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GENETICS OF PLANT VIRUS RESISTANCE

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■ **Abstract** Genetic resistance to plant viruses has been used for at least 80 years to control agricultural losses to viral diseases. To date, hundreds of naturally occurring genes for resistance to plant viruses have been reported from studies of both monocot and dicot crops, their wild relatives, and the plant model, *Arabidopsis*. The isolation and characterization of a few of these genes in the past decade have resulted in detailed knowledge of some of the molecules that are critical in determining the outcome of plant viral infection. In this chapter, we have catalogued genes for resistance to plant viruses and have summarized current knowledge regarding their identity and inheritance. Insofar as information is available, the genetic context, genomic organization, mechanisms of resistance and agricultural deployment of plant virus resistance genes are also discussed.

INTRODUCTION

Viruses are among the most agriculturally important and biologically intriguing groups of plant pathogens. Plant viral diseases cause serious economic losses in many major crops by reducing yield and quality and often determine whether and when a crop is planted in a cropping system. Although viruses are relatively simple genetic entities, still largely unknown are the mechanisms by which the many symptoms of disease are generated, and by which plants resist these effects. In this chapter, we review the literature pertaining to genetic resistance to plant viruses.

Genetic resistance is one of a number of approaches to protect crops from virus infection that also include control of biotic vectors, use of virus-free seed or plant materials, and cultural practices that minimize transmission (106). Resistant varieties, where available, however, are still considered the most cost-effective and reliable approach. Considerable time and cost may be involved in developing varieties with the appropriate range of resistances. If resistance proves durable, then the use of resistant crop varieties is clearly the preferred method to control agricultural losses.

The study of plant resistance genes (R genes), namely, plant genes in which genetic variability occurs that alters the plant's suitability as a host, also raises many fundamental questions regarding the molecular, biochemical, cellular, and physiological mechanisms involved in the plant-virus interaction and the evolution of these interactions in natural and agricultural ecosystems. Over the past decade, the cloning and analysis of numerous plant R genes (84, 134) have stimulated attempts to develop unifying theories about mechanisms of resistance and susceptibility, and coevolution of plant pathogens and their hosts. The focus has been mainly on monogenic dominant resistance to fungal and bacterial pathogens (84); however, there is clear evidence that common mechanisms can be involved in virus resistance.

Considerable progress is evident in the areas of R gene structure, identification of molecular interactions important in plant viral infection, and elucidation of mechanisms of resistance and viral evolution since the last Annual Review of plant virus resistance genes was published in 1990 (64). For this review, we emphasize the current status of R genes that have been characterized at a molecular level, possible connections to down-stream host responses, and factors that may influence durability of resistance in agricultural ecosystems.

TYPES OF RESISTANCE

Resistance to disease of plants has historically been divided into two major categories (64): nonhost resistance and host resistance. The former, which encompasses the case where all genotypes within a plant species show resistance or fail to be infected by a particular virus, specifically signifies the state where genetic polymorphism for susceptibility to a particular virus has not been identified in a host taxon. Clearly, most plant species are resistant to most plant viruses. Susceptibility is the exception to the more general condition of resistance or failure to infect. Although underlying mechanisms of nonhost resistance to viruses are largely unknown and are likely as diverse for viruses as they are for other classes of plant pathogens (152), improved understanding of the ways in which infection fails in these interactions may be particularly important for breakthroughs in the development of plants with durable broad-spectrum disease resistance.

Host resistance to plant viruses has been more thoroughly investigated, at least in part because, unlike nonhost resistance, it is genetically accessible. This general case, termed host resistance, specific resistance, genotypic resistance, or cultivar resistance, occurs when genetic polymorphism for susceptibility is observed in the plant taxon, i.e., some genotypes show heritable resistance to a particular virus whereas other genotypes in the same gene pool are susceptible. In resistant individuals, the virus may or may not multiply to some extent, but spread of the pathogen through the plant is demonstrably restricted relative to susceptible hosts, and disease symptoms generally are highly localized or are not evident.

