Multiple Disease Resistance in Plants

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Abstract

Many plants, both in nature and in agriculture, are resistant to multiple diseases. Although much of the plant innate immunity system provides highly specific resistance, there is emerging evidence to support the hypothesis that some components of plant defense are relatively nonspecific, providing multiple disease resistance (MDR). Understanding MDR is of fundamental and practical interest to plant biologists, pathologists, and breeders. This review takes stock of the available evidence related to the MDR hypothesis. Questions about MDR are considered primarily through the lens of forward genetics, starting at the organismal level and proceeding to the locus level and, finally, to the gene level. At the organismal level, MDR may be controlled by clusters of *R* genes that evolve under diversifying selection, by dispersed, pathogen-specific genes, and/or by individual genes providing MDR. Based on the few MDR loci that are well-understood, MDR is conditioned by diverse mechanisms at the locus and gene levels.

INTRODUCTION

Multiple disease resistance (MDR): host plant resistance to two or more diseases

Qualitative resistance: plant resistance that is (close to) completely effective, typically monogenic and race-specific

Quantitative resistance: plant resistance that is incompletely effective, typically oligo- to polygenic and non-race-specific

Multiple disease susceptibility (MDS): plant susceptibility to two or more diseases to which the plant species is normally resistant

Plants must defend themselves against a wide range of pathogens with diverse offensive strategies. This review considers the evidence regarding multiple disease resistance (MDR), with an eye to understanding its importance and mechanisms. Because we approach this evidence with crop improvement and protection in mind, we focus mostly on naturally occurring genetic variation affecting resistance, with a secondary interest in the potential of transgenic resistance. Although MDR is a highly desirable plant trait, the underlying genetic architecture and biological mechanisms are not as well understood as those of single-disease resistances. As such, in addition to reviewing the literature surrounding MDR, we also speculate as to what mechanisms may in the future be revealed to mediate MDR.

Defining Multiple Disease Resistance

We use "host plant resistance to two or more diseases" as the definition of MDR (98, p. 203). This definition includes all forms of heritable host plant resistance, including both qualitative resistance and quantitative resistance (see 101 for a review of relevant terminology). It does not necessarily imply shared causal loci; a plant with MDR could carry several distinct *R* genes effective against different pathogens.

Note that this definition excludes nonhost resistance. Because most plants are nonhosts to most diseases, MDR should be distinguished from the many nonhost resistances of any given plant. MDR is also distinct from multiple disease susceptibility (MDS), the loss of baseline levels of resistance. A loss-of-function mutation in some critical defense gene may lead to extreme susceptibility to many pathogens (i.e., MDS), whereas overexpression of the same gene may (or may not) impart MDR. Although both are biologically interesting, only the latter might be used to improve host plant resistance.

Multiple Disease Resistance: Why and Why Not?

There is reason to expect, a priori, that there might be a nonspecific component to disease resistance in plants. The plant innate immunity system, broadly speaking, has two main branches: a nonspecific form based on the recognition of pathogen-association molecular patterns (PAMPs) and a highly specific form based on the recognition of pathogen effectors, known as PAMP-triggered immunity (PTI) and effector-triggered immunity (ETI), respectively (29). Nonspecific PTI can result when plant pattern-recognition receptors (PRRs) detect highly conserved PAMPs such as bacterial flagellin or fungal chitin (9, 164). These PRRs are in turn targeted and silenced by pathogen effectors. Genetic variation that affects the sensitivity of plant PRRs, or their silencing by pathogens, would in turn affect resistance to many pathogens from similar taxa. Alternatively, if plants recognize host damage features that occur as a general consequence of pathogenesis [damage-associated molecular patterns (DAMPs)] (36, 102), they may be resistant to pathogens with similar effects on host tissue. Once signals (PAMPs, DAMPs, or effectors) have been recognized, genetic variation could affect the many downstream signaling cascades, in turn affecting the sensitivity, degree, or mechanism of the activated defense response.

Variation in constitutive defenses might also affect multiple resistances. Physical barriers and antimicrobial compounds, which have been implicated in both host and nonhost resistance (66), may hinder pathogens with similar invasion strategies or damage similar pathogen taxa. Other plant traits, like developmental timing or reduced herbivory, may allow the host to evade infection by pathogens with similar life cycles or vectors.

Considering the potential for general defense strategies, one might expect that MDR would be a common phenomenon. Before considering the available evidence, it is worthwhile to reflect on why MDR might not be common. Three hypotheses come to mind. The first is that although many defense systems can be broadly effective, they are not all constitutively active. Thus, plants must distinguish threats from nonthreats, creating room for specificity. The second is that the evolutionary arms race involves pathogens evolving to thwart plant basal defense mechanisms, which is in turn subject to reciprocal evolution by plants: a cycle of selection described by Jones & Dangl (66). The third is that defense strategies that defeat one set of pathogens may make the plant more vulnerable to another (e.g., cell death can stop biotrophs but facilitate pathogenesis for necrotrophs).

Genetic Scales

MDR can be conditioned by genetic variation at any scale, from many genes across the genome (e.g., of a highly resistant variety) to the single gene (e.g., the *Lr34* gene in wheat). Resistance at the whole-genome scale could be conditioned by multiple unlinked loci that each provide protection against single pathogens (**Figure 1*a***) or by chromosomal segment(s) that individually provide MDR (**Figure 1*b*,*c*,*d***). Resistance at the level of a chromosomal segment may be conditioned by clusters of tightly linked genes (**Figure 1*b***) or by individual genes with pleiotropic effects

