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RESISTANCE GENE COMPLEXES: Evolution and Utilization

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■ **Abstract** More than 30 genes have been characterized from different plant species that provide resistance to a variety of different pathogen and pest species. The structures of most are consistent with a role in pathogen recognition and defense response signaling. Resistance genes are very abundant in plant genomes and most belong to tightly linked gene families. Evolution of R genes is driven by selection on allelic variation created by mutation and re-assorted by recombination between alleles and sometimes between different gene family members. Selection favors genes that can recognize pathogen avr gene products that are present in pathogen populations. Selection at linked gene families favors haplotypes with useful combinations of genes but a limited physiological cost to the plant. Future utilization of R genes will include transfer between related genera and identification or construction of genes that condition durable resistance to variable pathogens. Genes with durable resistance may interact with conserved pathogen elicitors or condition resistance responses that are independent of specific Avr gene interactions.

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INTRODUCTION

Disease resistance in plants is often controlled by genes that confer high levels of resistance but only to specific pathogen genotypes. Resistance (R) genes that are employed on a large scale in agriculture typically lose their effectiveness over time owing to shifts in the pathogen population to forms that are virulent on cultivars carrying the gene. Genetic analysis of resistance in numerous host species and specific virulence in the corresponding pathogens has led to the general acceptance of the gene-for-gene model (43), where specific R genes interact with specific avirulence (Avr) genes in the pathogen to cause resistance. In the simplest models to account for gene-for-gene resistances, the R gene products somehow recognize the pathogen Avr gene, either by a direct interaction with its protein product or by an interaction with something made by the Avr gene product if it has a catalytic role (132). Once this recognition has occurred, defense responses are triggered. These are often characterized by a hypersensitive response, which involves the death of the first cell or cells infected and the local accumulation of antimicrobial compounds.

Over 30 disease resistance genes have now been isolated from a variety of plant species. In this review we discuss how analysis of these sequences has influenced how we think about the evolution of R genes and how they might be used to enhance crop production.

TYPES OF R GENES AND R GENE LOCI

Proteins Coded by R Genes

The proteins encoded by most characterized resistance genes carry motifs found in other receptor and signal transduction proteins (Table 1). The largest group of resistance genes carries leucine-rich repeats (LRRs) and nucleotide-binding site (NBS) domains. These genes are very abundant in plant genomes, comprising an estimated 1% of the genes in the *Arabidopsis* genome (95). In addition, no function other than disease resistance has yet been ascribed to them, aside from the fact that *Prf* is required for sensitivity to the organophosphate insecticide Fenthion. The NBS-LRR class of R genes can be further subdivided based on their ability to code for other recognizable domains. One subclass codes for a TIR domain (homology to the *Drosophila Toll* and mammalian *Interleukin-1* receptors) at the N terminus of the protein. NBS-LRR proteins without a TIR domain typically code for a coiled-coils structure near their N terminus, sometimes in the form of a leucine zipper. This latter type is much more common in cereals, where members with a TIR domain have not yet been identified (95, 106, 159). Three other classes of resistance genes carry LRRs or kinase domains or both LRRs and kinase domains. A number of excellent reviews have described the structure and function of these genes (4, 8, 28, 39, 40, 52, 132).

TABLE 1 Classes of characterized R genes

Class/gene	Interaction (Host/pathogen)	Predicted protein structure	Complex locus[a]	Introgressed from wild species	Reference
1 *L*	Flax/*Melampsora lini*	TIR-NBS-LRR	No	No	(81)
M	Flax/*Melampsora lini*	TIR-NBS-LRR	Yes	No	(2)
N	Tobacco/TMV	TIR-NBS-LRR	Yes	Yes	(154)
P	Flax/*Melampsora lini*	TIR-NBS-LRR	Yes	No	(35)
RPP1	*Arabidopsis/Peronospora*	TIR-NBS-LRR	Yes	No	(14)
RPP5	*Arabidopsis/Peronospora*	TIR-NBS-LRR	Yes	No	(107)
RPS4	*Arabidopsis/Pseudomonas*	TIR-NBS-LRR	No	No	(46)
Bs2	Pepper/*Xanthomonas*	NBS-LRR	Yes	Yes	(136)
Dm3	*Lettuce/Bremia*	NBS-LRR	Yes	No	(96)
Gpa2/Rx1	Potato/*Globodera* Potato/PVX (*Rx1*)	NBS-LRR	Yes	Yes	(144) (5)
I2	Tomato/*Fusarium*	NBS-LRR	Yes	Yes	(104, 122)
Mi	Tomato/*Meloidogyne*/ *Macrosiphum*	NBS-LRR NBS-LRR	Yes Yes	Yes Yes	(99) (117, 146)
Mla	Barley/*Blumeria*	NBS-LRR	Yes	No	(162)
Pib	Rice/*Magnaporthe*	NBS-LRR	Yes	No	(148)
Pi-ta	Rice/*Magnaporthe*	NBS-LRR	No	No	(18)
Prf[b]	Tomato/*Pseudomonas*	NBS-LRR	Yes	Yes	(118)
Rp1	Maize/*Puccinia*	NBS-LRR	Yes	No	(25)
RPM1	*Arabidopsis/Pseudomonas*	NBS-LRR	No	No	(48)
RPP8/HRT	*Arabidopsis/Peronospora* *Arabidopsis*/TCV (*HRT*)	NBS-LRR	Yes	No	(89) (27)
RPP13	*Arabidopsis/Peronospora*	NBS-LRR	No	No	(11)
RPS2	*Arabidopsis/Pseudomonas*	NBS-LRR	No	No	(9, 100)
RPS5	*Arabidopsis/Pseudomonas*	NBS-LRR	No	No	(149)
Rx2	Potato/PVX	NBS-LRR	Yes	Yes	(5)
Sw-5	Tomato/*Tospovirus*	NBS-LRR	Yes	Yes	(16)
Xa1	Rice/*Xanthomonas*	NBS-LRR	No	No	(158)
2 *Cf-2/5*	Tomato/*Cladosporium*	LRR-TM	Yes	Yes	(32)
Cf-4/9	Tomato/*Cladosporium*	LRR-TM	Yes	Yes	(69, 137, 141)
3 *Pto*	Tomato/*Pseudomonas*	Protein Kinase	Yes	Yes	(87)
4 *Xa21*	Rice/*Xanthomonas*	LRR-TM-Kinase	Yes	Yes	(129)
5 *HS1^{pro-1}*	Beet/*Heterodera*	Unique[c]	No	Yes	(20)
6 *Rpw8*	Arabidopsis/*Erisyphe*	Unique	Yes	No	(157)
7 *mlo*	Barley/*Blumeria*	Membrane Prot.[d]	No	No	(19)
8 *Hm1*	Maize/*Cochliobolus*	Toxin reductase	No	No	(68)

NBS = nucleotide binding site. LRR = leucine-rich repeat. TIR = domain with homology to the *Toll* gene of *Drosophila*, and the *Interleukin-1* receptor of mammals. TM = transmembrane domain. Domains are listed as they appear in the proteins from N to C terminal end.