The distinction between resistance to the pathogen and resistance to the disease is important to articulate. Resistance to the pathogen typically leads to resistance

to the disease; however, resistant responses involving necrosis can sometimes be very dramatic, even lethal, e.g., the *N* gene in tobacco for resistance to *Tobacco mosaic virus* (TMV) (47) or the *I* gene in *Phaseolus vulgaris* for resistance to *Bean common mosaic virus* (37). In the case of resistance to disease symptoms or tolerance to the disease, the virus may move through the host in a manner that is indistinguishable from that in susceptible hosts, but disease symptoms are not observed. If the response is heritable, these plants are said to be tolerant to the disease, although they may be fully susceptible to the pathogen. This host response is very prevalent in nature, and has been used to considerable benefit in some crops, e.g., the control of *Cucumber mosaic virus* (CMV) in cucumber, even though the genetic control of this response is typically difficult to study (64, 182). The genetics of tolerant responses are not be considered further due to the complexity of the biology and relative lack of information.

More recently, a third important category of host resistance has been identified, initially in studies involving TMV: systemic acquired resistance (SAR). This response can be activated in many plant species by diverse pathogens that cause necrotic cell death (184), resulting in diminished susceptibility to later pathogen attack. As SAR has recently been reviewed (56), this topic is not discussed further here. Virus-induced gene silencing, another induced defense mechanism to virus disease, has also been reviewed recently (10).

Transgenic approaches to plant virus resistance have been widely explored since the earliest experiments where by transgenic tobacco plants expressing TMV coat protein (CP) were challenged with TMV and shown to be resistant (74, 182, 185). It is now possible to engineer resistance and tolerance to plant viruses using transgenes derived from a wide range of organisms including plant-derived natural R genes, pathogen-derived transgenes, and even nonplant and nonpathogen-derived transgenes. The issues related to the creation and deployment of genetically engineered resistance in crop breeding have been recently reviewed elsewhere (55, 153, 206).

GENETICS OF VIRUS RESISTANCE IN NATURE

The first step in the study of genetics of viral resistance is to determine whether the resistant response is inherited, and if so, the number of genes involved and their mode of inheritance. [For reviews on sources of host resistance to plant viruses and inheritance of resistance to plant viruses and viral disease, see (46, 63, 64, 106, 175); for underlying general trends or common mechanisms of virus resistance, see (64, 65, 74, 170), and for specific crop or viral groups, see (159, 175, 198).] An updated comprehensive list of published virus R genes including previously summarized information based on literature through December, 2004 is presented in Supplementary Tables 1 and 2 (Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org). Over 200 virus R genes reported in studies of crops, their wild relatives, and the model species *Arabidopsis thaliana*, as well as both inheritance and information about

possible mechanisms, where known, are included. Genes reported to show dominant inheritance are listed in Supplementary Table 1 (Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org); genes reported to show recessive inheritance are listed in Supplementary Table 2 (Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org).

This discussion highlights key observations drawn primarily from studies of dicot species, the focus of most work to date. [For reviews on general trends regarding inheritance of naturally occurring plant virus R genes, see (64, 65, 106, 175).] Within the dicots, information regarding several plant families, notably the Solanaceae, Cucurbitaceae, and Leguminosae, predominate for historical and agricultural reasons. R genes reported from monocot species are almost exclusively limited to major crop species, e.g., barley, wheat, and rice.

More than 80% of reported viral resistance is monogenically controlled; the remainder shows oligogenic or polygenic control. Only slightly more than half of all reported monogenic resistance traits show dominant inheritance. In most but not all (63) cases, dominance has been reported as complete. The heterozygote may show a clearly different response from that of the homozygote, however this is rarely checked carefully in inheritance studies. Where incomplete dominance is observed, there are important implications for mechanisms that may involve gene dosage effects. The relatively high proportion of recessive viral R genes is in marked contrast to fungal or bacterial resistance where most reported resistance is dominant.

About one third of the R genes listed in Supplentary Tables 1 and 2 (Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) have been tagged with molecular genetic markers including RFLP, AFLP, RAPD, and various other PCR-based markers. Molecular markers linked to R genes can be used for indirect selection via genotype, for locating R genes in plant genomes, and for gene isolation. Relatively few quantitative trait loci (QTL) for plant viral resistance have been tagged or genetically mapped (3, 12, 26, 30, 127).

Both pathogen and host taxa are composed of dynamic populations and therefore unambiguous identification of host and pathogen genotypes is essential, ideally with representative genotypes archived in a stable and reliable location such as the USDA National Plant Germplasm System or the American Type Culture Collection. Historically, important collections of plant germplasm and viral cultures have been maintained at universities and research institutes, where shifts in staffing and resource allocation may put critical genetic resources at risk.