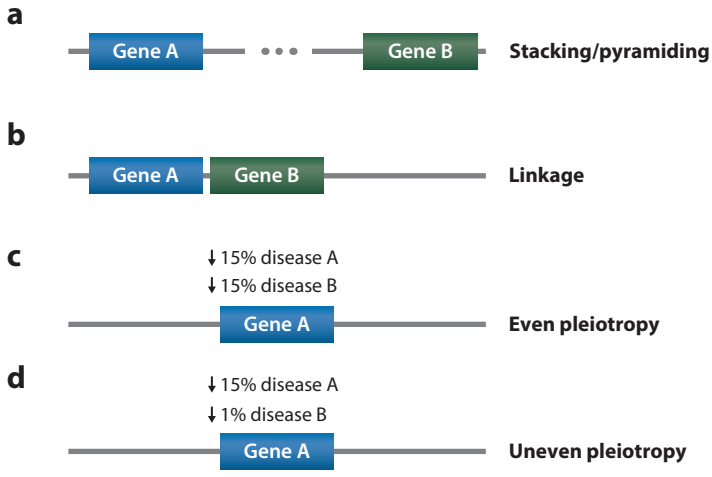

Figure 1

Four genetic scenarios by which a plant might be resistant to multiple diseases. (*a*) Loci conditioning resistance to single diseases (either *R* genes or quantitative trait loci effective against single pathogen species) may be stacked/pyramided within a single genotype. These loci may be on separate chromosomes or the same chromosome. (*b*) Loci conditioning resistance to single diseases may be in tight linkage with one another and thus typically transmitted as a unit from one generation to the next. These loci may be tightly or loosely linked, in coupling or in repulsion. (*c*,*d*) A single locus may have pleiotropic effects on multiple diseases. It may have roughly comparable effect sizes on both diseases, which we term (*c*) even pleiotropy, or highly divergent effect sizes, which we term (*d*) uneven pleiotropy. The key difference between even and uneven pleiotropy is that the former can be detected by genetic mapping methods, whereas the latter may be undetectable due to the small effect size on one of the diseases. The examples given here involve resistance to two diseases, but trade-offs are also possible; in some cases, within any of the above scenarios, resistance to one disease may be associated with susceptibility to another.

(**Figure 1*c*,*d***). There are a number of mechanisms by which a single gene might provide resistance to multiple diseases, several of which have been empirically implicated. The bulk of this review discusses the evidence for MDR at these varying genetic scales.

MULTIPLE DISEASE RESISTANCE AT THE WHOLE-GENOME SCALE

Given the abundance and diversity of plant pathogens, MDR is of clear evolutionary importance and agricultural interest. Potato, for example, is attacked by least 12 major diseases and pests in Europe (62). Wheat plants are often infected by multiple pathogens at a given time (49). Legumes are vulnerable to a large number of diseases of many taxa, with plants often infected by more than one pathogen (98). Resistance to multiple diseases is therefore of great importance to plant pathologists and breeders. MDR has been noted as a valued trait for more than a century; resistance to multiple diseases was documented in cowpea in 1902 (103, 146).

Multiple resistances are frequently described among the merits of plant genetic resources. To quantify the importance of MDR to modern plant breeding, we searched for relevant citations in the Journal of Plant Registrations (JPR), the official registration publication of the Crop Science Society of America since 2007. A Web of Science title search for "resistan*" (which captures resistance, resistant, etc.) in the JPR returned 115 results. Of these, 30 described new varieties, mapping populations, or other germplasm resources with resistance to single diseases, and 70 described germplasm resistant to multiple diseases. MDR is clearly a highly valued trait in plant genetic resources.

Germplasm Screening

Crop improvement programs routinely screen germplasm collections for resistance to multiple diseases (e.g., 11, 48, 49, 56, 107). The prevalence of lines with MDR varies highly from study to study, often even across studies in the same host-pathogen systems. In many instances, resistances to multiple diseases have been found to be correlated across the entirety of a germplasm collection (26, 49, 50, 93, 106, 148). These significant correlations can exist across panels even if individual lines with a high degree of MDR are rare. For example, in a screening of spring wheat landraces for five leaf spot diseases, resistances were correlated for 11 of the 15 pairs of pathogens tested, but only less than 1% of accessions were resistant to three or more diseases (50).

Even with similar diseases in the same species, the frequency with which MDR occurs can vary highly among studies, as in the case of resistance to multiple leaf spot diseases in wheat, which are caused by various fungal pathogens and one bacterial pathogen. In a panel of diverse lines screened for two fungal leaf spot diseases, 11% carried partial resistance to both (48). In another panel of lines screened for three fungal leaf spot diseases, only 2.4% carried partial resistance to all three pathogens (1). As noted above, less than 1% of spring wheat landraces screened for five leaf spot diseases were partially resistant to three or more diseases (50).

Multienvironment Trials

Most of the disease screening studies referenced above were done under controlled conditions at a single location. An alternative approach is to use multienvironment field trials to assess the stability of resistance to multiple pathogen species and genera. In a study on fava bean, 43 accessions were tested for reaction to two diseases (138). Eleven accessions with stable resistance to both diseases were identified and confirmed under controlled conditions. In a multilocation study of resistance to multiple *Fusarium* species, 25 winter wheat genotypes were tested at six locations across Europe

with 17 strains of three *Fusarium* species (137). When the wheat genotypes were assessed for their responses to the 59 combinations of strain, year, and location, resistances to different species were highly correlated. Resistance to *Fusarium* head blight caused by multiple species was therefore inferred to be species nonspecific.

Screening of Wild Relatives

MDR may be sourced from wild or cultivated crop relatives, sometimes in hopes of identifying genes with broader-spectrum resistance phenotypes than are available within the cultivated gene pool. Wheat-rye translocations have been used in several instances to bring MDR from rye to wheat (55, 162). Screening of wild crop relatives can capture highly effective forms of MDR. Jansky & Rouse (60), for example, identified an interspecific hybrid potato clone with resistance to five diverse diseases. Fetch et al. (37) tested accessions of the wild progenitor of barley (*Hordeum spontaneum*) for resistance to six fungal pathogens and found that resistance to most of them was present at high frequencies, with greater frequencies of resistance for populations sourced from more moist (likely disease-conducive) environments.

Accounting for Population Structure

To know whether correlations among resistances to different diseases reflect a common genetic basis, the population structure of the germplasm must be understood. Population structure refers to the patterns of genetic relatedness among populations of the same species. This can be estimated from the geographical origin of different lines or from known pedigrees but is most reliably inferred from molecular marker data. For example, population structure largely explained resistance correlations in two maize diversity panels, with tropical lines being generally more resistant than temperate lines (109, 148).

Such patterns may reflect historical selection for multiple resistances. If two pathogens thrive in similar environmental conditions, then plant breeders, including the farmers who selected landraces, will select for lines with resistance to both. Cox et al. (26) found higher levels of MDR in *Triticum tauschii* accessions from humid areas and hypothesized that the more severe disease pressure from diverse, humidity-loving pathogens led to more stringent selection for resistance. Among wheat accessions from European and Asian breeding programs, resistance to multiple leaf spot diseases was more strongly influenced by region of origin than whether the accession was a landrace or improved variety (49).

