The Plant Cell, Vol. 8, 1747–1755, October 1996 © 1996 American Society of Plant Physiologists

Genetics and Utilization of Pathogen Resistance in Plants

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INTRODUCTION

Until relatively recently, knowledge of plant resistance to pathogens has resulted primarily from research associated with the selective breeding of crop species. Although resistance is well described at the cellular, whole plant, and population levels in terms of genetics, histology, and associated biochemistry, a full mechanistic understanding of how pathogen resistance is mediated in plants is only now becoming feasible as a result of the isolation and sequencing of several putatively interacting plant and pathogen genes (see Alfano and Collmer, 1996; Bent, 1996; Dangl et al., 1996; Hammond-Kosack and Jones, 1996, in this issue). Nevertheless, plant resistance genes have been used beneficially in agriculture for decades, even though their effects have not always been durable. This review provides a short and selective overview of the genetics of pathotype-specific resistance in plants, its past utilization in crop improvement, and some indications of how recent advances may impact the future. Reference to data obtained from investigations with a few well-studied host–pathogen combinations (Table 1) is used to develop some general themes.

It is becoming evident that plant genomes contain a large number of genes that are apparently involved in the detection and discrimination of potential pathogens. Furthermore, these genes are commonly clustered in complex loci, sometimes comprising genes involved in resistance to taxonomically unrelated pathogens (examples are provided later in this review). The genetics of specific pathogen recognition is complex. For example, in wheat >90 genes that condition isolate-specific resistance to three rust species (*Puccinia striiformis*, *P. recondita*, and *P. graminis*) and powdery mildew (*Erysiphe graminis*) have been identified. Only one of these genes (*Lr20/Sr15*) is thought to be involved in the recognition of more than one pathogen species (see Crute, 1985, for references). For some genes, alleles with different pathotype specificity have been identified; there is also evidence that genes expressing identical specificity are present at different loci in the same plant species as well as in different species. It seems likely, then, that resistance genes are members of substantial multigene families, potentially well conserved among taxa. Evidence is also accumulating that novel discriminating capability may be generated at these complex loci by recombination or gene-conversion events (Prior and Ellis, 1993; see Bent, 1996, in this issue).

The existence of plant genes providing resistance to pathogens was demonstrated soon after the rediscovery of Mendel's seminal studies on inheritance. Biffen (1905) demonstrated that a single locus was responsible for the resistance of some wheat cultivars to yellow rust caused by *P. striiformis*. Many hundreds of genes associated with resistance to a diversity of pathogens have subsequently been identified in numerous plant species. At an early stage, it was discovered (McRostie, 1919) that genes at different loci could be responsible for resistance to different pathogenic variants (i.e., pathotypes), but the full significance of this observation only became evident after the gene-for-gene relationship was elucidated by Flor (1956, 1971) in the course of 40 years of research on the interaction between flax (*Linum ultissimum*) and the rust fungus *Melampsora lini*. After Flor's classic work, it became evident that for many host–parasite relationships, matching gene pairs (resistance [*R*] and avirulence [*Avr*] genes, respectively) controlled the outcome of interactions between different combinations of host and parasite genotypes (Crute, 1985).

THE GENE-FOR-GENE RELATIONSHIP

In interactions that follow a gene-for-gene relationship, the expression of resistance or susceptibility of the host to a particular pathogen is conditional on the pathogen genotype, and the degree of pathogen virulence observed is conditional on the host genotype. Specifically matching gene pairs determine the outcome of any particular genotype–genotype interaction. Compatibility (i.e., extensive pathogen development and reproduction in the absence of an effective host defense response) is the outcome of a host–pathogen combination unless an allele for resistance at a particular host locus is specifically matched by an allele for avirulence at a particular pathogen locus. Under these circumstances, the degree of incompatibility (i.e., reduced pathogen development and reproduction associated with an effective host defense response) that is

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Table 1. Well-Studied Host–Pathogen Combinations