Within a host gene pool, there may be several to many independent sources of resistance to a single virus or viral pathotype (a set of viral genotypes that interact similarly with a set of host lines showing differential response) (81, 115, 159, 166). The advent of molecular methods has demonstrated that these R genes may represent different loci with shared or independent evolutionary histories, or different alleles at the same locus. Numerous early studies concluded that R genes

with different resistance specificities necessarily occurred at distinct genetic loci; however, this is clearly not the case (81, 102, 169, 186). Whenever there is overlap of the resistance spectrum for a pair of alleles, genetic complementation must be formally assessed before different locus designations are accepted. Efforts are under way in many plant species and, to some extent, across the plant community to rationalize genetic nomenclature. Modern systems aim to reflect homology across sexually incompatible genera and the identity of the gene, where known.

When multiple loci control the same virus or viral pathotype, the mode of inheritance of the resistance may be similar, as expected if the loci had arisen via duplicative processes that have generated the high degree of redundancy observed in plant genomes (e.g., 175), or the mode of inheritance may be different (115). One way whereby independent genes for resistance to the same pathogen can be distinguished may be the range of protection afforded by each allele.

There are a number of examples of dominant and recessive genes that appear to control a relatively wide range of viral genotypes that span multiple viral species, according to current delineation of viral taxa. The most dramatic examples appear to involve members of the Potyviridae, e.g., the *I* gene in *Phaseolus vulgaris* (4) now appears to control a dominant resistance or a dominant necrotic response to ten different related potyviruses, *Azuki mosaic virus*, *Bean common mosaic virus* (BCMV), *Bean necrotic mosaic virus*, *Blackeye cowpea mosaic virus*, *Cowpea aphid-borne mosaic virus*, *Passionfruit woodiness virus*-K, *Soybean mosaic virus* (SMV), *Thailand Passiflora virus*, *Watermelon mosaic virus* (WMV), and *Zucchini yellow mosaic virus* (61). Furthermore, this locus has been implicated in modulating a necrotic response to *Bean severe mosaic virus*, a member of the *Comoviridae* (144, 145). Recombination between any of the specificities listed above has never been observed despite more than 75 years of backcross breeding with this R gene, which has not been isolated, and independent sources of the *I* resistance allele show identical resistance spectra. Detailed physical mapping of the *I* locus has established that it occurs in a large cluster of TIR-NBS-LRR sequences (E. Vallejos & S. Mackenzie, personal communication).

Conversely, there are cases where resistance alleles at two or more loci are required to observe the resistant response. Because of the paramount agricultural importance of losses to BCMV, a well-known example is the *bc-u* system in *Phaseolus vulgaris* for resistance to a wide array of BCMV pathotypes. Resistance is observed only when the *bc-u* locus is homozygous recessive and one or more pathotype-specific genes, *bc-1*, *bc-2*, and *bc-3*, are also homozygous at one or more of three additional loci (53). In some cases, alleles at these loci affect pathotype specificity. In *Capsicum*, for example, full resistance is observed to another potyvirus, *Pepper veinal mottle virus*, only when the resistance alleles $pvr1^2$ (formerly $pvr2^2$) and *pvr6* are homozygous (25). Here the *pvr1* locus encodes an eIF4E homolog (102), and *pvr6* is likely to encode eIF(iso)4E (102).

Physical clustering of distinct R genes that control different pathotypes of the same viral species, closely related viral species, or diverse plant pathogen groups (e.g., viral, fungal, bacterial, or nematode pathogens) has also been widely noted

and discussed in terms of R gene evolution and plant breeding (142). Two distinct types of gene clusters are clearly evident. One type of R gene cluster contains a set of genes, showing similar inheritance and resistance phenotypes that control very closely related viral genotypes. Presumably this type of cluster arose from the classic evolutionary trend of gene duplication, followed by divergence. This mechanism classically results in genes with related but slightly altered function. A notable example of this pattern occurs in *Pisum sativum* where recessive resistance has been mapped to two R gene clusters on linkage groups II and VI. In LG II, six very tightly linked monogenically inherited recessive loci (*bcm*, *cyv1*, *mo*, *pmv*, *sbm2*, and *wmv*) for resistance to BCMV, *Bean yellow mosaic virus* (BYMV), *Clover yellow vein virus* (ClYVV), *Pea mosaic virus* (PMV), *Pea seed-borne mosaic virus* (PSbMV-L1), and WMV, respectively, occur in a cluster but are separable by recombination. On LG VI, five distinct but very tightly linked loci have been identified that overlap with the specificities observed for the cluster on LG II. In this cluster, the loci *cyv2*, *sbm1*, *sbm3*, *sbm4*, and *wlv* confer resistance to ClYVV, PSbMV-P1, PSbMV-L1 or -P2, PSbMV-P4, and *White lupin mosaic virus*, respectively (172–175).

