candidatus Liberibacter asiaticus*, the causal agent of huanglongbing (HLB)³⁷. Expression of *de novo* designed AMP SP1-1 in tomato fused with secretion of the signal from radish defensin provided resistance to bacterial spot³⁸. Using pathogen physiology against itself has also provided promising results. Diffusible signal factor (DSF) is a mobile extracellular signal molecule produced by bacterial pathogens which controls cell density-dependent patterns of gene expression. In *Xylella fastidiosa*, DSF production is conferred by the gene *rpff*. Ectopic production of DSF results in hypervirulence but decreases transmissibility by vectors owing to interference with bacterial gene regulation³⁹. Susceptible scion grafted to transgenic rootstock also displayed resistance to the pathogen in field trials. Similar reductions in disease severity were also observed by ectopic expression of *rpff* in citrus and tobacco⁴⁰.

Strides in genome editing, particularly the CRISPR–Cas9 system, have increased interest towards the development of disease resistance through the modification of susceptible (S) genes of the plant⁴¹. The classic example is *mlo*, a recessive R gene of barley with resistance toward powdery mildew⁴². The null allele provides broad, durable resistance against the pathogen *Blumeria graminis* f. sp. *hordei*. Simultaneous editing of all three homoeoalleles of *MLO* locus in hexaploid wheat conferred recessive resistance against powdery mildew in one generation⁴³. Disruption of downy mildew resistance-6 (*DMR6*) was originally identified in *Arabidopsis* and suppresses free salicylic acid (SA) levels⁴⁴. Enhanced SA levels are associated with reduced susceptibility to a variety of pathogens, particularly bacterial pathogens. Mutations created by CRISPR–Cas9 in *DMR6* orthologs in tomato were reported to confer resistance to a number of pathogens, including *P. syringae* pv. *tomato*, *Phytophthora capsica*, *X. perforans*, and *Xanthomonas gardneri*⁴⁵. Modifications of the SA pathway adds to the widespread experimental utilization of ectopic expression of the SA receptor *nonexpressor of pathogenesis related genes 1* (*NPR1*), which has been reviewed extensively^{46,47}.

Diseases that involve transcription activator-like effectors (TALEs) are excellent candidates for genome editing. TALEs, which are deployed by many members of the bacterial genus *Xanthomonas*, function by binding to specific DNA sequences, known as effector binding elements (EBEs), in the promoters of S genes and promote heroic levels of S gene expression and, consequently through S gene product function, enhance disease susceptibility. Polymorphisms in EBEs by preventing TALE binding can provide recessive resistance in cases where TALEs play a critical role in disease development. The citrus gene *CsLOB1* is a susceptibility factor for citrus canker induced by the TALE PthA4 of *Xanthomonas citri*. CRISPR–Cas9-mediated modification in the EBE in the promoter region of

CsLOB1 improved canker resistance and reduced canker development in sweet orange and grapefruit^{48–50}. Bacterial blight of rice is highly dependent on TALE-mediated expression of sucrose transporters known as SWEET genes. Three SWEET genes are known to be targeted by strains of Xoo, and natural polymorphisms occur in the SWEET gene promoters that provide recessive resistance to some strains of the pathogen Xoo. *OsSWEET14* is an S gene in rice for infections by Xoo. Mutations in the promoter EBE region for the TALE effectors AvrXa7 and PthXo3 using TALE nucleases (TALENs) led to loss of expression of S gene and resistance to strains depending on those two TALEs for virulence^{51–53}. The S gene *OsSWEET13* is upregulated by TALEs, leading to bacterial blight⁵⁴. Modification of the promoter of *OsSWEET13* rice by CRISPR–Cas9 treatment resulted in resistance against strains that require *OsSWEET13* expression⁵⁴. Modification of all three genes simultaneously has been accomplished with CRISPR–Cas9 and provides broad resistance against extant strains⁵⁵.

Disruption of S genes, by either editing or silencing, potentially comes with its own set of problems. First, these resistances are recessive, requiring homozygous mutant plants to screen for resistance. Second, these genes often have functional roles in the plant, and deletion or modification of expression may result in growth defects and/or loss of yield⁵⁶. For example, a CRISPR–Cas9-mediated complete disruption of the *OsSEC3A* gene in rice caused enhanced defense response against blast caused by *Magnaporthe oryzae*. However, the resistant plant showed dwarf stature and lesion-mimic phenotype^{57,58}. Similarly, the mutations in wheat *MLO* conferred resistance against powdery mildew, but some mutants have been reported to have a leaf chlorosis phenotype similar to what is sometimes observed in barley^{43,59}.