Host	Pathogen	Key References
Flax (*Linum ultissimum*)	Rust (*Melampsora lini*)	Islam and Shepherd (1991a)
Wheat (*Triticum aestivum*)	Stem and leaf rusts (*Puccinia* spp)	Roelfs (1988); Browder (1980)
Barley (*Hordeum vulgare*)	Powdery mildew (*Erysiphe graminis* f sp *hordei*)	Jørgensen (1994)
Lettuce (*Lactuca sativa*)	Downy mildew (*Bremia lactucae*)	Crute (1991)
Common bean (*Phaseolus vulgaris*)	Bean common mosaic virus (BCMV)	Spence and Walkey (1995)
Common bean (*P. vulgaris*)	Halo blight (*Pseudomonas syringae* pv *phaseolicola*)	Jenner et al. (1991)
Tomato (*Lycopersicon esculentum*)	Leaf mold (*Cladosporium fulvum*)	J.D.G. Jones et al. (1993)
Maize (*Zea mays*)	Rust (*Puccinia sorghi*)	Hulbert and Bennetzen (1991)

expressed depends on the particular matching gene pair. *R–Avr* gene pairs resulting in incompatibility are epistatic (exhibit nonallelic dominance) over gene pairs that would otherwise result in compatibility. Gene pairs conditioning higher degrees of incompatibility are in general epistatic over gene pairs associated with lower degrees of incompatibility, although phenotypic variation indicative of genetic additivity has also been reported when more than one gene pair conditioning incompatibility is effective (see below). Table 2 illustrates the features of a hypothetical gene-for-gene relationship involving three epistatic matching gene pairs.

The suggestion that gene-for-gene specificity is in some way an artifact of cultivation is not substantiated by an increasing number of investigations of natural plant pathosystems. In fact, their narrow genetic base may mean that some crop species are relatively impoverished with respect to genes for resistance to pathogens. Consequently, the exploitation of additional genetic diversity among wild progenitor species is a familiar approach for plant breeders seeking to enhance resistance to disease. Studies on two ruderal weed species (*Senecio vulgaris* and Arabidopsis) have readily demonstrated the existence of a substantial number of *R* genes, identified by their ability to discriminate among a relatively restricted sample of pathogen isolates (*Erysiphe fischeri* and *Peronospora parasitica* for the two host species, respectively; Bevan et al., 1993a, 1993b, 1993c; Holub et al., 1994).

ORGANIZATION AND STRUCTURE OF RESISTANCE LOCI

Studies of the inheritance of pathotype-specific resistance to flax rust by Flor and others have identified the existence of genes expressing at least 32 different specificities that are organized in five linkage groups (*K*, *L*, *M*, *N*, and *P*; reviewed in Islam and Shepherd, 1991a). Although the existence of separate loci within linkage groups *K*, *N*, *M*, and *P* has been demonstrated, the 14 specificities at the *L* locus appear to be allelic. Demonstration of allelism and evidence for the generation of novel specificity at the *L* locus come from studies that have been made of progeny from test crosses between a homozygous susceptible genotype and 27 of the 91 possible combinations of the 14 *L*-group heterozygotes (Islam and Shepherd, 1991a). Among large numbers of individuals, rare susceptible plants were identified, as were plants expressing nonparental resistance phenotypes (so-called modified recombinants); however, no individuals were found that expressed the specificity of both parents (demonstrating allelism at the *L* locus). Some susceptible individuals yielded resistant revertants on selfing, and plants expressing novel specificity to nine different rust pathotypes were identified among the progeny of revertants, susceptible recombinants, and modified recombinants. Interallelic recombination, which would provide a

Table 2. Features of a Hypothetical Gene-for-Gene Relationship Involving Three Interacting Gene Pairs[a]

Host Genotypes[b]	Pathogen Genotypes[b] *A1 A2 A3*	*a1 A2 A3*	*A1 a2 A3*	*A1 A2 a3*	*a1 a2 A3*	*a1 A2 a3*	*A1 a2 a3*	*a1 a2 a3*
R1R2R3	0	1	0	0	2	1	0	3
r1R2R3	1	1	2	1	2	1	3	3
R1r2R3	0	2	0	0	2	3	0	3
R1R2r3	0	1	0	0	3	1	0	3
r1r2R3	2	2	2	3	2	3	3	3
r1R2r3	1	1	3	1	3	1	3	3
R1r2r3	0	3	0	0	3	3	0	3
r1r2r3	3	3	3	3	3	3	3	3

[a] An interaction phenotype scoring 3 represents complete compatibility (i.e., susceptibility/virulence) and a score of 0 represents the highest level of incompatibility (i.e., resistance/avirulence). Incompatibility is the result of any specific *R/A* combination, that is, *R1-A1*, *R2-A2*, and *R3-A3*, and incompatibility is epistatic over compatibility. Gene pairs conditioning incompatibility have an epistatic relationship such that *R1/A1* is epistatic to *R2/A2*, which is epistatic to *R3/A3*. Hence, the interaction phenotype observed is that conditioned by the gene pair expressing the highest level of incompatibility.