The second type of R gene cluster contains viral resistance along with R genes that control unrelated pathogens. These clusters may include a relatively large number of R genes and span megabases of genomic sequence (76). This type of R gene cluster occurs widely in monocots and dicots. For example, the wheat *Bdv1* allele conferring resistance to *Barley yellow dwarf virus* (BYDV) is linked to fungal R genes *Lr34* and *Yr18* (197). This type of cluster may, in fact, emerge as the most common genomic context for plant disease R genes, as more complete information about plant genome structure develops. Information regarding the content and distribution of R gene clusters is probably best understood in the dicot family, Solanaceae, the focus of major investments in genetic and genomic analyses. As tomato, potato, pepper, tobacco, and many minor solanaceous crops are affected by well-known viruses, extensive information is available regarding inheritance and mapping of viral R genes and many other R genes (70, 76). A comprehensive genome-wide analysis of R gene clusters and their distribution within a series of crop genomes linked by comparative genetic mapping has been published for the Solanaceae (76). This study clearly demonstrated that R gene clusters often occur at homologous positions in related genomic regions, even in genera that diverged tens of millions of years ago. Furthermore, across genera, clusters contained either dominant R genes and QTL, or recessive genes and QTL, but not both dominant and recessive genes. These clusters may therefore consist of evolutionarily related sequences that diverged to control very different pathogen groups. When the sets of pathogens controlled by R genes in a given cluster were compared across taxa, no overlap of resistance specificities (i.e., the group of pathogen taxa controlled by R genes in the cluster) was initially observed, except in two cases on chromosomes 4 and 11. Both of these involved *Phytophthora* pathogens, *P. capsici* in pepper and *P. infestans* in potato. As additional R genes have been mapped, a striking pattern that includes viral R genes has now emerged (Table 1). On potato chromosome

TABLE 1 Some cross-generic R gene groups that include virus resistance genes in Solanaceae

	Chromosome and resistance genes						
Plant	**Chr 4**	**Chr 5**	**Chr 7**	**Chr 10**	**Chr 11**	**Chr 12**	**References**
Tomato	*Hero* (n)	—	*Ph-1* (p)	*Ph-2* (p)	*Ty-2* (v), *I2* (f), *Sm* (f)	—	(11, 66, 85, 196)
Potato	*R2* (p), *Ny* (v)	*Grp1* (n), *Gpa* (n), *Gpa5* (n), *R1* (p), *phyt3* (p), *Pi1*(p), *Rx2* (v), *Nb* (v)	*Gro1* (n), *Rpi1*, *R9* (p)	*Gro1.2* (n)	*R3* (p), *R6* (p), *R7* (p), *Gro1.3* (n), *phyt7* (p)	*Gpa2* (n), *Rx1* (v)	(8, 39, 58, 59, 91, 112, 113, 137, 181, 208)
Pepper	*Phyto5.2* (p)	—	—	—	*L* (v), *cmv11.1* (v), *phyt3* (p)	—	(12, 25, 120)

Positions are inferred, therefore the precise linkage relationships of these loci remain unclear in many cases.

Gene names are followed by letters designating the major pathogen group controlled:

(b) bacteria, (f) fungi, (n) nematode, (p) *Phytophthora* spp., (v) virus.

12, the *Rx1* gene conferring resistance to *Potato virus X* (PVX) is tightly linked to the *Gpa2* locus for resistance to the cyst nematode *Globodera pallida* (208). This pair of specificities is also found very tightly linked in a second R gene cluster on potato chromosome 5. This cluster on chromosome 5 also contains resistance to *P. infestans*. When the inferred positions of all mapped R genes from tomato, potato, and pepper are collected on one comparative genetic map, at least five R gene groups can be discerned that contain a dominant R gene to *Globodera* and a dominant gene for resistance to *Phytophthora*, several of which also contain R genes or QTL for plant viruses including PVX, as mentioned above, TMV, CMV, *Tomato yellow leaf curl virus* (TYLCV), and potato virus Y. A prediction, based on this observation, but not yet confirmed, is that despite these striking differences in pathogen specificity, the basic molecular structure of these genes will be generally similar, even between relatively distantly related host genera. This similarity may facilitate the molecular cloning and characterization of genes that reside in these clusters. Insofar as this prediction has been examined within a single R gene cluster in one plant taxon, e.g., *Rx* and *Gpa2*, it has been upheld (208).