[a]'Complex locus' indicates the gene belongs to a tightly linked family of highly homologous genes.

[b]*Prf* is required for *Pto* mediated resistance to *P. syringae* pv *tomato* strains carrying *avrPto* and for the *Fen* mediated, hypersensitive-like reaction to the organophosphate insecticide Fenthion.

[c]The predicted *HS1^{pro-1}* protein was originally reported to have a LRR-TM signature though it poorly fits the LRR consensus and has minimal similarity to other known resistance genes (40).

[d]Predicted 60-kDa protein is membrane anchored with at least 6 membrane spanning helices.

LRR domains are typically thought to be the major determinant of specificity in R genes that carry them based on their known history in other proteins (76, 77) and the high levels of polymorphism between alleles in these domains. This conclusion has also been supported by allelic comparisons and domain-swapping experiments between different alleles at the *L* and *P* loci of flax (35, 41). Recent experiments with the rice resistance gene *Pi-ta* and its cognate avirulence gene from *Magnaporthe grisea* have provided direct evidence of an interaction between the LRR domain of a R gene and its cognate Avr gene. In both the yeast two-hybrid system and in vitro binding assays, *Avr-Pita* protein was shown to bind specifically to the LRR domain of the *Pi-ta* protein (66). Consideration of the LRR region as the "specificity domain" is apparently an oversimplification. Domain swaps between alleles of the L locus demonstrated that sequences at the amino-terminal end of the protein are also involved in specificity (38, 85). Domain swaps between the *Mi* gene and one of its paralogues implicated a role for the LRR domain in defense response signaling (62). A mutation in the LRR motif of the *RPS5* gene of Arabidopsis also implicated it in defense response signaling since it interfered with resistance conferred by several other NBS-LRR genes (149). It may not be possible to make generalizations about the specific functions of what we recognize as different domains in R gene products. Rather, these studies have illustrated how the different regions of an R gene product must function together to conduct both the pathogen recognition and signal transduction functions.

The predicted cellular location of an R gene protein reflects where it interacts with its corresponding elicitor. The LRR-TM (transmembrane domain) and LRR-TM-Kinase classes of proteins are predicted to span the cell membrane, with an extracellular LRR. The *Cf* genes confer resistance to the fungus *Cladosporium fulvum*. Two small cysteine-rich peptides, encoded by two *Avr* genes interacting with *Cf-4* and *Cf-9*, have been found to be secreted into the intercellular spaces (70, 143, 145). In contrast, the NBS-LRR genes are predicted to be cytoplasmic, although they may be membrane associated (15). A cytoplasmic location is suitable for interaction with viral components or bacterial Avr genes that are introduced into the host cell by a type III secretion system (Leach et al., this volume: chapter 9). These genes also confer resistance to an amazing diversity of different organisms including fungi from three different taxonomic classes and very different modes of pathogenicity, from biotrophic rusts, powdery mildews, and downy mildews, to hemibiotrophic fungi like *Magnaporthe* and vascular wilts like *Fusarium*. They also control resistance to nematodes and insects (Table 1). The observed interaction with intracellular R gene products should stimulate research into how these diverse organisms deliver elicitors into plant cells.

Resistance gene products do not act alone in controlling defense reactions. Although beyond the scope of this review, other genes involved in R gene–mediated resistance have been identified by mutagenesis or biochemical approaches (64, 86, 163, 164). Some of these other components are involved in downstream signaling steps, but some may be components of an elicitor recognition complex. The NBS-LRR protein encoded by *Prf* is required for the *Pto* kinase-mediated resistance

in tomato. A similar mutagenesis approach identified a kinase that was required for resistance mediated by the NBS-LRR resistance gene *RPS5* of *Arabidopsis* (135, 150). This establishes a trend for the involvement of kinases and NBS-LRR proteins in the same resistance-signaling pathway. They may function together in recognizing pathogen elicitors, possibly as co-receptors, since members of both classes of genes have been demonstrated to physically interact with their Avr gene products (66, 119, 138). The similarity in structure of the tomato *Cf* proteins (LRR-TM class) to the *Xa21* protein (LRR-TM-Kinase) suggests that the LRR-TM genes may also include a kinase in their defense-signaling pathway.

Not all simply inherited disease resistances fit the mold of a receptor or signaling component involved in pathogen recognition. This is exemplified by the last two entries in Table 1. Despite their traditional consideration as R genes, most plant molecular biologists do not consider them as such. The *mlo* gene is unusual in that the allele conferring resistance to the barley powdery mildew fungus is functionally recessive and has been isolated numerous times by mutagenesis (71). Resistant alleles also show resistance to all known mildew isolates. The functional *Mlo* allele codes for a putative membrane protein whose function may be a negative regulator of certain defense responses (19). Barley lines that are homozygous for the nonfunctional allele show spontaneous defense responses like cell wall appositions in the epidermal cells and even some cell death (155). Mutations causing increased resistance to disease by altering expression of defense responses have also been isolated in Arabidopsis, for example (45), and are generally not considered to be disease-resistance genes. The *Hm1* gene of maize is also unlike other known R genes in that it codes for an enzyme, HC-toxin reductase, that detoxifies the toxin made by race 1 of *Cochliobolus carbonum* (68, 92). The resistance allele is dominant over recessive alleles that do not code for a functional enzyme.