Resistance correlations may vary among subpopulations, driven by either highly resistant or susceptible lines. For example, in papaya, different genetic subgroups were found to have distinctive tendencies to provide resistance to various pathogens (139). Resistance to cassava bacterial blight was found to be correlated with resistance to cassava anthracnose disease in one panel of improved cassava varieties (31) but not in a partially overlapping panel of varieties from the same breeding program (40). In a wheat diversity panel, resistances to two fungal leaf spot diseases were correlated in spring wheat accessions, many of which were highly susceptible to both diseases, but not in winter wheat accessions, which were mostly somewhat resistant (48).

Structured Populations

Correlations in biparental families and other structured populations are more straightforward to interpret than correlations in diverse germplasm. To determine whether MDR at the whole-genome level is due to one or more loci, the typical approach is to make crosses and to evaluate

patterns of segregation in the progeny. Resistance imparted by a dominant gene of substantial effect (e.g., an *R* gene) segregates in a 3:1 ratio in an F_2 population, whereas multiple genes of small effect give a continuous phenotypic distribution. When multiple resistances are correlated in a biparental family, they can be inferred to be controlled by similar chromosomal segments, which can be mapped through cosegregation with molecular markers. For example, resistances to two bacterial diseases were correlated in segregating populations of sweet corn (107). In a diallel analysis of alfalfa resistance to multiple pathogens, correlations were observed within several biparental populations (53). For one pair of pathogens, correlations were positive in two populations and negative for another, suggesting different architecture of causal loci in different populations. In contrast, if multiple resistances do not cosegregate in a biparental population, it implies that they are mediated by different genes, as was shown to be the case for MDR derived from an elite Australian wheat variety (68).

Correlated resistances have also been seen in recurrent selection programs. In alfalfa, recurrent selection for resistance to root rot caused by a single *Fusarium* species led to improved resistance to three *Fusarium* wilts (90). In *Brassica rapa*, Mitchell-Olds et al. (91) conducted three cycles of selection for resistance to each of three diseases and tested the responses for the one selected and two nonselected diseases. Resistance to both an oomycete and an ascomycete responded strongly to direct selection, and each of these diseases also responded significantly to selection for the other. Resistance to a third disease responded less strongly to direct selection and did not respond to selection for either of the other diseases.

Quantitative trait loci (QTLs): genetic loci impacting some quantitative (i.e., nonqualitative) trait

QTL mapping: linkage mapping of QTLs in a structured mapping population

Genome-wide association study (GWAS): genetic study testing associations between genetic polymorphisms and a physical trait in a collection of diverse lines

MULTIPLE DISEASE RESISTANCE AT THE LOCUS LEVEL

Genetic mapping, supported by the use of molecular markers, has allowed genes influencing both quantitative and qualitative traits to be associated with particular chromosomal segments [quantitative trait loci (QTLs); 124]. We use the term QTL mapping to refer to linkage mapping in structured populations (77, 158) and the term genome-wide association study (GWAS) to refer to the identification of trait-associated loci in diversity panels (112, 161).

Quantitative Trait Loci Colocalization

As QTLs for different resistances are mapped on plant genomes, the spatial relationships among them (in the chromosomal context) can be assessed. Colocalization of QTLs for different diseases can provide suggestive evidence for MDR loci. Most QTL mapping studies have focused on a single disease, and we could only find a few studies characterizing QTL colocalization for resistance to multiple diseases. Some examples are provided below, and a case study on maize is presented later.

For a given host and set of pathogens, different resistances might be conditioned by the same loci or by distinct loci, and it is not always easy to distinguish these two scenarios. QTLs for resistance to three *Phytophthora* species, all causing cocoa black pod, were found to greatly overlap (115). In ryegrass (*Lolium* spp.), a forage crop important in Europe and Australia, between one and seven QTLs were identified for each of four diseases in an interspecific mapping population (64). One locus, syntenous with a QTL for MDR in rice (149), conferred resistance to three of the four diseases. Clustering of resistance loci has been observed in several legume species (89, 129) and for loci conditioning rust resistance in wheat (18, 84). In other cases, genome-wide MDR is found to be the result of single-disease resistance QTLs that co-occur, as with the nonoverlapping QTLs for resistance to two *Phytophthora* diseases in pepper (12).

Genome-Wide Association Study Colocalization

Colocalizing GWAS associations can also imply a common genetic basis of multiple resistances. A multivariate GWAS of resistance to three fungal foliar diseases in a maize diversity panel identified a single marker significantly associated with all three diseases, implicating a glutathione S-transferase gene (see Oxidative Stress below) (148). Subsequent GWAS analysis in the maize nested association mapping (NAM) population found additional evidence for MDR loci (see Case Study: Maize below). In a combined GWAS for spring wheat resistance to five leaf spot diseases, 32 loci were significantly associated with the different resistances, but no loci were associated with more than one disease (50).

Nested association mapping (NAM): a maize mapping and association panel consisting of 25 biparental families of 200 recombinant inbred lines

Meta-Analysis

After resistance QTLs have been mapped in different populations of a given plant species, the overall architecture of MDR can be further clarified by meta-analysis, the rigorous integration of QTLs from studies in multiple mapping populations. A meta-analysis of the many QTL studies on barley disease resistance published since 1992 allowed integration of 166 QTLs from 28 studies (119). From these, 20 meta-QTLs were inferred, eight of which corresponded to MDR loci. Some MDR QTLs were associated with resistance to diverse fungal pathogens with a range of lifestyles (biotrophic, hemibiotrophic, and necrotrophic), whereas others were associated with resistance only to biotrophs.

Several meta-analyses have suggested that MDR loci are relatively common in rice. When 94 disease resistance QTLs from 16 mapping studies were integrated onto the same genetic map, QTLs and known *R* genes were found to cluster by several measures, although the analysis was limited by the low resolution of the mapping studies (149). A subsequent meta-analysis of 572 rice disease resistance QTLs from 56 mapping studies found evidence for 116 meta-QTLs, 76 of which conferred resistance to more than one disease (71).

Quantitative Trait Loci in Repulsion

Just as tightly linked QTLs can cause positive correlations between resistances, QTLs that are linked in repulsion can cause negative correlations between resistances. For example, mapping of QTLs for resistance to seven diseases in a wheat biparental family revealed a QTL cluster on chromosome 3DL (165). Resistance QTLs for yellow leaf spot and Septoria tritici blotch, inherited from one parent, were linked in repulsion to resistance QTLs for leaf rust and stem rust, which were inherited from the other. Similarly, the wheat *Sr2* locus, which confers resistance to stem rust, powdery mildew, and leaf rust (84), was tightly linked in repulsion to the *Fhb1* locus, which confers resistance to Fusarium head blight (38). Understanding the genetic architecture of resistance to multiple diseases gives insight into the potential challenges and opportunities for improving MDR.