Dominant resistance is often, although not always, associated with the hypersensitive response (HR) (63), possibly due to the frequent use of HR as a diagnostic indicator for field resistance by plant breeders. HR, induced by specific recognition of the virus, localizes virus spread by rapid programmed cell death surrounding the infection site, which results in visible necrotic local lesions. HR-mediated resistance is a common resistance mechanism for viruses and for other plant pathogens. Because the extent of visible HR may be affected by gene dosage (37), genetic background, environmental conditions such as temperature, and viral genotype, etc., schemes that classify or name virus R genes based on presence or absence of HR may obscure genetic relationships (see discussion of the *Ry*-mediated resistance to PVY in potato below).

Over the past 10 years significant advances have been made in the understanding of the molecular basis of the HR-mediated resistance. More than 40 plant R genes showing monogenic dominant inheritance have been cloned. Several of these confer resistance to plant viruses (134). These include *N* for resistance to TMV in tobacco (211), *Rx1* and *Rx2* for resistance to PVX in potato (14, 16), *Sw5* for resistance to *Tomato spotted wilt virus* (TSWV) in tomato (21), and *RTM1*, *RTM2* to TMV (34, 212), and *HRT* for resistance to *Turnip crinkle virus* (TCV) (38), *RCY1* for resistance to CMV (204), respectively, in *Arabidopsis* (see below).

In contrast to dominant R genes, many recessive R genes appear to function at the single cell level or affect cell-to-cell movement. More than half of the recessive R genes identified to date confer resistance to potyviruses, members of the largest and perhaps the most economically destructive family of plant viruses (195). This may be a consequence of some bias that affects the scope of our knowlege, or may be due to specific features of potyvirus biology. In general, considerably less is known regarding the mechanisms that account for recessively inherited resistance mechanisms. Several recessive R genes have recently been

cloned and/or characterized including *pvr1* (=*pvr*^{2}), *mo1*^{1}, *sbm1*, and *rym4/5* (67, 102, 154, 186, 215), as described below.

Despite the possibility of bias affecting the comprehensiveness of available data, trends can be noted in the types of genetic resistance available to control viruses belonging to specific plant virus families. For example, resistance to CMV often shows complex inheritance. Very few monogenically inherited R genes are known (22), despite the enormous host range of this virus and its economic impact. Most resistance or tolerance of economic significance to this pathogen is quantitatively inherited. In contrast, resistance to tobamoviruses is widespread and is often monogenic dominant. For some viral families of extreme agricultural importance, most notably the Geminiviridae, naturally occurring genetic resistance can be difficult to locate, and is often highly strain-specific and/or quantitatively inherited (i.e., each gene has a relatively slight positive effect on host response), making resistant varieties extremely difficult or impossible to develop without molecular markers and/or transgenic approaches.

NATURAL RESISTANCE MECHANISMS

To complete their life cycles, viruses undergo a multistep process that includes entry into plant cells, uncoating of nucleic acid, translation of viral proteins, replication of viral nucleic acid, assembly of progeny virions, cell-to-cell movement, systemic movement, and plant-to-plant movement (27). Plant viruses typically initiate infection by penetrating through the plant cell wall into a living cell through wounds caused by mechanical abrasion or by vectors such as insects and nematodes. Unlike animal viruses, there are no known specific mechanisms for entry of plant viruses into plant cells (194). When virus particles enter a susceptible plant cell, the genome is released from the capsid, typically in the plant cytoplasm. Although not yet comprehensively analyzed, current work suggests this uncoating process is not host-specific, e.g., TMV and *Tobacco yellow mottle virus* were uncoated in both host and nonhost plants (107, 135). Once the genome becomes available, it can be translated from mRNAs to give early viral products such as viral replicase and other virus-specific proteins. Hereafter the virus faces various constraints imposed by the host and also requires the involvement of many host proteins, typically diverted for function in the viral infection cycle.

Successful infection of a plant by a virus therefore requires a series of compatible interactions between the host and a limited number of viral gene products. Absence of a necessary host factor or mutation to incompatibility has long been postulated to account for recessively inherited disease resistance in plants, termed "passive resistance" by R.S.S. Fraser (63, 64).