Chromosomal Arrangement of R Genes

R genes exist in a number of different genomic arrangements in plants. The simplest arrangement is a locus consisting of a single R gene. A simple locus may carry considerable genetic variation in an allelic series. The best characterized is the *L* locus of flax, where multiple alleles have been identified by their differential reactions to flax rust (*Melampsora lini*) races. The *Rpp13* locus of *Arabidopsis* is another simple locus with functionally distinct alleles (11). In most other cases of simple R gene loci, like the *Rpm1* and *Rps2* loci of *Arabidopsis*, one resistant allele has been characterized and other alleles do not confer resistance to any known pathogen isolates. It is possible that other alleles of these loci are indeed functional in interactions with unknown avirulence factors. Sequence comparisons of alleles from different ecotypes have indicated that both *Rpm1* and *Rps2* show a high rate of sequence divergence and are thus evolving at a relatively rapid rate (21, 131). Most of the molecularly characterized R genes belong to families of tightly linked genes (Table 1). In species with a high gene density, like *Arabidopsis* and

rice, the genes are typically physically close to each other. In species with a lower gene density the genes are usually farther apart. R gene haplotypes at the *Rp1* (133) locus of maize, the *mlo* locus of barley (151), and the *RGC2* (*Dm3*) family of lettuce span a few hundred Kb or more. *RGC2* family members are estimated to be over 100 Kb apart, with few if any genes in between (96).

Some resistance gene clusters carry different resistance genes that are clearly not derived from recent duplication events. The most striking example is the *Pto* locus of tomato. This locus contains five genes coding for kinases, one of which is *Pto*. An NBS-LRR gene, *Prf*, lies within this cluster of kinase genes. The *Prf* gene product is required for *Pto*-mediated resistance to *Pseudomonas* isolates carrying *AvrPto*. How the unrelated *Prf* gene became embedded in the *Pto* gene family is an interesting question. The structural difference between components of these multifunctional loci precludes the possibility that they arose by duplication and divergence of a single ancestral gene. Some type of transposition or rearrangement most likely brought the two types of genes in proximity to each other, and selection favored the arrangement because of the codependence of the genes upon each other for the resistance phenotype (below). There are few examples in plants of tight clustering of unrelated genes involved in the same physiological processes. Another notable example is the self-incompatibility loci of *Brassica* species where very tightly linked, unrelated genes control the pollen and pistil components of the interaction (17). Both R gene-mediated resistance and self-incompatibility systems involve recognition (pathogen or self-pollen) processes. The components of these recognition complexes may be somewhat unique in that they are completely dependent on each other for a specific function and they can have a very big influence on the fitness of the progeny, at least in certain environments.

Other complex resistance gene loci carry related but highly divergent sequences. For example, Wei et al (151) found the *mla* powdery mildew resistance locus of the barley cultivar Morex carried three different families of NBS-LRR genes coding for proteins with sequence identities of less than 33%. Two or more members of each family were interspersed within a 240-kb interval. A simpler example is the *Rps4* gene of Arabidopsis, which is adjacent to a highly diverged NBS-LRR gene (53). Examination of the genomic sequence databases indicates that this organization of NBS-LRR genes is common in rice. Several fragments in genomic sequence databases carry more than a single NBS-LRR sequence within 10 to 40 kb of each other that include genes coding for proteins with less than 40% sequence identity. The origin of these heterogeneous NBS-LRR gene clusters is not apparent. Most are probably the product of ancient duplication events where the members have diverged. The divergent genes in others may have been brought together by chromosomal rearrangements. If linkage arrangements of resistance genes change frequently over evolutionary time, the syntenic relationships of these genes should be less conserved than other genes when their map positions are compared in related species. The emerging picture is not yet clear. When Leister et al (83) compared the map positions of several NBS-LRR genes in rice, barley, and

foxtail millet, map positions were poorly correlated with what would have been expected based on the known syntenic relationships of the corresponding chromosomal regions. In contrast, map positions of cloned resistance genes appear to be well conserved in the *Solanaceae* (50, 105). Part of the difficulty of examining syntenic relationships between distantly related cereals comes from the chromosomes having diverged sufficiently that many exceptions to synteny are observed with any type of genetic marker (6, 7). The question of whether resistance genes change their linkage relationships more frequently than other genes over the course of evolution of plant chromosomes will have to be addressed by very thorough comparative mapping and sequencing experiments.

Resistance gene clustering can also be observed at a larger genomic scale than the clustered gene family. Traditionally, these regions have been viewed as chromosomal regions where numerous disease resistances grouped within a span of a few to 20 centiMorgans (59, 110). Genomic clustering of resistance genes is also observed when NBS-LRR sequences are mapped (13, 26, 73, 80, 82, 83, 120, 160). They are referred to as major resistance gene complexes in *Arabidopsis* (55). This phenomenon can now be observed directly in Arabidopsis genomic sequences as mega-clusters (159) or sequenced fragments of several megabases that carry numerous NBS-LRR sequences from different families.

Some haplotypes of complex R gene loci carry multiple genes with detectable resistance functions (14, 109, 147). Most have carried multiple paralogues with no detectable function. At the *Rpp5* and *Xa21* loci, most family members had open reading frame–disrupting mutations (102, 130). In some cases, the truncated members may have some function; the truncated *Xa21D* gene, with an LRR domain but no membrane-spanning or kinase domains, confers partial resistance with the same resistance spectra as the *Xa21* gene. Truncated NBS-LRR genes in some *Rpp5* and *Rp1* haplotypes could code for proteins resembling those of alternatively spliced transcripts of the L and N genes, but no function has been associated with these (3, 25, 31, 107). At many complex loci, most paralogues are not obvious pseudogenes and appear capable of coding for proteins similar to the functional R genes (32, 89, 97, 109, 122, 133). This situation is not unique to complex loci since plant species carry hundreds of R gene sequences, some of which belong to simple loci, and relatively few have phenotypes associated with them. It is likely most paralogues are capable of interacting with unknown elicitors or were able to in their recent evolutionary past. This is suggested by evidence that diversifying selection is acting on these sequences (below). Also, most of the mutant alleles examined at the *Rpp5* locus had ORFs that were disrupted by a single mutation event and had not accumulated additional mutations (102). Similarly, most of the *rp1* genes characterized with obvious mutations were caused by single events in the ORF or had intact ORFs but had mutations in the promoter regions (133). This indicates that these genes have functioned in their recent history. Unequal recombination events may help keep coding regions intact, and recombination events with nonfunctional R genes may contribute to the generation of novel genes.