Intermediate Model: Uneven Pleiotropy

We have discussed scenarios in which a genetic locus confers resistance to either a single disease or to multiple diseases. There is evidence for an intermediate model as well, in which a locus has differential effects on different pathogens, which we term uneven pleiotropy (**Figure 1*d***). When QTLs were mapped in pepper for resistance to two *Colletotrichum* species, the major QTLs for resistance to the two species did not colocalize, but the major QTL for each colocalized with

a minor QTL for the other (79). This could also explain instances in which QTL mapping for multiple resistances finds few to no loci with pleiotropic effects, even though those resistances are correlated, as suggested by Balint-Kurti et al. (6).

R-Gene Clusters

Results from several systems have shown that a given MDR locus may be either simple (when a single gene underlies an MDR locus) or complex (when multiple genes underlie the locus). Fine-mapping studies for dozens of pathosystems have revealed that complexes of homologous *R* genes often underlie resistance loci (54), including MDR loci. A well-studied example is the lettuce Resistance Gene Candidate 2 (*RGC2*) cluster, which contains several dozen *R*-gene homologs (88). The gene complement varies across lettuce accessions (74), and most of the genes confer resistance to the oomycete *Bremia lactucae*, but one gene provides resistance to the root aphid (152). Given the size and diversity of this cluster, it is possible that other, as-yet-undiscovered specific resistances are encoded by other *RGC2* genes. Given the prevalence of *R*-gene clusters in plant genomes and some examples of *R*-gene clusters at MDR loci, we expect that more MDR loci will eventually be explained by clusters of tightly linked *R* genes.

R genes within a cluster can provide resistance for distantly related pathogen taxa because variations in *R*-gene sequences among paralogs or even homologs can result in novel specificities. For example, the allelic *Arabidopsis* genes *HRT* and *RPP8* confer resistance to Turnip crinkle virus and the oomycete *Peronospora parasitica*, respectively (25). The potato cyst nematode resistance gene *Gpa2* and *Potato virus X* resistance gene *Rx1* are two members of a four-gene cluster with 88% sequence similarity (136). This is likely not a unique phenomenon in potato, as most resistance gene homologs and known *R* genes cluster tightly on the potato genome (5). The multiple resistance complex J (*MRC-J*) cluster in *Arabidopsis* is fascinating both for the diversity of *R*-gene targets and the genetic arrangement of the *R* genes it contains. Genes imparting race-specific resistance to several bacteria, viruses, a fungus, and an oomycete have all been characterized within this cluster, which also contains roughly a dozen or so uncharacterized resistance gene homologs (25, 43, 97, 127). Two *R* genes arranged head-to-head in the cluster, *RRS1* and *RPS4*, were found to both be necessary for three of these resistances (96).

GENE-LEVEL INSIGHTS

Relatively few disease resistance QTLs have been cloned to date. Among these, several have been shown to have conferred MDR, including *Lr34* and *Lr67* in wheat (72, 95), *GH3-2* in rice (42), and *mlo* in barley (61). Below, we review the literature on cloned MDR loci, as well as speculate on what mechanisms might underlie as-yet-undiscovered cases of single-gene MDR.

Recognition of Conserved Signals

Disruption of recognition pathways can lead to the loss of multiple resistances (51, 52, 67), and successful pathogens have evolved ways to rapidly suppress the basal resistance provided by PAMP-triggered immunity (66). Conversely, variation in plant genes can perhaps produce MDR by altering the perception of certain PAMPs by plant PRRs or by affecting the inhibition of these PRRs by pathogen effectors. Another potential mechanism for single-gene MDR is the recognition by single plant *R* genes of effectors from multiple pathogens. Several instances of dual-specificity *R* genes have been noted within single pathosystems; for example, the *Arabidopsis RPM1* gene

confers resistance to strains of *Pseudomonas* carrying either of two *avr* genes (46), and the tomato *Pto* gene recognizes *Pseudomonas* strains with either of two dissimilar effectors (69).

For *R* genes to recognize effectors from distinct pathogens, effector motifs would have to be conserved across species. This is not unlikely; comparison of predicted effector proteins from a wide range of fungi and oomycetes found that effector sequences were often fairly conserved within clades, even for species of differing lifestyles (73). Groups of effectors from *Pseudomonas* and *Ralstonia* induced similar patterns of necrosis on diverse panels of tomato, pepper, and lettuce lines, even when the effector sequences were fairly divergent, suggesting similar targets in the hosts (151). Effector targets can be conserved among even extremely distant taxa. A yeast two-hybrid screening of effectors from *Pseudomonas syringae* and the oomycete *Hyaloperonospora arabidopsidis* found that effectors from these two distant species targeted several common *Arabidopsis* proteins (94). Host variation in effector targets might thus allow a plant to elude multiple pathogens. We further hypothesize that MDR may result, in some instances, from multispecificity *R* genes.

Hormone Signaling

Once threats have been recognized, plants rely on shared signaling pathways to initiate defense responses; recent reviews have described the roles of salicylate (140), jasmonate (17, 118), ethylene (15), abscisic acid (28), and the crosstalk between these pathways (13, 70, 116) in response to biotic and abiotic stress. Loci affecting hormone pathways have been suggested to underlie known resistance QTLs. Natural variation in the potato *aos2* gene, which affects jasmonic acid production, is suspected to underlie resistance QTLs against *Phytophthora infestans* and *Erwinia carotovora* (105). The rice *GH3-2* locus, which mediates resistance to *Xanthomonas oryzae* and *Magnaporthe grisea*, was found to encode a synthetase that produces the main form of auxin in rice (42). Less-direct evidence has also connected QTLs for MDR to loci controlling hormone signaling. Mapping of predicted defense genes in maize suggested several homologs of the rice Myb transcription factor, implicated in regulation of the jasmonic acid pathway, as candidate genes underlying QTLs for MDR (145).

Sugar Signaling and Partitioning

A successful pathogen is able to draw nutrients from the host plant, whereas a successful plant is able to deny the pathogen these nutrients. Changing concentrations or ratios of sugars in plant tissue can induce plant defense genes, influence plant hormone pathways, and induce resistance to various diseases (10). Certain genes underlying sugar signaling and transport have been shown to have roles in MDR.