[b] Assuming that genes controlling the interaction are at separate loci, and ignoring heterozygotes, there are 2^n possible host and pathogen genotypes and $(2^n)^2$ unique genotype–genotype combinations (where n is the number of matching gene pairs). In this example, $n = 3$, but n is known to be large in many host–pathogen combinations (see text for examples).

mechanism for the generation of novel recognition capability, has been postulated as an explanation of these data (Islam et al., 1989, 1991; Islam and Shepherd, 1991b). It is entirely feasible that there is sequence variation among alleles for susceptibility that is undetected phenotypically. This variation could also play an important part in the generation of novel specificity through rare interallelic recombination events. Recently, the *L6* allele has been isolated and sequenced (Lawrence et al., 1995). This too will provide the means to allow more informed experimentation on the generation of novel resistance specificities and altered interaction phenotypes in flax.

Allelism is also evident at the *Mla* locus for powdery mildew (*E. graminis* f sp *hordei*) resistance in barley. More than 20 different alleles, with different degrees of dominance, have been identified on the basis of their pathotypic specificity (Jørgensen, 1992; Jahoor et al., 1993). Crosses between barley lines carrying different *Mla* alleles occasionally gave rise to rare susceptible progeny after test-crossing to a susceptible genotype lacking either of the two parental specificities. In common with the example of flax and flax rust, progeny expressing the specificity of both original resistant parents were never recovered. This implies that resistance specificities at *Mla* are indeed allelic, with interallelic recombination accounting for the occurrence of susceptible progeny and potentially (although undemonstrated) providing the mechanism for the generation of new alleles with novel specificity.

A more common circumstance than allelism is the clustering of genes mediating pathotype-specific resistance within large, complex loci. Saxena and Hooker (1968) conducted a classic study of maize genes conditioning resistance to the rust fungus *P. sorghi*. Sixteen specificities (*Rp5*, *Rp6*, and 14 genes previously thought to be alleles of *Rp1*—termed *Rp1A* to *Rp1N*) map within this region. The existence of separate but linked loci was demonstrated by recombination between resistance specificities that produced progeny with the predicted parental combinations of resistance to a range of diagnostic pathogen isolates.

More recent studies of loci at *Rp1* have shown that unequal crossing-over, as indicated by the segregation of linked restriction fragment length polymorphism markers, explains the meiotic instability that is manifested as the unexpected appearance of susceptible individuals in test-cross progeny between homozygous susceptible and homozygous resistant parents (Hulbert and Bennetzen, 1991; Hong et al., 1993; Sudupak et al., 1993). Mispairing of repeat sequences provides a mechanism that could lead to *R* gene duplication and loss. The repetitive sequences necessary to facilitate mispairing could be provided by the exisitence of multiple *Rp1* homologs distinguished by their diagnostic pathogen recognition capability. Additional evidence for the occurrence of repetitive sequences in the *Rp1* region was provided by the discovery of two genomic clones that identify a variable number of loci tightly linked to *Rp1* in different maize lines. Gene conversion and intergenic recombination events giving rise to new resistance specificities may also occur at *Rp1* (Hu and Hulbert, 1994; Richter et al., 1995).

In lettuce, identified linkage groups contain genes for recognition of several unrelated parasites. One linkage group (*I*) contains a gene for resistance to an aphid species (*Pemphigus bursarius*) in addition to eight genes for specific resistance to downy mildew (*Bremia lactucae*). Two additional downy mildew *R* genes occur in another linkage group (*II*) along with a gene for resistance to turnip mosaic virus and a gene for resistance to the root pathogen, *Plasmopara lactucae-radicis* (Landry et al., 1987; Kesseli et al., 1993; Wistenboer et al., 1995). The tomato genes for resistance to root-knot nematode (*Meloidogyne* spp) and leaf mold (*Cladosporium fulvum*) are also linked (Dickinson et al., 1993; D.A. Jones et al., 1993). These complex loci may provide several selective advantages. Such arrangements allow multiple specificities to be assembled and retained in a single haplotype, thus preserving the potential for variation and the evolution of novel specificities through mispairing, intergenic recombination, and gene duplication.