The affinity of TALEs to bind to specific EBE sequences can be hijacked for activation of resistance by TALEs. R gene promoters have been modified to include a concatemer of EBE sites for TALEs from multiple strains of a pathogen^{60,61}. TAL EBEs can also be added to promoters to recruit TALE-mediated expression of autonomous R genes or avirulence proteins leading to resistance reactions^{62,63}.

Because of their dependence on host functions, viruses are vulnerable to manipulations of host genes. Eukaryotic translation initiation factors (eIF4E) are essential for infection by single-stranded positive-sense RNA viruses⁶⁴. They are also vital for normal initiation of translation in host cells. Due to the presence of two isoforms, null mutants of any one isoform can result in resistance to a number of viruses^{65,66}. However, simultaneous knockout of both isoforms can lead to lethality or impaired growth⁶⁷. Genome editing can be used to create novel functional alleles by mimicking natural variation of eIF4E in resistant plant species⁶⁸. These synthetic genes for eIF4E confer resistance to viruses without affecting plant physiology.

Site-specific nucleases have also been deployed as functional components in plants for resistance against viruses. This approach imitates the viral immunity in prokaryotes in which the CRISPR

system recognizes and cleaves the viral genome *in vivo*⁶⁹. The CRISPR–Cas9 system expressed transiently in *Nicotiana* along with sgRNA that recognize the viral genome significantly reduced geminivirus accumulation not just in inoculated areas but also systemically^{70,71}. The ability of viruses to overcome immunity is much lower when targeting intergenic regions compared to coding regions⁵⁷. A powerful system to control multiple viruses in cotton leaf curl disease related to begomovirus complex can be achieved by multiplex CRISPR system, imitating CRISPR function in bacteria⁷².

The analyses of naturally occurring resistances, particularly cases of single gene broad R genes, has provided a remarkable variety of genes beyond the now-classic PRRs and NLRs. Wheat breeding and characterization of many wheat relatives has provided many broad, durable R gene candidates, and the characterization of a number of rust R genes of wheat warns us that knowledge of broad, durable resistance will likely come with considerable advances in our understanding of plant physiology. The broad R genes, *Lr34* and *Lr67*, provide broad partial resistance to wheat leaf rust (*Puccinia triticina*) and to other pathogens, for example, yellow rust (*Puccinia striiformis* f. sp. *tritici*). The two genes were discovered to encode ABC-type and hexose transporters, respectively^{73,74}. Despite the novel properties of the gene products, transfer of the genes, at least within the cereal family, indicates that the genes can function similarly in related species^{75–79}. *Lr67* appears to be impaired in sugar transport, while *Lr34* product was shown recently to be capable of transporting abscisic acid (ABA)⁸⁰. Whether these attributes are relevant to the broad and multi-pathogen resistance is unknown. At the same time, the functionality in related species indicates a conserved function.

Success of many of the advances in engineering disease resistance in crop species, of course, depends on societal acceptance of various approaches to plant genome modification. Ectopic expression of heterologous transgenes or silencing of genes generally comes under the guise of foreign DNA transfer and still faces considerable headwinds owing to acceptance and regulatory protocols. Modification of transgenic classifications, for example, the concept of cisgenics (allowing the addition of genes from a crossable species) as opposed to transgenics (the addition of a gene or genes from a non-crossable species), may increase the workable space in crop modification⁸¹. Genome modification using site-specific nucleases and removal of vector sequences by crossing, or use of vector-free approaches, has been accepted in some agencies not requiring regulation as a transgenic event. However, acceptance has not been universally accepted. Regardless of regulatory issues, our understanding of plant resistance mechanisms has increased considerably in the last five years, and new insights into defenses against resistance that incorporate abiotic and other physiological pathways of plants will undoubtedly be forthcoming. The discoveries will inform mutational and traditional breeding strategies in the absence of adoption of gene transfer or gene editing technologies and help meet the future needs for food output for a growing world population and climate-challenged food production system.

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