Feeding sucrose to rice plants through the roots was shown to induce expression of defense-response genes in a manner highly similar to a challenge by *Magnaporthe oryzae* (44). This relationship seems to apply to multiple diseases. Rice plants transformed with the maize *PRms* gene accumulated higher levels of sucrose in the leaves and showed increased resistance to infection by several fungi and a bacterial pathogen. Rice lines with constitutive overexpression of the cell wall invertase gene *GIF1* accumulated more apoplastic hexoses and sucrose, leading to constitutively activated defense genes and elevated resistance to several diseases (125). The resistance allele of the wheat *Lr67* gene (shown to underlie the loci *Pm46*, *Sr55*, *Yr46*, and *Ltn3*), which confers resistance to leaf rust, stripe rust, stem rust, and powdery mildew, encodes a hexose transporter that inhibits hexose uptake from the apoplast by host cells (94). This inflation of the apoplastic hexose:sucrose ratio is thought to be associated with sugar signaling of pathogen invasion. Similar

sugar transporters (STP genes) in *Arabidopsis* have been shown to play a role in basal defense (80) and to be upregulated in response to pathogen infection (41).

Lesion mimics: plant mutants with a phenotype resembling hypersensitive response or lesions caused by pathogens

As with any disease resistance mechanism, the benefits of altering sugar transport must be considered in light of potential trade-offs for other traits. Constitutive expression of defense response genes may hinder plant growth, and alternative modes of sugar partitioning may alter critical plant traits such as yield, staygreen, etc. Resistance is ultimately useful to the farmer when it results in improved productivity, nutrition, stability, or quality.

Cell Death and the Hypersensitive Response

Plant cell death is an important defense mechanism against biotrophic pathogens and a gateway to infection for necrotrophic pathogens. Several genes implicated in cell death have been shown to contribute to MDR. The most famous example of this is the recessive *mlo* gene in barley, which provides resistance to several biotrophic pathogens (19). *MLO* is a negative regulator of the defense response, and genotypes that are homozygous for weak or null alleles at this locus manifest an overactive defense response. The gene was originally implicated in resistance to *Blumeria graminis* ssp. *hordei* and has been implicated in response to leaf wounding, leaf senescence, herbicide treatment, and a challenge with rice blast pathogen *M. oryzae* (108). It has also been implicated as a susceptibility factor for multiple necrotrophic pathogens. Plants homozygous for *mlo* show leaf-tip necrosis, reflecting the overactive induction of cell death. A similar but more exaggerated phenomenon is seen with the accelerated-cell-death6 (*ACD6*) gene in *Arabidopsis*, which conditions resistance to diverse pathogens as well as to herbivory (134). This gene is associated with necrosis and plant stunting, highlighting the fitness trade-offs that may be associated with defense strategies.

Lesion mimics are mutant plants that spontaneously develop lesions resembling a hypersensitive response or lesions caused by pathogens (99). These mutants offer an excellent system in which to study cell death and its effects on MDR. In rice, lesion mimic lines have been repeatedly shown to have increased resistance to *M. oryzae* and *Xanthomonas oryzae* pv. *oryzae* (92, 153, 154). Interestingly, the mutations that impart dual resistance, or any resistance at all, are only a small subset of the characterized lesion mimic mutations in rice. Lesion mimic mutants also vary in terms of their physiological trade-offs. *Arabidopsis* lines heterozygous for two distinct lesion mimic mutations were healthier than homozygous mutants but still retained an elevated hypersensitive response when challenged with virulent *Pseudomonas* isolates (47).

Although cell death can be used to stop pathogens that require living tissue, it can facilitate infection by those that feed on dead tissue. In addition to being more resistant to powdery mildew, *mlo* barley is more susceptible to the necrotrophic *Ramularia collo-cygni* and to laboratory infection by the biotrophic *M. oryzae* (61, 87). Similarly, a barley lesion mimic mutation conferring high levels of resistance to the biotrophic fungus *Puccinia hordei* also conferred hypersensitivity to the necrotrophic oomycete *Pyrenophora teres* f. sp. *teres* (150). Variation in cell death can also work in the opposite direction, with deficiencies in hypersensitive response conferring resistance to necrotrophs but susceptibility to biotrophs. *Arabidopsis* mutants deficient in hypersensitive response, although more susceptible to *P. syringae*, were much more resistant to the necrotrophic fungi *Botrytis cinerea* and *Sclerotinia sclerotiorum* (45).

Oxidative and Chemical Stress

Upon challenge by a pathogen, plants begin to form a wide array of reactive oxygen species (ROS) in a process known as the oxidative burst (135). These ROS strengthen plant cell walls, serve as a signal to induce the disease defense response, and potentially create a hostile environment

for invading pathogens. Necrotrophic pathogens, in turn, can elicit host production of ROS and secrete toxic compounds to kill host tissue (45). Mitigating this chemical and oxidative stress is critical for maintaining plant health. Plants produce enzymes that detoxify ROS in response to all manner of abiotic and biotic stresses (3). There is evidence that genes affecting these processes of generating and mitigating toxic compounds can underlie MDR.

In addition to managing exogenous chemicals, plants must manage the endogenous ROS they produce in response to pathogen attack. Multivariate analysis of resistance to three fungal foliar diseases in a maize diversity panel implicated a glutathione S-transferase (GST) gene (148). As GSTs have been noted for their roles in mitigating oxidative stress and detoxifying xenobiotic compounds (86), this is a plausible candidate for resistance to multiple, mostly necrotrophic, fungal diseases.

As indicated above, the wheat *Lr34* gene provides resistance to several diseases of wheat (72, 76, 123). It has been effective and in wide use for more than 100 years. The *LR34/Yr18/Pm38* locus was assumed to be a complex of multiple genes, but when it was cloned in 2009, MDR was found to be conferred by a single gene encoding an ATP-binding cassette (ABC) transporter (72). Although neither the substrate of the ABC transporter nor the mechanism by which it provides resistance is known, it is suspected to have a role in transporting or sequestering xenobiotic compounds.

Oxalate oxidases, which catalyze the production of hydrogen peroxide from oxalate, have been hypothesized to underlie MDR loci in rice (114) and wheat (35). Rice has four tandemly duplicated oxalate oxidase genes that have been suggested to underlie a QTL for resistance to rice blast and bacterial blight in rice (114). However, overexpression lines of these four oxalate oxidase genes were not more resistant to either *Xanthomonas oryzae* pv. *oryzae* or *M. oryzae* (160). Still, it is possible that natural variation in oxalate oxidases or similar proteins could affect MDR, as a cluster of 12 germin-like proteins (formerly known as oxalate oxidase-like proteins) was shown to underlie a major rice blast QTL and also to contribute to sheath blight resistance (85).