In contrast to the occurrence of complex loci comprising several genes with distinct recognition capabilities, recent data also indicate the existence of functionally identical *R* genes at independent loci (J.D. Taylor and D. Teverson, personal communication). In *Phaseolus vulgaris* (common bean), for example, crosses were made between cultivars previously demonstrated to carry functionally identical recognition genes for the bacterial pathogen *Pseudomonas syringae* pv *phaseolicola*, as indicated by their reaction to transconjugant strains of the bacterium carrying single cloned *Avr* genes (either *avrPphB1.R3* or *avrPphC1.R1*; notations for bacterial *Avr* genes follow the proposals of Vivian and Mansfield [1993]). The digenic and trigenic segregation ratios observed among F_2 progeny indicated the existence of functionally identical genes at independent loci. Intriguingly, one of the genes apparently occurring at duplicate loci (*R3*) appears to be identical with or more probably tightly linked to the so-called *I* gene in bean, which provides isolate-specific resistance to bean common mosaic virus and several other related potyviruses (J.D. Taylor, D. Teverson, and N.J. Spence, personal communication).

The existence of *R* genes in different plant species that mediate seemingly identical recognition capabilities has now been firmly established. Sequencing of two *Avr* genes, isolated respectively from the crucifer pathogen *P. syringae* pv *maculicola* (*avrPmaA1.RPM1*) and the pea pathogen *P. syringae* pv *pisi* (*avrPpiA1.R2*) proved them to be nearly identical. In transconjugant strains of the two pathovars, these *Avr* genes also exhibited identical specificity of interaction with the respective host genes: *R2* (from pea) and *RPM1* (from Arabidopsis), indicating functional homology (Dangl et al. 1992). Furthermore, in bean, recognition genes at two independent loci were identified by a transconjugant of the bean pathogen *P. s. phaseolicola* carrying *avrPpiA1.R2* (Fillingham et al., 1992). The *RPM1* gene from Arabidopsis provides a further intrigue, because it confers resistance after specific interactions with unrelated *Avr* genes from two different *P. syringae* pathovars: *avrPmaA1.RPM1* (see above) and *avrPgyB1.Rpg1* (Bisgrove et al., 1994; Grant et al., 1995).

A number of genes conferring pathotype-specific resistance to a diversity of pathogens have been isolated from several different host species (Martin et al., 1993; Bent et al., 1994; Jones et al., 1994; Mindrinos et al., 1994; Whitham et al., 1994; Ellis et al., 1995; Grant et al., 1995; Lawrence et al., 1995; Loh and Martin, 1995; Song et al., 1995; Zhou et al., 1995; see Bent, 1996, in this issue, for a review). The use of these genes as probes is facilitating the detection of homologous sequences within and between species. However, attributing function to *R* gene look-alikes is not straightforward, requiring not only a specifically matching pathogen variant but also appropriate recombinant plant populations to confirm cosegregation of the resistance phenotype and the candidate gene. However, the molecular evidence so far available substantiates conclusions that plant *R* genes will frequently prove to be members of substantial, linked, multigene families that are well conserved between plant families.

DOMINANCE AND NONALLELIC INTERACTIONS

Alleles mediating pathotype-specific resistance have often been described as dominant over susceptiblity alleles, and the interpretation of an "active" role for the *R* allele has been based largely on arguments in which dominance and recessivity equate with gain of function and loss of function, respectively. However, it is usually possible to discriminate phenotypically between plants homozygous or heterozygous at *R* loci, indicating that gene dosage can influence the degree of incompatibility. *Avr* gene dosage has also been shown to influence the interaction phenotype in diploid or dikaryotic fungal pathogens (Hooker, 1967; Crute, 1985; Fraser, 1986; Crute and Norwood, 1986; Roelfs, 1988; Ilott et al., 1989; Hammond-Kosack and Jones, 1994; Kolmer and Dyck, 1994; Mindrinos et al., 1994). Reported examples of resistance resulting from homozygous recessive alleles at a locus can often be explained by gene-dosage effects in which the heterozygous host genotype is classed phenotypically as susceptible, although pathogen growth is nevertheless more restricted than it would be in the homozygous susceptible genotype. Phenotypic variation and an apparent alteration in dominance relationships can also result from interactions between the environment, particularly temperature, and certain *R* genes (Dyck and Johnson, 1983; Islam et al., 1989; Judelson and Michelmore, 1992).