FORCES AFFECTING R GENE EVOLUTION

Effects of Recombination on Evolution of R Genes and Gene Families

Genetic recombination events between alleles or family members re-assort the genetic variation created by mutation to create new alleles. The importance of this process in resistance gene evolution is illustrated by the fact that most of the spontaneous R gene variants with novel phenotypes that have been selected have been associated with recombination events (38, 60). For example, intragenic crossover events in the L gene of flax have created alleles with different specificities from those of the parents. Recombinants from *L2/L6* heterozygotes were identified that had the *L7* race specificity, and recombinants between *L9* and *suL10* generated an allele designated *RL10* that has a novel race specificity (85). Recombinant *Rp1* genes have been isolated that confer modified resistance phenotypes or race nonspecific reactions (133). Several novel race specificities have also been found at *Rp1* (112), and most have been associated with crossovers by flanking marker analysis, but the recombinant genes have not yet been characterized.

Genetically linked gene families have more possibilities for recombination than simple loci composed of single genes. Unequal crossing over occurs regularly in some linked gene families; family members at different positions in the array mispair in meiosis. Crossovers that occur while the genes are mispaired change the number of family members in the progeny haplotypes and rearrange them into new combinations. The crossovers may be intergenic (in the regions between the genes) or intragenic. Susceptible variants from a maize *Rp1-D* homozygote were mostly derived by intragenic crossovers (133). In contrast, five susceptible variants selected from *Cf4/Cf9* heterozygotes were all generated by crossovers in intergenic regions (109). The *Cf4* $\times$ *Cf9* cross was essentially an interspecific cross with respect to this locus, since the haplotypes were introgressed from different species, but sequences with high levels of homology existed in some of the intergenic regions of the two haplotypes. A single recombinant isolated from a similar *Cf2/Cf5* heterozygote was derived from an intragenic crossover (32). In addition to creating novel genes and re-assorting them into new combinations, unequal recombination within a gene family tends to homogenize them (54, 128). Members of gene families that do not interact by recombination evolve more independently, as if they were unlinked. The homogenizing effect of unequal recombination events slows divergence of family members and may actually hinder acquisition of new functions, such as the ability to recognize a novel class of Avr genes.

Different gene families vary in the extent to which they mispair and recombine in meiosis. Duplicated genes at the *R* locus of maize, which regulates anthocyanin pigmentation, appear to mispair as frequently as they pair normally (114), whereas mispairing at other duplicated genes appears to be very rare. The same disparity is observed when comparing *R* gene loci. Members of the *Rp1* family of maize mispair frequently (60), and unequal recombinants from most haplotypes can be

readily identified by phenotype or even by examination of progeny haplotypes by gel blot analysis. Genetic analysis of the *Rp3* rust resistance locus of maize indicates that many haplotypes also mispair frequently (unpublished). Alternatively, five susceptible recombinants from a *Cf4/Cf9* cross all resulted from crossovers following the same arrangement of meiotic pairing, and unequal crossovers were not detected from Cf9 homozygotes. Unequal recombination events are thought to be rare at other loci such as *Dm3* of lettuce and *Pto* of tomato (98). This is indicated by the relatively stable structures of the loci and sequence comparisons of orthologous and paralogous genes. Orthologous genes, in two different species or two different lines, are genes derived from a single ancestral gene. Barring unequal crossing over or other events giving rearrangements, orthologues will occupy identical positions within a gene family (Figure 1). Paralogous genes are those that arose within a species by duplication. At loci like *Dm3* and *Pto*, the observation that orthologous genes from two different lines or species were more similar to each other than they are to the paralogous genes within the family suggests that unequal recombination is rare. Unequal recombination occurs at least at

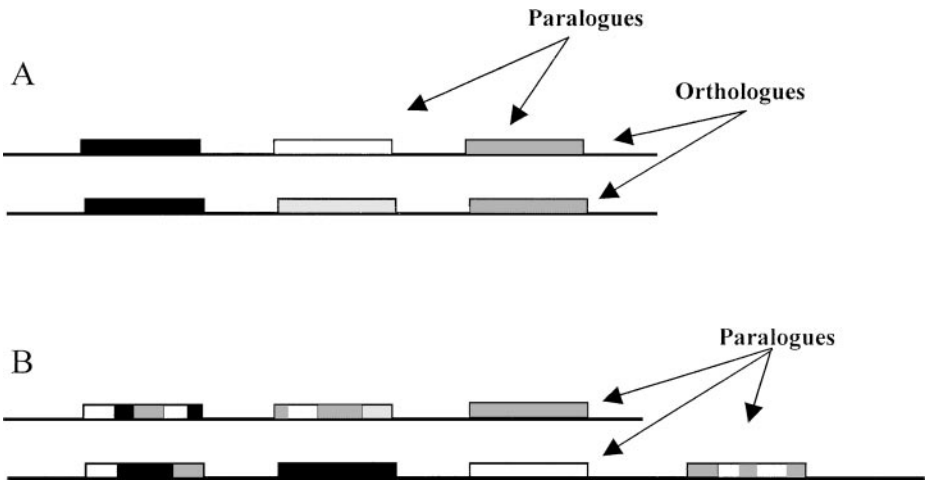

Figure 1 Structures of linked R gene families. Different R gene family members are represented by boxes and similar shading implies sequence similarity. *A.* The same chromosome segment from two different genotypes carrying a linked R gene family (two haplotypes). In gene families that do not mispair and recombine, different haplotypes typically have equal numbers of genes. Orthologues, at the same position in the array, from different haplotypes are more similar in sequence than paralogues from in a single haplotype. *B.* Two haplotypes of a gene family where the members frequently mispair and recombine. Different haplotypes vary in the number of family members, and genes within a haplotype may sometimes be more similar than genes between haplotypes. Genes at different positions in the array show stretches of sequence identity or similarity.

a low frequency even in relatively stable gene families. This would account for the differences in gene number that are frequently observed when different lines, or closely related species, are compared (32, 89, 109). This is also indicated by comparative sequence analysis of genes at complex loci. Paralogues at the *Cf4/9* and *Rpp5* loci show patchwork sequence affinities where different genes are similar to each other for stretches of up to several hundred nucleotides. Both the *Cf2* and *Cf5* haplotypes carry pairs of genes that are nearly identical in amino acid sequence, suggesting recent duplications (32, 33).