Antimicrobial Peptides

Plants, animals, bacteria, and fungi produce peptides with broad antimicrobial activity (157). Antimicrobial peptides vary greatly in structure, targets, and efficacy. Plant defensins, for example, are small, cysteine-rich antimicrobial peptides that have long been recognized as an ancient, basal component of plant defense against diseases (131). These compounds, found in high concentration in plant seeds and cell walls, have been shown to inhibit a diverse array of fungi and oomycetes, as well as a more limited number of bacteria in vitro (22, 100).

Although the use of antimicrobial peptides as transgenic sources of resistance has been well documented, there is more limited evidence that they may underlie resistance QTLs. The pea Pi39 defensin has been implicated in QTLs conferring resistance to *Fusarium solani* f. sp. *pisi* (27) and Ascochyta blight, caused by three distinct species of fungi (133). Given the abundance, diversity, and broad-spectrum activity of antimicrobial peptides, it is likely that variation in other genes encoding antimicrobial peptides affects MDR as well.

CASE STUDY: MAIZE

A series of studies, beginning with forward genetics, was conducted to understand the genetic architecture of disease resistance in maize. In 2006, Wisser et al. (147) summarized the available evidence from 50 QTL mapping studies on maize diseases. Although QTLs and *R* genes for multiple diseases showed significant clustering, finding candidate MDR loci was limited by the resolution of mapping studies at the time. Subsequent mapping studies for resistance to three

fungal, predominantly necrotrophic foliar diseases—southern leaf blight (SLB), northern leaf blight (NLB), and gray leaf spot (GLS)—have described the genetic architecture of these three resistances at increasingly high resolution.

Populations and Correlations

Many maize populations have been screened for these three diseases. In diversity panels, these resistances have been highly correlated. Roughly 250 lines of the Goodman diversity panel (39), representative of the genetic diversity of maize, were screened for these three diseases (148). Resistances were correlated ($r = 0.55$ to 0.67) even after adjusting for population structure, kinship, and maturity effects. A subset of lines from this panel was used as parents to construct the maize NAM population. The NAM consists of 25 biparental families generated by crossing 25 diverse founders to a common parent, B73 (156). Across the entire population of ~5,000 lines, resistances were also correlated ($r = 0.42$ to 0.59), in large part because of population structure rather than segregation within families (109). In both the Goodman panel and the NAM, tropical lines tended were more broadly resistant than temperate lines (109, 148). This is likely because tropical environments tend to have more disease pressure, historically necessitating stronger selection.

Structured Populations

These resistances were found to be less correlated in structured mapping populations. Within the NAM, correlations were much weaker within each of the biparental families ($r = -0.07$ to 0.41) than among their diverse parental lines ($r = 0.62$ to 0.77) (109). These three resistances are also loosely correlated in other structured families: the intermated B73 × Mo17 (IBM) biparental population ($r = 0.16$ to 0.42) (6), a biparental population derived from an MDR line (Ki14) and B73 ($r = 0.25$ to 0.62) (166), and a set of near-isogenic lines (NILs) derived from an SLB-resistant line (NC250P) and B73 ($r = 0.09$ to 0.38) (8). Altogether, this suggests that MDR is mostly mediated by multiple unlinked QTLs conferring resistance to single diseases, rather than mostly by pleiotropic QTLs.

Quantitative Trait Loci Colocalization

In each of the studies mentioned above, resistance QTLs for SLB, NLB, and GLS were mapped, giving deeper insight into the genetic architecture of MDR. Resistance QTLs rarely colocalized in any population. In the IBM biparental population, in only one instance did QTLs for two diseases colocalize (6). In the Ki14 × B73 biparental population, a greater degree of MDR was detected (166). Seventeen resistance QTLs were identified, five of which conditioned resistance to two or more diseases. One locus (in the 1.06 bin of the maize genome, discussed below) conditioned resistance to all three diseases and was also associated with an effect on flowering time.

The NAM population was designed to permit both QTL mapping and GWASs. Joint linkage mapping (i.e., locating QTLs in one or more biparental population) identified 32 QTLs for SLB resistance, 29 for NLB resistance, and 16 for GLS resistance (7, 75, 110). Of these, five colocalized between NLB and SLB, six between GLS and NLB, and one between GLS and SLB resistance (although the two QTLs had opposite effects) (7). The results of QTL meta-analysis tell a similar story: tightly linked and pleiotropic resistance QTLs are either rare or difficult to find. There are several plausible explanations for this (see Missing Loci? below).

Genome-Wide Association Study Colocalization

Significant associations identified by GWASs can also be used to dissect these correlated resistances at greater resolution. An initial multivariate GWAS for these three diseases in ~250 lines of the Goodman diversity panel found only a single polymorphism associated with all three diseases, despite high genetic correlations between the traits (148). This early study was based on a relatively small number of single-nucleotide polymorphism (SNP) markers ($n = 858$), likely limiting its resolution.

Gene pyramiding: combining desirable genes from multiple parents into a single line, often through marker-assisted selection

GWASs have also been conducted in the NAM for SLB resistance (75), NLB resistance (110), and GLS resistance (7). We compared the associations found in these studies in much the same way as the QTLs above. These studies should have more power to detect causal MDR loci, given the larger number of lines ($n = 5{,}000$) and SNPs ($n = 1.6$ million) utilized. Because of the limited LD breakdown in the NAM population (P. Bradbury, personal communication), we considered SNPs to colocalize if they were within 1 megabase of each other. This was supported empirically; at more stringent cutoffs for physical proximity, association results for the same disease with slightly different mapping approaches showed almost no colocalization.

GWAS co-localization has demonstrated several aspects of MDR in maize. Associations from GWASs were integrated into the same physical map and then combined if they were within 1 megabase. After this, there were 121 regions significantly associated with NLB resistance, 115 with SLB resistance, and 99 with GLS resistance. Of these, 21 chromosomal regions colocalized between NLB and SLB, 25 between NLB and GLS, 14 between GLS and SLB, and 4 between all three diseases. From another multitrait GWAS in the NAM, which included the same NLB and SLB phenotypic data as above (141), there were 44 regions associated with NLB resistance and 68 with SLB resistance, only 6 of which overlapped. That standardized effect estimates of co-localizing associations were positively correlated ($r = 0.36$ to $r = 0.47$) suggests that these co-localizing associations are truly pleiotropic or linked loci, rather than spurious coincidences. This supports the hypothesis that pleiotropic or linked loci are rare.