Gene-for-gene relationships are conceived of as being essentially epistatic (see Table 2), but there is evidence for the occurrence of other forms of nonallelic interactions. For example, a gene located on the long arm of chromosome 7D in wheat, which is either tightly linked or allelic with *Lr34* (which conditions resistance to leaf rust caused by *P. recondita*), suppresses resistance to stem rust (*P. graminis* f sp *tritici*; Kerber and Green, 1980; Dyck, 1987). So-called background effects, where the phenotypic expression of specific *R* genes differs, depending on the host genotype, are frequently encountered by breeders. For example, in lettuce, the efficacy of the *mo* gene for resistance to lettuce mosaic virus varies among cultivars (Walkey et al., 1985).

Resistance in bean (*P. vulgaris*) to BCMV is dependent on complementary gene interactions. The *P. vulgaris* gene *bc-u*, which is present in all but one cultivar examined, has no independent effect itself. However, it is required for the expression of specific resistance to BCMV, which is determined by a set of apparently recessive *R* genes, *bc-1*, *bc-2*, and *bc-3* (Drijfhout, 1978). In oat stem rust caused by *P. graminis* f sp *avenae*, the phenotypic expression of the *R* gene *Pg-12* is enhanced by a complementary gene with no independent phenotypic effect (Martens et al., 1981).

It is tempting to speculate that genes that have been identified through their nonallelic interaction with genes determining pathotype specificity are involved in signal transduction events. Systematic attempts are now being made through mutational analyses to uncover additional loci that are essential for, or have an influence on, the expression of pathotype-specific resistance. For example, in barley, the loci *Rar1* and *Rar2* (previously referred to as *Nar-1* and *Nar-2*) have been shown to be required for Mla_{12}-specified pathotype-specific resistance to powdery mildew (Freialdenhoven et al., 1994). Similarly, in tomato, two loci named *Rcr-1* and *Rcr-2* that are required for race-specific resistance to *C. fulvum* specified by the gene *Cf-9* have been identified (Hammond-Kosack et al., 1994; see also Hammond-Kosack and Jones, 1996, in this issue). It is likely that such "genes required for resistance" encode components of the signal transduction pathway or network that leads from the perception of the signal provided by the *Avr* gene to the expression of resistance (Dangl et al., 1995; Staskawicz et al., 1995; Hammond-Kosack and Jones, 1996, in this issue).

Direct evidence to support this notion has been provided by Zhou et al. (1995), who identified a tomato gene, *Pti1*, that encodes a serine/threonine kinase phosphorylated by the *Pto* *R* gene (also encoding a protein kinase). *Pti1* is not phosphorylated by *Fen*, another serine/threonine kinase genetically linked and closely related to *Pto* (Loh and Martin, 1995); this indicates that resistance specificity may also be a function of interactions between these downstream gene products (Bent, 1996, in this issue). Further evidence for specificity in the signaling pathway comes from other studies of resistance to barley powdery mildew. Two loci, *Ror1* and *Ror2*, have been identified by mutational studies as being required for the function of the pathotype-nonspecific recessive resistance attributed to the *mlo* gene (Freialdenhoven et al., 1996). Gene interaction studies indicate that the *Rar* genes (described above) are not required for *mlo* function and that *Ror* genes have no role in the race-specific resistance specified by alleles at the *Mla* locus. In contrast, the *ndr-1* mutation in Arabidopsis, which segregates as a single recessive locus, renders plants carrying different *R* genes susceptible to a bacterial (*P. syringae* pv *tomato*) and a fungal (*P. parasitica*) pathogen. This observation indicates a common step in the pathways of resistance to a prokaryotic and eukaryotic pathogen (Century et al., 1995).