A number of factors would be expected to affect the degree to which members of a linked R gene family recombine with each other. Gradual sequence divergence would presumably reduce the frequency with which they recombine. Recombination in general is inhibited by sequence heterogeneity (12, 36, 94). The frequency of mitotic recombination in yeast can be affected noticeably by less than 1% nucleotide sequence divergence (30). Sequence divergence between members of clustered gene families is typically more extensive than between alleles of a single locus, even if the family members mispair. The degree to which sequence divergence influences meiotic recombination in different plant species is not known. Unequal recombination in the *rp1* complex of maize does not appear to require a high level of nucleotide identity. In the *HRp1-D* haplotype, the *Rp1-D* gene recombines frequently with a paralogue (*rp1-pd5*) that is only 94% identical. The observed exchange points between these two genes were sometimes, but not always, in the regions where they were most similar (133). The rice *Xa21* locus has a small highly conserved region in each of its family members. Sequence comparisons indicated that recombination events between family members might occur preferentially in this region (113, 130). Physical separation of family members to different chromosomal loci will reduce the frequency with which family members recombine, but may not prevent it entirely. This is well illustrated by the *Hcr9* family, which maps to three distinct loci on tomato chromosome 1, including the *Cf4/9* complex and two others. The genes at one locus have diverged significantly from the others, except for one family member. This family member was probably reintroduced to the divergent gene cluster by an ectopic recombination between different loci (108). Chromosomal orientation will also affect how linked R gene paralogues interact. Gene families that are arranged as direct repeats are free to recombine unequally. If there are additional genes between the linked paralogues (e.g. *Prf* in the *Pto* kinase family), this may affect recovery of unequal recombinants since these genes will be deleted and duplicated along with the paralogues. Alternatively, products of crossovers between inverted repeats lead to dicentric and acentric chromosomes and will not generally be transmitted to the next generation. Gene conversion events and crossovers between inverted members on the same chromatid are tolerated, but these types of events may be much less frequent. Experimentally derived recombinants at the maize *Rp1* locus are usually the result of interchromosomal crossing over (56). Examination of tightly linked NBS-LRR genes in rice genomic sequences indicates that these genes do diverge more rapidly than most directly arranged genes. There are more than 20 sequence contigs (i.e. sequence corresponding to a genomic fragment)

in the Monsanto rice genomic sequence database that carry multiple NBS-LRR genes (www.rice-research.com). In most, the genes are in the same orientation and show a variable range of inferred amino acid sequence identity (50–90% identity in the NBS region). In five contigs that carry genes in the inverted orientation, the inverted genes were all less than 45% identical to the other genes on the chromosome fragments. This supports the idea that linked genes in an inverted orientation diverge more quickly, possibly similar to the rate that unlinked duplications diverge.

The LRR regions of some R genes have regions with high levels of sequence homology between the repeats. This allows mispairing and recombination of different regions within a single gene, leading to genes with different numbers of repeats. Variant genes derived from these intragenic events have been identified in genes at the *Rpp5* (107) and *M* loci (2), and sequence comparisons of the *L* (41), *Cf4/9* (109), and *Cf2/5* loci show evidence of its occurrence. This intragenic misalignment has probably contributed significantly to the evolution of the *Cf2/5* gene family, where family members show a range of repeat number. The individual repeats in this gene family are unusually conserved in length and sequence, allowing increased potential for misalignment (32).

Effects of Mutation and Selection on R Gene Evolution: Diversifying Selection

Host parasite evolution is often thought of as an arms race. The host plant carries a large arsenal of resistance genes, some fraction of which will provide resistance to strains of a given pathogen. In gene-for-gene systems, the pathogen acquires new virulence alleles by changing, or losing, the Avr genes that code for the elicitors recognized by the resistance genes. Since many pathogens can do this quite readily, it seems there should be strong selection on plant species to generate R genes that can recognize additional pathogen-derived ligands (new specificities). While there are no demonstrated examples of new R gene specificities arising by point mutation, the effects of natural selection for mutations can be observed by sequence comparisons of alleles or R gene family members. When comparing DNA sequences of alleles of most genes, synonymous substitutions (those that do not change the amino acid) are more common than nonsynonymous substitutions because of selection to maintain the function of the gene. In theory, if a gene was under strong selection for the generation of new variants, it would show a different pattern of nucleotide substitutions: one where nonsynonymous substitutions are more common. In resistance genes, this was first observed comparing sequences of family members of the *Cf4/9* family (109). The observation has now been extended to the LRR domains of different family members of the *Xa21* gene family (147), and LRR coding regions of several NBS-LRR gene loci including *Rpp8* (89), *Rpp5* (102), *Rpp1* (14), *Dm3* (97), and *Rp1* (133). Evidence of diversifying selection is generally most noticeable in regions of the LRR domain that are predicted to be solvent exposed, as would be expected if these amino acids were involved in ligand binding.

The LRR domains of R proteins are typically composed of 20 to 40 or more repeat units that average approximately 24 residues each. Each unit shows noticeable homology to a consensus sequence centered on an xxLxLxx motif (where L is a leucine or other aliphatic amino acid and x is any other residue). Based on the crystal structure of the porcine ribonuclease inhibitor LRR protein, xxLxLxx motifs of LRRs are thought to form a parallel β-sheet structure. The conserved leucines are expected to serve as the backbone of the structure with the other residues being solvent exposed where they can interact with potential ligands. These "x" residues are typically among those that show the highest ratio of nonsynonymous to synonymous substitutions. This is consistent with the idea that these residues interact with pathogen ligands and that natural selection favors changes that can recognize novel ligands. Other regions of resistance genes, like those coding for NBS domains, typically do not show evidence of diversifying selection. An exception is a region in the TIR domain of the L gene, at the opposite (5′) end of the gene as the LRR-coding region (85). Interestingly, the 5′ region was also demonstrated to be involved in determining recognition specificity in the L gene (41, 85).