Missing Loci?

Why are loci with pleiotropic disease effects hard to identify, even with similar diseases and correlated resistances? Several phenomena, or a combination thereof, could explain this. It may be that most pleiotropic loci have effects that are too small to be detected by mapping, or that loci with large effects on resistance to one disease may have weaker effects on resistance to another (uneven pleiotropy) (**Figure 1*d***), as suggested by Balint-Kurti et al. (6). Uneven pleiotropy would be quite difficult to detect in the case of quantitative disease resistance, as most loci conditioning quantitative resistance are expected to have small effects, but loci with negligibly small effects will not pass the significance threshold during QTL mapping; thus, the minor effect of a locus with uneven pleiotropy would be difficult to detect. It may simply be that QTLs for single-disease resistances, selected in environments with high disease pressure, co-occur in lines with a high degree of MDR (gene pyramiding) (**Figure 1*a***).

Dissection of Quantitative Trait Loci

Although most large-effect disease QTLs in maize appear to be disease-specific, genetic dissection has revealed several QTLs that provide resistance to multiple diseases. A series of studies has been conducted to dissect putative MDR loci using NILs. A study typically identifies a pair of lines differing for a locus that conditions resistance to a disease of primary interest and then analyzes

the response of the lines to other diseases. Below, we review a series of such studies conducted on NILs derived from a cross between B73 and Tx303 that collectively illustrate the complex genetics and diverse mechanisms that can underlie MDR (24, 59).

Two QTLs, located on the same chromosome but in different bins (genome sections roughly 20 cM in length), were introgressed from the broadly resistant line Tx303 into the more susceptible B73 line (24). One (in bin 1.06) conferred resistance to NLB and Stewart's wilt, whereas the other (in bin 1.02) conferred resistance to NLB, Stewart's wilt, and common rust. Both NLB and Stewart's wilt are vascular diseases, with the former caused by a fungus and the latter by a bacterium.

The QTL in bin 1.06, which was shown to hinder leaf penetration by the NLB pathogen *Setosphaeria turcica* (24), proved recalcitrant to conventional genetic analysis, as recombination rates were vanishingly low (59). Whether this QTL is truly pleiotropic (**Figure 1*c***) or a cluster of linked loci affecting separate diseases (**Figure 1*b***) remains to be seen. This region is considered an important adaptive region in maize because of the many other QTLs for important traits that have been found there, including an MDR QTL derived from another population (166). Although limited recombination hindered the fine-mapping of this QTL, a mutant for a leucine-rich repeat receptor-like kinase (LRR-RLK) gene, *Pan1*, in the region showed resistance to both NLB and Stewart's wilt (59). This suggests that the wild-type allele is useful in pathogenesis for both vascular pathogens. *Pan1* had previously been shown to play a role in cytoskeletal dynamics (actin organization) required for proper stomatal development (21).

The QTL in bin 1.02, which was shown to restrict entry of *S. turcica* into the vascular tissue (24), could be dissected through recombination. This showed that although the Stewart's wilt and common rust resistances may be due to pleiotropy, the NLB locus is a tightly linked, separate locus (58) (**Figure 1*b***). Multiple cycles of recombination allowed the narrowing down to four genes, which were further assessed using mutants, implicating a remorin gene. Members of the remorin gene family, involved in membrane rafts and plasmodesmatal function, have been implicated in inhibiting *Potato virus X* mobility through plasmodesmata (113) and in promoting infection by *P. infestans* (14). Thus, a nonspecific role in restricting plasmodesmatal movement by different pathogens is plausible.

TRANSGENIC MULTIPLE DISEASE RESISTANCE

With direct transfer of genes among genotypes and species, the potential scope of resistance sources expands to different species, genera, and kingdoms. The extent to which this opportunity will be realized to produce MDR depends on whether known MDR genes are effective in heterologous systems, the technical ease of transformation, and the social and political context that influences the regulatory environment. Although the GMO debate has been politically fraught, the use of resistance genes from wild species could lead to reduced reliance on pesticides and thus could have some appeal from an environmental perspective. Here, we review the existing literature on transgenic methods and their implications for MDR.

Constitutive Defense and its Drawbacks

Most defense mechanisms require the plant to recognize threats and to activate defense response pathways. Constitutive expression of defense response genes can enable plants to bypass the recognition step, creating a hostile environment for invaders. There are many routes to affecting resistance via constitutively expressed defense genes. *R*-gene overexpression can lead to activation of defense response pathways and subsequent MDR, as was the case with the *Pto* gene in *Arabidopsis* (128). Defense-response genes on the downstream end can also be used. Overexpression of the rice

peroxidase *OsPrx114*, which catalyzes oxidation of substrates by peroxides during the oxidative burst, imparted resistance to multiple necrotrophs in carrot (143).

The *Arabidopsis NPR1* gene, which regulates systemic acquired resistance and has homologs in other crops, has been suggested as a source MDR (32). Overexpression of *NPR1* has led to MDR in *Arabidopsis* (20, 155), tomato (83), carrot (142), and strawberry (120). Interestingly, the baseline expression of pathogenesis-related (PR) proteins in these *NPR1* overexpression lines was not different from the wild-type expression level in *Arabidopsis* or carrot but was higher in tomato and strawberry. Because *NPR1* activates defense response pathways in a dosage-dependent manner (32), it seems that constitutive expression of this upstream defense regulator can induce MDR in multiple ways: by constitutively activating defense pathways (an undesirable trait) or by increasing the sensitivity, intensity, or duration of the defense response (a potentially desirable trait).

There are good reasons why plants do not typically show constitutive activation of defense pathways, however. Many defense responses are expected to incur a cost to the host plant in some way, by either consuming limited resources or indirectly affecting growth (16, 122, 144). Evidence for fitness costs of transgenic MDR supports this. Overexpression of the *RPM1 R* gene in *Arabidopsis* led to stunted plants with lower seed production (134). Although *Arabidopsis NPR1* overexpression lines are developmentally normal, *NPR1* overexpression led to reduced growth in strawberry (120). *Arabidopsis* mutants that overexpressed the MAP kinase kinase 7 gene, previously shown to regulate basal and systemic acquired resistance, had high levels of MDR, but this was associated with a bushy, dwarf plant morphology (159). Constitutive expression of defense-related genes will ultimately be useful from a crop improvement standpoint if the transgene increases sensitivity only to signals from relevant threats, without sacrificing plant performance in the absence of pathogens.