PRACTICAL UTILIZATION AND DEPLOYMENT OF RESISTANCE GENES IN CROPS

After the dramatic demonstration early in this century that disease resistance could be conferred by single genes, breeders of many crops initiated breeding programs with the expectation that the resulting control of plant diseases would be permanent (Stakman et al., 1918). Durable disease resistance (as defined by Johnson and Law, 1973) based on the utilization of one or more single dominant *R* genes has been achieved in some cases. More frequently, however, the rapid evolution of matching pathotypes virulent on previously resistant cultivars has forced breeders into a repetitive cycle of cultivar replacement demanding the continual introgression of new resistance specificities. Indeed, this boom and bust cycle of events, in which a new resistant crop cultivar becomes increasingly planted only to succumb to the pathogen, was explained after the elucidation of the gene-for-gene relationship. As the popularity of the cultivar increases and it occupies an increasing proportion of the crop area, selection pressure against the matching *Avr* allele in the pathogen population also increases. Because new resistance specificities have generally been deployed singly in new crop cultivars, in theory only a single mutational event at the corresponding *Avr* locus may result in a new virulent pathotype. Thus, for many crop diseases, the efforts of plant breeders simply guide the evolution of virulence in the pathogen (Johnson, 1961). The breeders' response of "pyramiding" several specificities into a single cultivar is based on the notion that the introduction of several novel specificities into a single cultivar would require mutational events at each of the matching *Avr* loci before resistance would become ineffective. However, in general this strategy has not resulted in greater durability of resistance, although there are reported exceptions and the theory behind the practice has spawned an interesting debate (Pederson and Leath, 1988; Mundt, 1990, 1991; Kolmer et al., 1991). In any case, the process of introducing more than one new resistance specificity simultaneously into breeding material is not easy using traditional breeding methods. Consequently, pyramiding has been performed by using *R* genes for which the matching virulence specificity is already frequent in the pathogen population (thus providing diagnostic isolates for each component gene of the pyramid). Enhanced durability is expected to result not from the reduced likelihood of mutational events at several *Avr* loci but rather from the time taken for recombination to generate the necessary *avr* (virulence) gene combinations to match the *R* gene pyramid.

Additional strategies to improve the durability of resistance are based on the concept of reducing the *R* gene homogeneity to which the pathogen population is exposed. Varying the spatial and temporal deployment of different *R* genes by rotating cultivars over seasons, or by planting cultivars with different *R* gene complements in adjacent fields, reduces the risk of catastrophic total crop loss. However, within a single field, a genetically uniform host population is still presented to the pathogen. This disadvantage can be circumvented by deploying either cultivar mixtures or multilines (i.e., a mixture of near-isogenic lines differing only in their *R* genes), which would present a heterogeneous host population within a field. Disease development on these mixed populations may be reduced as a consequence of several possible mechanisms, both physical, such as barrier effects, in which host genotypes compatible with different components of the pathogen population are spatially isolated from each other, and physiological, such as systemic acquired resistance, in which incompatible interactions may induce resistance to otherwise compatible pathotypes (Wolfe, 1985; Wolfe and Finckh, 1996). The strategy relies on the hypothesis that a pathotype possessing multiple virulences (i.e., mutations that counter all of the *R* genes present in the mixture or multiline) would carry a fitness deficit compared with pathotypes without such mutations at *Avr* loci that are functionally beneficial to the pathogen.

However, there are practical problems associated with the deployment of both mixtures and multilines. Farmers and consumers require uniformity for agronomic traits, and increasing crop uniformity has been a high priority for breeders of most crops. Mixtures have not been widely adopted because they exhibit variation in critical agronomic characteristics such as time to harvest. Multilines do not have these disadvantages but are nonetheless impractical for most crops because it takes an excessive amount of time and resources to produce a multiline that may then be superseded by a higher yielding "single" cultivar.

Pathotype-specific resistance can also be deployed as a component in integrated control systems in which disease control relies on the combined use of agrochemicals, cultural practices, or biological control measures (see Handelsman and Stabb, 1996, in this issue, for a discussion of biocontrol). A practical disease control strategy for lettuce downy mildew illustrates the principle (Crute, 1992). Over the last 30 years, seven *R* genes (*Dm2*, *Dm3*, *Dm6*, *Dm7*, *Dm11*, *Dm16*, and *Dm18*) located in two linkage groups have contributed to the control of downy mildew in lettuce crops grown under protection (glass or polyethylene) in northern Europe. The occurrence of various combinations of the *Dm* genes in commercial lettuce cultivars has been dictated by the pathotypes of *B. lactucae* used in their selection but has been restricted by linkage in repulsion between the *Dm* genes.