SELECTIVE FORCES MAINTAINING ALLELIC DIVERSITY Selection for novel or diverse recognition capabilities is not the only type of selection acting on R gene loci. Clearly, the selective advantage of carrying an R gene allele depends on the frequency of the corresponding Avr gene in the pathogen population. A previously important R gene allele may confer no fitness advantage if the pathogen population has essentially lost the corresponding Avr gene. It is often thought that alleles conferring resistance may even confer a fitness disadvantage in the absence of a pathogen carrying the corresponding Avr gene. Models for ecology and evolution of host parasite interactions commonly include fitness costs for alleles conferring specific virulence in the pathogen and resistance in the host to explain the allelic diversity in natural populations (84). A negative effect on aggressiveness has now been associated with mutations at a number of pathogen avirulence loci, particularly from bacterial pathogens (see Leach et al., this volume: chapter 9). Fitness or performance costs from resistance genes have also been reported, but these are usually the result of comparisons of lines or genetic material with, and without, the resistance gene. These estimates can therefore be easily attributed to linkage drag, the transfer of additional genes genetically linked to the gene being transferred. Even after numerous backcrosses one expects to have a sizeable segment of chromosome transferred (111). A survey of published reports of resistance gene costs (10) found performance costs were much more frequently observed when the donor of the resistance gene was a different species than the recipient cultivar. This supports the idea that linkage drag may account for most of these differences, since chromosome segments introduced from uncultivated donor species are more likely to carry alleles that detract from agronomic performance, and these introduced chromosome segments may also be larger due to reduced rates of recombination during backcrossing. In contrast, the cost of the *mlo* gene conferring broad-spectrum powdery mildew resistance in barley has been examined

by comparing alleles derived from mutation in both the background in which they arose and after breeding into different backgrounds. In this case, the resistant allele is a mutant loss-of-function mutation and has a measurable performance cost. Presumably, this results from the physiological costs of the spontaneous defense responses that occur in homozygous *mlo* lines, including cell wall reinforcement and even cell death (19). Evidence for resistance gene cost in genes that work in a gene-for-gene fashion is not as apparent, but the isolation and manipulation of these genes has shed light on the subject. Like most other loci, resistance gene loci generally carry homologous sequences in alleles that have no apparent phenotype. Frequently, these genes show nucleotide differences from the resistant allele but code for similar proteins. One might expect that these genes would have a similar physiological cost to the plant as an allele that confers resistance to a characterized pathogen isolate. On the other hand, in some simple R gene loci, like *Rps5* and *Rpm1* of *Arabidopsis*, susceptible ecotypes sometimes carry no homologous sequences (48, 53). It is not clear if these deletion variants, or null alleles, occur any more frequently at R gene loci than they do at most other loci, but there are some indications that the null allele at *Rpm1* has a selective advantage in some environments. Sequence analysis of different *Arabidopsis* ecotypes has indicated that it is a stable polymorphism in the species that occurred very long ago (101). Furthermore, the same deletion has occurred in orthologous loci in the related species *Brassica napus* (49).

At complex R gene loci, differences between haplotypes could easily differ in their physiological cost. Complex loci that recombine unequally will differ in the number of genes carried in a haplotype; different maize lines carry from one or a few to 20 or more genes in their *rp1* haplotypes. They also vary considerably in the levels of *rp1* gene transcript observed by RNA blot analysis (unpublished). Some *Rp1* haplotypes, like *HRp1-D* and several recombinant haplotypes, confer spontaneous chlorotic or necrotic spots on the older leaves of adult plants that can be severe in certain backgrounds (58, 61). Resistance gene loci introgressed from related species sometimes have different structures than the loci of the cultivated species, and often differ in gene number. Gross overexpression of R genes in transgenics can have an obvious physiological cost to the plant (103, 139). Smaller differences in gene expression due to changes in gene number or alterations in expression probably have similar, but perhaps less noticeable, effects.

Selection at Multi-Gene Complexes

Allard (1) proposed that the population genotypes of many plant species are organized into highly integrated multi-locus units. He considered mating designs, like self-fertilization, to be important in promoting these multi-locus associations by reducing gene flow between differently adapted populations that occupy close, but unlike habitats. In cross-pollinated and less sessile species, genetic linkage is required to maintain multi-locus associations (34). The fitness of the genes tied up in these linkage complexes is determined partly by the fitness of the complex

as a whole. Mayr (34) considered coadapted gene complexes to be sufficiently important to fitness that he viewed the break up of these complexes by recombination as a type of genetic load. The common linkage associations between resistance genes makes them prime examples of genes that are involved in multigene associations. Associations between alleles at different linked R loci could be favored by the different environments in which a species is found, with different environments favoring different types of diseases. Clusters of resistance genes in genomic regions with low levels of recombination would favor strong multi-locus associations. Interestingly, two of the most striking R gene-rich regions in the maize genome where disease resistances to multiple organisms map are near the centromere on chromosome 3 and near the nuclear organizer region (NOR) on chromosome 6 (91), two areas thought to be low in recombination. For example, Simcox and coworkers were unable to identify recombinants between the NOR and *Mdm1*, which confers resistance to *Maize dwarf mosaic virus* (121). It may be that for highly out-crossing species, like maize, tight linkage is required for multilocus associations. The selective advantages of these associations were probably the driving force behind the formation of some of the resistance gene-rich regions in plant genomes.

The fitness contribution of individual genes in a clustered R gene family is very dependent on the other genes in the haplotype. Haplotypes expressing multiple specificities may be able to exclude lineages of the pathogen where haplotypes carrying the individual genes may not (161). Haplotypes expressing a more than optimal number of R genes may have a selective disadvantage, particularly in environments with low disease pressure. The level of recombination between members of gene families is also influenced by selection. Recombination events, which constantly create haplotypes with new combinations of genes, may be favorable in gene families controlling resistance to highly variable pathogens but unfavorable in families that control resistance to pathogens with low genetic plasticity. In the latter case, most recombinant haplotypes may be less favorable than the well-adapted parental haplotype.