In contrast, dominant resistance has been shown in a number of plant pathosystems to result from an active recognition event that occurs between host and viral factors, resulting in the induction of host defense responses (modeled in Figure 1*A*) (64). Despite the availability of well-characterized genetic systems and

intensive investigation in this area, the biochemistry of this recognition event is still not thoroughly understood. Genes that contribute to this response are likely to be dominant or incompletely dominant, unless the resistant response occurs as a result of derepression of a defense pathway (23). In theory, passive or active resistance can function at any stage of the virus life cycle, although most known viral resistance mechanisms appear to target virus replication or movement (Figure 1*B*). It is still technically difficult to quantify levels of viral accumulation with precision in asynchronous infections of intact tissue (as opposed to protoplasts). Even with the use of fluorescent reporter genes, the extent to which viral accumulation reflects replication and translation versus variations in virus movement cannot be easily discerned. Several lines of evidence suggest that the level of viral accumulation may affect the ability of virus to move systemically. For example, the amount of the α and γ protein produced by RNA 3 of *Barley stripe mosaic virus* can determine systemic movement of the virus (168), and dose-dependence has been observed in a number of viral/host interactions, e.g., (37, 168). Caution may therefore be needed before concluding that the molecular defect resulting in resistance specifically affects the viral infection cycle stage at which the defect, i.e., resistance, is observed.

Cellular Resistance to Plant Viruses

Resistance at the single cell level may be characterized as a state where virus replication does not occur, or occurs at essentially undetectable levels in inoculated cells. This type of resistance has been termed "extreme resistance" (ER), "cellular resistance," or "immunity" (63, 64). A classical example of this type of resistance is observed when *Vigna unguiculata* 'Arlington' is challenged with the Comovirus *Cowpea mosaic virus* (CPMV) (171). A protease inhibitor that prevents CPMV polyprotein processing was proposed as a candidate for the mechanism by which replication was prevented, but this has not been confirmed (171).

For plant viruses with both RNA- and DNA-encoded genomes, diverse host factors that are involved in or required for completion of the viral infection cycle have been identified (Table 2). Most of these factors were identified through the analysis of large experimental collections of mutagenized hosts (2, 213). For example, *Arabidopsis* mutants homozygous for the *tom1* and *tom2A* lesions do not support TMV accumulation in single cells (92, 93, 158). *Tom1* encodes a transmembrane protein localized in the tonoplast that interacts with the helicase domain of the tobamovirus-encoded replicase protein (219). *Tom2A* also encodes a transmembrane protein that interacts with *Tom1* (207); both proteins define important components for tobamoviral replication complex (78). Another illustration of this approach from the *Arabidopsis* model was the identification of the allele *lsp1*, the result of a mutation at this locus that encodes a homolog of the eukaryotic translation factor eIF(iso)4E (121). When homozygous, this defect resulted in plants that did not support infection by *Tobacco etch virus* (TEV), a result presaging later

TABLE 2 Examples of host factors involved in plant viral life cycles and resistance mechanisms

Plant	Virus[a]	Gene or protein	Gene expression control	Effects on viral infection	Known or predicted protein function	References
Translation and replication						
Arabidopsis	CLCV	AtNSI	Over expression	Enhanced infection efficiency	Acetyl transferase	(28, 136)
	CMV	*ssi-2*	Knock out		Plastid-localized stearoyl-ACP desaturase	(193)
	TEV TuMV	*1sp1*	Knock-out	Defective in TuMV and TEV replication	Translation initiation factor, eIF(iso)4E	(121)
	TMV	*tom1*	Knock-out	Affects TMV RNA accumulation in protoplasts	Essential constituent of replication complex	(92, 93)
		tom2A	Knock-out	Affects TMV RNA accumulation in protoplasts	Formation of RNA replication complex	(207)
Nicotiana	*TGMV*	NbSCE1	Suppression	Suppresses TGMV replication	SUMO-conjugating enzyme	(29)
Cell-to-cell movement						
Arabidopsis	CMV	*cum1-1*	Knock-out	Cell-to-cell movement of CMV blocked	Translation initiation factor, eIF4E	(222–224)
	TCV	*cum2-1*	Knock-out	Cell-to-cell movement of CMV Blocked	Translation initiation factor, eIF4G	(222–224)
Systemic movement						
Arabidopsis	TMV	PME	Suppression	Defective in viral exit out of vascular system	Pectin methylesterase	(32, 33)

[a]CLCV, *Cabbage leaf curl geminivirus*; CMV, *Cucumber mosaic virus*; TEV, *Tobacco etch virus*; TGMV, *Tomato golden mosaic virus*; TMV, *Tobacco mosaic virus*; TuMV, *Turnip mosaic virus.*

observations from pepper, lettuce, pea, and tomato that implicate host translation factors in resistance to potyviruses and CMV (102, 154, 163, 167, 186).