In the United Kingdom, a pathotype of *B. lactucae* insensitive to phenylamide fungicides, such as metalaxyl, emerged in 1978 and became prevalent throughout lettuce production areas in subsequent years. The specific virulence of this pathotype was identical to that of the previously described phenylamide-sensitive pathotype NL10, with lettuce cultivars carrying *Dm11*, *Dm16*, or *Dm18* exhibiting resistance. Consequently, an integrated control strategy based on the utilization of metalaxyl, which is effective against all sensitive pathotypes, on cultivars carrying *Dm11* provided effective control in the United Kingdom until 1987, when a second phenylamide-insensitive pathotype began to cause problems. The specific virulence of the second pathotype, which also caused problems

in The Netherlands and France, was identical to that of the previously described phenylamide-sensitive pathotype NL15. Cultivars carrying *Dm6*, *Dm16*, or *Dm18* but not *Dm11* were resistant to NL15. Consequently, an appropriate change in the cultivar recommendations for use in the integrated control strategy was successfully promulgated. In 1992, a third pathotype dictated that control should be based on metalaxyl use with cultivars carrying *Dm3*, *Dm6*, or *Dm18*. In 1995, a metalaxyl-insensitive pathotype became prevalent, against which only cultivars carrying *Dm18* provided protection. Variations of the integrated control strategy have therefore provided effective control for >15 years.

DISCUSSION AND A VIEW OF THE FUTURE

Recent advances, elaborated here and in other reviews in this issue, suggest that a fuller understanding of the mechanisms by which plants perceive a potential pathogen, discriminate among pathogen genotypes, and respond effectively to resist invasion cannot be far away. The challenge now is to utilize advances in knowledge and technology to better protect from loss due to disease those crops on which the human race depends. A major focus of the effort will be to provide more durable disease control systems than has commonly been the case hitherto. Some specific prospects for future advances are the subject of the discussion below.

Generating effective combinations of *R* genes by conventional hybridization and gene introgression by backcrossing can be a lengthy process, particularly if a wild relative of the crop species in question provides the source of resistance. However, it is now a reasonably straightforward task to identify easily scored molecular markers that are linked to *R* genes. This facilitates marker-aided selection strategies that can improve the efficiency with which novel or particularly valuable *R* genes can be incorporated into well-adapted commercial cultivars. Moreover, by using markers that map to regions of the genome not associated with the target gene, it should be possible to speed up the selection process by ensuring that backcross progeny predominantly carrying the genome of the desired recurrent parent are preferentially selected.

The availability of sequence data from isolated *R* genes and the prospect of different classes of *R* genes being conserved between taxa provide the prospect of being able to isolate large numbers of similar genes, which may or may not function in pathogen recognition. Studies of collinearity between the genomes of different taxa may allow conclusions to be drawn about related genes residing in homologous regions. However, a demonstration of functionality will demand substantial collections of potential pathogenic variants of the target organism and plant populations derived from appropriate crosses to allow the necessary cosegregation studies. These latter two requirements may prove to be rate limiting in advancing rapidly from the several genes isolated in the last few years to having available large numbers of isolated *R* genes of demonstrated function.

Although marker-aided selection will undoubtedly make the directed pyramiding of *R* genes more feasible than at present, the exploitation of transgenic technology will make such a strategy comparatively straightforward because it will not be constrained by the limitations imposed by the often-encountered linkage between *R* genes. The availability of isolated *R* genes of known function will also make the production of multiline cultivars feasible. The response time for introduction of new cultivars in temporal gene deployment strategies, such as the one described above for the integrated control of lettuce downy mildew, may also be abbreviated. *R* gene deployment strategies based on the exploitation of temporal and spatial genetic heterogeneity are likely to feature more prominently in crop protection in the future. For example, "mixed and matched" dynamic multilines that will have the agronomic uniformity required by farmers but a changing complement of *R* genes to prevent continuous selection pressure against matching *Avr* genes could be produced.

The often-suggested prospect of using transgene technology to move *R* genes between sexually incompatible taxa can now be evaluated. The *Pto* gene from tomato, which confers resistance to *P. s. tomato*, has recently been transferred to tobacco (Rommens et al., 1995), and the resulting transgenic plants proved to be resistant to *P. syringae* pv *tabaci*. However, this example involves resistance to pathovars of the same bacterial pathogen. It will be interesting to observe the interaction phenotype in response to infection by unrelated compatible pathogens when an *R* gene is transferred to a species that is a nonhost of the pathogen originally recognized by that gene. There will undoubtedly be limits to the function of *R* genes when they are moved between taxa that could relate to the specificity of signal transduction pathways in distantly related plant species. Indeed, there is some evidence that genes involved in defense signal transduction are specific to particular *R* genes (Freialdenhoven et al., 1996), which may make it difficult to predict how *R* genes introduced as transgenes will function.