UTILIZATION OF RESISTANCE GENES AS TRANSGENES

Control of plant disease by the development of disease-resistant plant varieties is the most efficient and environmentally friendly way to control disease, as long as sources of resistance are available. Disease resistance controlled by R genes will continue to be used far into the future. Although numerous other transgene approaches have been proposed and tested (115), none are currently used commercially to control bacterial or fungal diseases. The main limitations to most of these approaches are either the lack of effectiveness or an unacceptably high physiological cost to the plant. Resistance genes are unique in that they have evolved to control many different defense responses, but to trigger these defenses only where and when they are necessary, minimizing the physiological costs to the plant.

Interspecific Transfer of R Genes

Development of disease-resistant cultivars is an effective way to control diseases as long as sufficient genetic variation for resistance is available. When sources of resistance are limited, breeders typically look to the secondary gene pool for species that can be hybridized with the cultivated species (Table 1). Molecular cloning of R genes is now allowing them to be transferred between much more distantly related species. Two types of observations have been made in recent years that imply that interspecific transfer may be an important addition to our future arsenal of R genes. The first is that plants carry resistance genes that interact with avirulence genes from pathogens of other species (29, 42, 63, 75, 134, 152, 153, 156). These genes may account for a significant portion of the hundreds of R gene sequences that exist in plant genomes for which no function is known. The second important observation is that several resistance genes have been demonstrated to function after transfer as transgenes to different, but related, species. Several R genes from species in the *Solanaceae* have now been transferred to other *Solanaceous* species (e.g. tomato to tobacco) and have been demonstrated to be able to confer resistance reactions to pathogens carrying the appropriate avr gene (5, 51, 67, 116, 136, 140, 154). Attempts to demonstrate function in species outside of the family from which the gene was initially isolated have been unsuccessful. The reason for this "restricted taxonomic functionality" (136) is probably an indication that the other components of the resistance signal transduction pathway are not present in a form that can interact with the resistance gene in the recipient species (44, 52, 64). If similar successes are found in the *Poacea*, this could have a very significant impact on breeding disease-resistant cereals. Given the thousands of different species of grasses, the R gene supply should be plentiful if efficient methods can be developed to identify them and determine their function. It is not clear how predictable R gene function will be, in terms of what taxa an R gene might function against. Will orthologous genes in related species control resistance to pathogens of the same taxa? Considering that the *Gpa2/Rx1* family controls resistance to a nematode and a virus, the *Rpp8/Hrt* family to a fungus and a virus, and the *Mi* gene to an aphid and a nematode (Table 1), prediction of taxonomic function would seem hopeless. Comparative mapping experiments in the *Solanaceae* have also suggested that taxonomic specificity is not predictable (50), but mapping experiments are probably not sufficiently high in resolution to provide a robust test of this hypothesis given the propensity of clustering of different R gene families. Alternatively, the fact that some gene families, like the *Rp1* family of maize and the *L/M* family of flax, include over a dozen genes conferring resistance to a single pathogen species indicates that some gene families may have affinities for Avr genes from certain genera. Whether this is an indication that the orthologous gene family in a closely related species has a similar affinity remains to be determined.

A separate issue in R gene functionality is whether an R gene with a known function in one species will have a role in a different species if the recipient species does not share the same pathogen. For example, the frequency in which a rust pathogen of wheat like *P. graminis* carries an avirulence gene corresponding

to a maize rust (*P. sorghi*) resistance gene is not known. Therefore, even if the maize rust resistance gene is able to function in wheat, it will not be effective unless the wheat rust fungus carries the Avr gene. The frequency with which these related pathogen species carry functionally identical Avr genes must be examined experimentally. If two plant species are attacked by the same pathogen species, then a functioning R gene transferred from one species to the other would be expected to interact with the same Avr gene. In some cases, however, this may simply increase the exposure of that R gene and thus compromise its efficacy. For example, transferring a *Wheat streak mosaic virus* resistance gene to wheat from maize (also a WSMV host) would likely reduce the efficacy of that gene in maize for controlling the virus. For such broad host range pathogens, an uncultivated species would be a preferred donor for an R gene. All things considered, it may be that only a fraction of the *R* genes transferred between species are useful in the recipient species. Transient transformation assays for resistance gene function will be necessary to make R gene transfer efficient. Viral expression systems (for example, see 24) may be particularly useful because of their ability to transform large areas of tissue, which is necessary for some disease assays. But viral vectors must be made that can replicate and express R genes as part of their genomes, and many R genes are relatively large genes.

Identification or Construction of Durable Resistance

The main drawback to the use of R genes to control resistance is that their effects are often not durable owing to shifts in the pathogen populations. Ideas vary on how to develop plant varieties with durable resistance. The topic has been examined very closely in the cereal rust and mildew diseases where R genes have been used for decades to control the diseases, albeit with mixed success. Most feel the only true test of resistance durability is the test of time for a crop variety grown on large acreages. There are a few successful wheat varieties that have remained durable to leaf rust for many years. These varieties typically have one or more genes, like *Lr34*, which confer partial resistance that is expressed mainly in adult plants (37, 47, 78, 125, 127). The reason for the success of these genes and gene combinations is not apparent. One reason an R gene may remain effective is if the loss of the corresponding Avr gene from the pathogen has a significant cost in terms of fitness or pathogenicity (reviewed in Leach et al., this volume: chapter 9). The resistance conferred by R genes that provide only partial resistance in adult plants may be particularly stable if their effects on pathogen reproduction are only as detrimental as a loss of the corresponding Avr gene. Scientists are beginning to specifically target those R genes that are thought to interact with important or widespread Avr genes. An example is the recently isolated *Bs2* gene from pepper (136), whose cognate Avr gene is very widespread in *Xanthomonas campestris* pathovars and is also a virulence factor (74). In another approach, an extracellular protein from *Cladosporium fulvum* that was known to be important for virulence was used to screen tomato lines. Lines were identified that carried an R gene that conferred a

hypersensitive reaction to the protein and a resistance reaction to the fungus (80a). Such strategies to identify genes that recognize important and conserved pathogen components will govern our abilities to develop varieties with resistance that is stable over many years.