The second type of mechanism that can result in resistance at the single-cell level involves an active resistant response to virus infection that occurs rapidly enough to limit virus replication before cell-to-cell movement occurs. Plants with this response may show no symptoms or extremely limited necrosis (pinpoint lesions). Well-known examples of this response include resistance controlled by *Tm-1* for TMV in tomato (147, 209), the R gene against CPMV in cowpea (171), *Nx* and *Rx* for PVX and *Ry* for *Potato virus* Y (PVY) in potato (199), *Sw5* in tomato (21), and *Rsv1* in soybean (80). This response has been studied in some detail using the *Ry* gene for ER in potato as a model. Plants carrying the *Ry* gene do not show any visible symptoms when challenged with PVY. Virus accumulation is not detected in the inoculated leaves by either RNA hybridization or ELISA. Furthermore, protoplasts isolated from resistant genotypes do not support viral replication. Because HR was not evident, it was postulated that these genes might encode inhibitors of virus accumulation (64). However, there may be no mechanistic distinction between reactions previously categorized as ER and HR. When each of the PVY-encoded proteins was expressed in leaves of PVY-resistant plants, the nuclear inclusion of a protease (NIaPro) induced HR, demonstrating that the HR mechanism may be a component of the ER response. The same trends hold true for *Rx*/PVX-CP in potato (14), *Sw5* in tomato (21), and *Rsv* in soybean (79). For elicitation of *Ry*-mediated resistance, the protease domain of PVY NIaPro, specifically the integrity of the protease active site, is required (140). Mutant analysis of NIaPro, however, demonstrated that NIa protease activity is not sufficient for elicitation of resistance because elicitor-defective mutants still retained a high level of protease activity (141). The location of *Ry* in a genomic region containing many NBS-LRR sequences is consistent with the possibility that *Ry* may encode a NBS-LRR-type protein typical of genes controlling HR (82).

Resistance to Virus Movement Within and Between Cells

Once viral multiplication has been established in the cytoplasm and/or nucleus of a single plant cell from a susceptible host, plant viruses must move from the initially infected cells to adjoining cells, eventually resulting in systemic infection. An important class of host response to viral infection is apparent when the virus appears to establish infection in one or a few cells, but cannot move beyond the initial focus of infection. Resistance at this level can result from either failure of interactions between plant and viral factors necessary for cell-to-cell movement, or from active host defense responses that rapidly limit virus spread.

As described above for viral replication and translation, intra- and intercellular viral movement also requires both virus-encoded components and specific host factors (27, 118). For some viral families, mainly viruses with DNA genomes, crossing the nuclear membrane represents a potential barrier for virus movement (214). For these viruses, it is necessary to import the viral genome to the nucleus

for replication and export progeny genomes back to the cytoplasm for translation and virion assembly. The viral proteins required for these functions are known, at least for some viruses. For example, the nuclear import and export of bipartite geminivirus DNA is mediated by the BV1 (BR1) protein (27), but interference with these processes by host factors resulting in resistance has not yet been reported. With respect to intercellular movement, it is well established that movement proteins (MP), identified for most families of both DNA and RNA plant viruses [for reviews, see (42, 73, 132, 188)], perform dedicated functions required for cell-to-cell movement by modifying pre-existing pathways in the plant for macromolecular movement such that viral material can translocate between plant cells (27, 117). In the case of potyviruses, which do not encode a dedicated MP, the movement functions have been allocated to several proteins, including CP, HC-Pro, the cylindrical inclusion (CI) protein, and the genome-linked protein (VPg) (180). In mutant viruses defective in these proteins, movement from the initially infected cell to adjacent noninfected cells did not occur.

A number of mutations in host genes are known that prevent cell-to-cell movement of plant viruses. The *Arabidopsis cum1* and *cum2* mutations inhibit CMV movement (223, 224). In protoplasts prepared from plants homozygous for these alleles, CMV RNA and CP accumulate to wild-type levels, but the accumulation of the CMV 3a protein, necessary for cell-to-cell movement of the virus, is strongly reduced. Positional cloning demonstrated that *CUM1* and *CUM2* encode eukaryotic translation initiation factors 4E and 4G, respectively (222). Similar results for members of a different viral family have been obtained from tobacco, pepper, and pea. In tobacco, the movement of *Tobacco vein mottling virus* and PVY is controlled by the recessive gene *va* (71). In pepper and pea, *pvr1*^{1} (formerly *pvr2*^{1}) and *sbm1* were identified as mutations at a locus encoding eIF4E (67, 186). A functional analysis of the product of the dominant allele suggested a function for eIF4E in cell-to-cell movement, in addition to its proposed role in viral RNA replication or translation (102, 121).