Understanding why some *R* genes or *R* gene combinations provide durable disease control, whereas control in other cases is ephemeral, will require more information about the molecules of pathogen origin that are perceived by the plant. Durability is a function of the fitness deficit implicit in the allelic variation at an *Avr* locus or in particular *avr* (virulence) gene combinations. The selective advantage that an *Avr* gene product confers on a pathogen in the absence of a matching host *R* gene determines the fitness deficit of a mutation to virulence (i.e., avoiding detection by the matching *R* gene). An understanding of the function of *Avr* gene products in pathogenesis should allow the identification of *R* genes, or *R* gene combinations, that recognize those particular pathogen *Avr* gene products that impose lethal or debilitating phenotypes when a mutation to virulence occurs. The organization of *R* genes in plant genomes and such structural data as are available imply that considerable molecular variation may be possible among *R* gene products. When more is known about structure–function relationships between *Avr* and *R* gene prod-

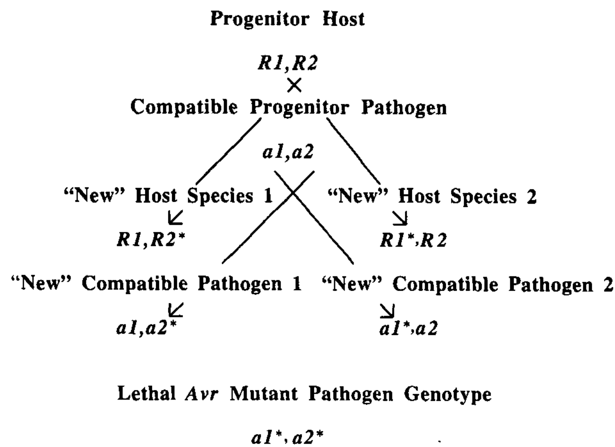

Figure 1. Evolution of Taxon Specificity.

The progenitor host species carries two *R* genes (*R1* and *R2*) for which the progenitor-compatible pathogen lacks matching avirulence (i.e., it carries the virulence alleles *a1* and *a2*). Evolution of the "new" host species 1 and 2 is associated with an alteration in the resistance specificity of *R1* to *R1** and of *R2* to *R2**, respectively, such that *a1* and *a2* are specifically recognized. This results in incompatibility with the progenitor pathogen. "New" pathogens 1 and 2 coevolve compatibility with the "new" host species 1 and 2, respectively, by changes in *a1* and *a2* to *a1** and *a2**. Individually, these mutations do not adversely affect fitness. However, in combination, the mutations *a1** and *a2** are lethal, and *R1** and *R2** therefore become genes controlling taxon specificity or nonhost resistance. This evolution of taxon specificity results from disruptive selection plus a severe fitness deficit for the pathogen. The resistance of "new" host species 1 to "new" pathogen 2 and "new" host species 2 to "new" pathogen 1 is durable. In other words, you can walk (a1) and chew gum (a2*) but you cannot scuba dive (a1*) and chew gum (a2*).

ucts, it should be feasible to create *R* genes whose products are designed to recognize pathogen molecules that are unable to sustain genetic variation without a lethal effect.

In the search for durable resistance, it is not necessary to look further than so-called nonhost resistance, which is defined by the limits in the host range of a particular pathogen. The gene-for-gene relationship provides the basis for the discrimination of pathotypes by their virulence or avirulence on particular genotypes within an individual host species. However, in addition to this subspecific variation among genotypes within a pathogen species, pathotypic variation is also frequently evident at the level of host species, genus, or family. For example, the downy mildew pathogen *P. parasitica* is pathogenic only on cruciferae. Although it has been reported to infect >50 host genera, pathotypes are restricted to the host genus or species of origin. Hence, isolates from Arabidopsis are avirulent on *Brassica* spp and vice versa. It is clear that such specificity represents the outcome of coevolution. Moreover, there is some evidence that species or higher taxa specificity may also be a reflection of gene-for-gene recognition. Although the subject continues to be debated (Heath, 1987, 1991; Newton and Crute, 1989; Tosa, 1992), it may be within the context of taxon specificity that gene combinations will be identified for which matching virulence is lethal (as described in Figure 1). Such genes thereby become genes for nonhost resistance and should provide practical value by their durability.

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