Resistance genes transferred individually from outside the gene pool may not provide any more durable resistance than native R genes. However, some nonhost R genes may be more durable if they recognize general or genera-specific elicitors. Examples may include the plant genes that appear to interact with flagellin from *Pseudomonas avenae* (23) or elicitin from *Phytophthora infestans* (72); these elicitors may be more conserved or important to the pathogen than most Avr genes. Regardless of their durability, nonhost R genes are still more likely to confer resistance to all races when first employed if the pathogen population has not yet been exposed to the R gene. This may make them extremely useful when used in combinations. Typical examples of gene pyramids cited in the literature are mainly composed of R genes that are not effective against all isolates of the pathogen. Pyramids of *undefeated* R genes may actually require the pathogen to lose or mutate several avr genes simultaneously. There is evidence suggesting durable resistance in some cereals (e.g. wheat) to other formae speciales of its pathogens (e.g. powdery mildew of rye) may be due to a small pyramid of resistance genes (88, 142). Manipulation of R genes as transgenes should also enable them to be placed at a single linkage block in the genome. This should also promote durability of the complex by preventing the single deployment of the component genes in other cultivars by various breeding programs.

Another reason the resistance conferred by an R gene might be stable is if the R gene confers some level of resistance that is independent of an interaction with a pathogen Avr gene. In this case the gene might affect the physiology of the plant even before the pathogen is present. The *mlo* gene is an example, in that spontaneous defense reactions, even limited cell death, can be observed in the absence of the pathogen. As mentioned above, however, the *mlo* allele is unusual in that it is a recessive, loss-of-function mutation in a gene that does not show homology to other resistance genes. The *Lr34* gene is also associated with some spontaneous cell death, observed as leaf tip necrosis (123, 126). Several other wheat genes that confer partial resistance to leaf rust at the adult plant stage have also been associated with leaf tip necrosis (93). One indication that the *Lr34* gene may act independently of an interaction with an Avr gene is the fact that it has been associated with partial resistance to other diseases, including stripe rust and stem rust, but linkage to other genes has not been ruled out as a possible reason for these other resistances (90, 124). The nature of these adult plant rust resistance genes is not known, but some parallels exist with certain haplotypes of the maize *Rp1* rust resistance locus. Several recombinant *Rp1* haplotypes have been identified that confer nonspecific rust resistance and that are associated with aberrant defense reactions in the older leaves of adult plants (58). The most extreme examples are the *Rp1* lesion mimic haplotypes, like *HRp1-D21*, which confers an extensive necrotic reaction to all rust isolates tested, including nonhost rusts (e.g. *P. recondita*), but

also confers a severe necrotic spotting phenotype in seedlings and adults (57). The *HRp1-D21* haplotype arose by an unequal crossover from an *HRp1-D* haplotype homozygote. It has only two *rp1* genes, instead of the nine from the parental haplotype, but one of the genes has a recombinant LRR that probably accounts for the unusual phenotype (133).

There is some evidence that altering the level of expression of certain resistance genes can affect the type of resistance they confer. Resistance genes are typically expressed at low levels and transcripts can be difficult to detect by gel blot analysis. Detailed expression analysis has not been conducted on very many R genes, but most resistance genes are expressed before pathogen challenge. Transcript levels of several NBS-LRR genes have been found to be unaffected by pathogen inoculation (3, 15, 25, 27, 87, 148). Alternatively, transcription of the rice *Xa-1* and $Hs1^{pro-1}$ genes appears to increase following inoculation. Pathogen infection has also been demonstrated to affect turnover of *Rpm1* protein (15) and splicing of *N* gene transcripts (31). Overexpression of both the *Pto* gene (139) and the *Prf* gene (103) in transgenic tomato conferred partial resistance to virulent isolates of *Pseudomonas syringae* pv. tomato as well as partial resistance to several other pathogens. In both cases resistance was associated with constitutive defense responses. This method of engineering broad-spectrum resistance should be durable, since it is independent of an interaction with a specific Avr gene. Utilization of these approaches in agriculture will probably require considerable fine-tuning of the expression levels and genetic background effects. The objective will be a balance between levels of resistance and an acceptable physiological cost of the resistance. It will also be important to examine the effects of the transgene on the range of pathogens that occur on the crop. The *mlo* gene of barley confers nonspecific resistance to the biotrophic powdery mildew fungus *Blumeria graminis*, but actually increases susceptibility to some non-biotrophic fungi, like *Magnaporthe grisea* (65) and *Cochliobolus sativus* (79).

Other attempts to engineer broad-spectrum or durable resistance have included overexpression of signaling components and defense response genes that act downstream of R genes (reviewed in 115). Of particular interest was the *Npr1* gene of Arabidopsis, which regulates systemic acquired resistance (22). Overexpression in Arabidopsis increased resistance to virulent isolates of *Pseudomonas syringae* and *Peronospora parasitica*. In addition, no obvious detrimental effects to the plant, like constitutive PR gene expression or spontaneous cell death occurred. Overexpression of cereal versions of *Npr1* in wheat and rice has had mixed success (115) but it remains an exciting approach for the development of disease-resistant crop plants.

In Vitro Construction of Resistance Genes

Future laboratory construction of R genes will require a thorough understanding of how the different domains of resistance genes function together to recognize pathogen elicitors and induce defense responses. Included in this must be an

understanding of the higher-order structures of the receptor complexes when multiple gene products are involved. Rational design of R genes will also require a thorough understanding of how, when, and where (15) the different classes of R genes or receptor complexes recognize their cognate Avr genes. The characterization of directly interacting R gene and Avr gene products (66, 119, 138) has provided important tools and preliminary information. The outcome of initial directed mutagenesis experiments and in vitro exchanges of different R gene domains have been largely unpredictable to date (38, 85). Ultimately, we may be able to design an R gene to interact with a selected pathogen elicitor. In this way we may be able to select pathogen elicitors that are highly conserved or important to pathogenicity. This type of engineering might couple mutation or in vitro recombination techniques with high throughput assays for the ability to interact with the elicitor and function as a resistance gene. An alternative approach might be to identify proteins that can bind conserved or general elicitors and couple these to receptor complexes capable of initiating defense responses following elicitor binding. Clearly, there is much to learn about how R genes recognize elicitors and initiate defenses, but the rewards will be significant.

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