Antimicrobial Peptides

As with other disease defense mechanisms, plants that constitutively express antimicrobial compounds may be able to bypass the recognition of effectors. Transgenic constitutive overexpression of the potato Snakin-1 peptide, originally found to have antibacterial function in vitro, imparted resistance to the bacteria *Rhizoctonia solani* and *E. carotovora* in potato (2). Plant defensins have also been transferred from one plant species to another with great success in many cases. Both tobacco and peanut plants transformed with the mustard defensin gene *BjD* are highly resistant to multiple distinct fungal diseases (126). The radish defensin gene *Rs-AFP2* has been transformed into tobacco (130), tomato (23), pear (78), wheat (82), and rice (63), providing in vitro resistance to a wide range of economically important fungal pathogens. Transformation of potato with the *Nicotiana megalosiphon*–derived peptide NmDef02 conferred resistance to *Alternaria solani* and *P. infestans* (111). Using plant defensins in transgenic plants is still a fairly conservative strategy, as the defensins are less likely to have broad phytotoxic properties.

Of course, transgene sources are not limited to the plant kingdom. Transforming plants with antimicrobial peptides from distantly related taxa arms them with chemical weapons that may be quite novel to potential pathogens. Synthetic analogs of magainin, an antimicrobial peptide from the African clawed frog, have been used to confer MDR in transgenic tobacco (22, 81) and banana (22). The *msrA1* gene, which encodes for a chimeric protein derived from antimicrobial peptides of the giant silk moth and bee venom, imparted resistance to fungal and bacterial pathogens in potato (104) and to fungal pathogens in *Brassica juncea* (117). As many of these authors have noted, the broad antimicrobial activity of these peptides comes with a caveat: Novel transgenic peptides may have unforeseen impacts on the plant, its pollinators, the beneficial microbes of the rhizosphere, and/or its human consumers.

IMPROVING MULTIPLE DISEASE RESISTANCE

Marker-assisted selection: the use of molecular markers instead of, or in addition to, phenotypes to choose individuals for selection or crossing in a breeding scheme

As we learn more about the underlying genetic and biological mechanisms behind MDR, how do we translate this knowledge into improving MDR in different crops? Methods for producing crop varieties with whole-genome MDR vary, with the strategy depending on the nature of inheritance of MDR. To make efficient use of a resistance source, it is necessary to have a clear understanding of its inheritance. For example, the breeding strategy required for utilizing monogenic resistance is distinct from one based on quantitative resistance. It would be relatively easy to manage a single gene that provided resistance to multiple diseases, and a much greater technical challenge to make practical use of a large number of loci of small effect.

A common strategy for producing MDR at the whole-genome level is to combine multiple major genes into a single line. The pyramiding or stacking of *R* genes or other major genes can be achieved by phenotypic selection and/or marker-assisted selection (MAS). For example, Singh et al. (121) and Zhou et al. (163) used MAS to pyramid *R* genes for rice blast and/or bacterial diseases in Basmati rice. Eibach et al. (33) used MAS to pyramid resistance QTLs for downy mildew and powdery mildew in grape, avoiding the long generation times needed to conduct phenotypic selection.

Efforts to combine major genes are influenced by the distribution and nature of those genes within the species. If loci for different resistances are not closely linked, they must be introgressed independently of one another. If they are linked, they are easy to introgress if linked in coupling and more difficult to introgress if they are linked in repulsion. For example, the wheat MDR locus *Sr2* was difficult to combine with the *Fusarium* head blight resistance locus *Fhb1* because the two were linked in repulsion (38). Screening by molecular markers eventually identified recombination events between the two loci; the resultant recombinant lines can be used as donors of both the *Fhb1* and *Sr2* loci with limited loss of stacked resistance due to further recombination.

Although molecular markers can be useful, phenotypic selection can also be used to combine resistances. Terán et al. (129) describe a strategy for developing breeding lines with resistance to the five most important diseases of common bean in Latin America by screening multiparent populations with multiple pathogens. They found relatively high co-incidence of resistance to three fungal diseases and a viral disease. The authors note that their success in creating MDR lines was probably enhanced by the clustering of resistance genes in the bean genome. Elgin et al. (34) compared a range of selection methods for developing alfalfa populations with resistance to multiple diseases. They found that sequential selection for one disease at a time was ineffective (resistance to a given disease would respond to selection but would be lost when the population was later selected for resistance to other diseases), suggesting that resistances were genetically unlinked.

The reliance on major genes can be appealing because of their potential to provide complete resistance and the relative ease with which they can be analyzed. The main downside to their exploitation is their potential lack of durability, or their long-term performance in the face of pathogen evolution (65). Polygenic, quantitative resistance is considered to be the most durable form of resistance (124). Single *R* genes are generally race specific and relatively rapidly overcome as pathogen populations evolve under selection pressure. Broad-spectrum resistance is logically more likely to be durable than resistance for which compatible pathogen strains are already known. MDR can be regarded as an exceptional form of broad-spectrum resistance and thus potentially particularly difficult to overcome. Consistent with this, single genes associated with MDR, such as *mlo* and *Lr34*, are among the rare major resistance loci to have demonstrated durability.

CONCLUDING REMARKS

Only a few genes for quantitative resistance have been cloned to date. Some of these have been MDR loci, and their cloning has shed light on the types of mechanisms that can underlie resistance to multiple diseases. As more MDR loci reveal their secrets, we will gain insights of relevance to host-pathogen interactions and of importance to crop improvement and protection. The loci thus far associated with MDR have ranged from clusters of diversifying *R* genes to those involved in chemical warfare. The patterns of MDR also vary with regard to similarities in pathogen relatedness; some loci are associated with resistance to various obligate biotrophs, whereas others provide resistance to more diverse pathogens. Optimal exploitation of the potential of MDR will benefit from a deeper understanding of the underlying mechanisms and the potential trade-offs with other traits of interest to pathologists, breeders, and growers.

FUTURE ISSUES

1. Many plant defense strategies for broad resistance against biotrophs lead to susceptibility to necrotrophs and vice versa. What genes or mechanisms lead to resistance against both necrotrophic and biotrophic pathogens?
2. As more is learned about the genetic architecture underlying MDR in different crops, how can this knowledge translated into crop improvement?
3. As genetic engineering falls in price and difficulty, it will be easier to move genes from nonhosts of a given pathogen into hosts. How will this affect our understanding of host and nonhost resistance to multiple diseases? How will it change breeding for multiple resistances? Will the public accept this?

DISCLOSURE STATEMENT

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