The HR also serves to disrupt cell-to-cell movement of plant viruses. Recognition of the viral elicitor results in the induction of a cascade of host defense responses that include oxidative H_2O_2 bursts and up-regulation of hydrolytic enzymes, PR proteins, and callose and lignin biosynthesis. As a consequence, viral movement may be limited to a small number of cells, illustrated by such classic examples as the tobacco *N* gene (160) and the tomato *Tm-2* and *Tm-2*^{2} alleles (147). Protoplasts isolated from the plants carrying these R genes allowed replication of TMV; no cell death was observed. Despite the strong correlation of HR and disease resistance, necrotic cell death is now thought to be an ancillary consequence of the resistant response, not necessary for pathogen suppression. For example, in *Phaseolus vulgaris* carrying the *I* allele to BCMV, a continuum of viral infection phenotype responses that range from no necrosis to a lethal systemic response can be manipulated by allele dosage and temperature (37). The *defense no death* (*dnd1*) mutant in *Arabidopsis* is another example of independent resistance and HR (225), consistent with results from several viral-host systems including

Sw-5-mediated resistance against *Tomato spotted wilt virus* (21), *Rsv-1*-mediated virus resistance to SMV in soybean (80), and resistance against *Cauliflower mosaic virus* in tobacco (36). Furthermore, when *HRT* was introgressed into Col-1, most of the *HRT*-transformed plants developed HR upon TCV infection, yet the virus spread systemically without systemic necrosis (38).

Resistance to Long-Distance Movement

In susceptible hosts, plant viruses that do not show tissue restrictions move from the mesophyll via bundle sheath cells, phloem parenchyma, and companion cells into phloem sieve elements (SE) where they are translocated, then unloaded at a remote site from which further infection will occur (27, 188). This pathway is typically part of an elaborate symplastic network in plants through which viruses establish systemic infection (130). Plasmodesmata, elaborate and highly regulated structures with which viruses interact for both cell-to-cell and long-distance movement, provide symplastic connectivity between the epidermal/mesophyll cells and cells within the vasculature, including sieve elements (27, 131, 188). Entry into the SE-companion cell complex is currently thought to be the most significant barrier to long-distance movement (50, 216). Once present in a companion cell, a virus potentially has direct access to the sieve tube, the conducting element of the phloem that serves as the pathway for both nutrient and virus transport throughout the plant (117).

Virus particles loaded in the phloem apparently follow the same pathway as photoassimilates and other solutes, albeit not necessarily via strictly passive processes (149, 188). Most plant viruses require CP for long-distance movement, independent of any requirement for CP in cell-to-cell movement. Analysis of CP mutants for a number of viruses including TMV and TEV suggests that CP is essential for entry into and/or spread through sieve elements (117, 118). Some DNA viruses also require CP for long-distance movement (20), although other white fly–transmitted geminiviruses do not require CP for systemic infection (68). Phloem-limited viruses, e.g., *Luteovirus*, are typically limited to phloem parenchyma, companion cells, and SE, and apparently lack the ability to exit phloem tissue (205) or possibly to infect nonphloem tissue (9). A few viruses, most notably members of the *Sobemovirus* genus, use xylem for long-distance movement. The mechanisms of viral interaction with xylem are largely unknown (117, 146).

Because systemic movement is more difficult to study than cell-to-cell movement, relatively few host factors that are essential for this process thereby defining potential R gene candidates have been identified to date. Down-regulation of pectin methylesterase, shown to interact with TMV MP, resulted in impaired movement of TMV, probably by blocking virion exit from phloem. This finding is consistent with the hypothesis that phloem loading and unloading of virus involve distinct factors (32).

Some examples of natural virus resistance appear to involve mechanisms that negatively affect systemic movement. For instance, the V20 strain of tobacco

exhibits a strain-specific defect in supporting systemic infection by TEV (190). Using a TEV clone that expressed a reporter protein, β-glucuronidase (GUS), genome amplification, cell-to-cell and long-distance movement were measured in V20 tobacco and a susceptible line. Long-distance movement from leaf to leaf was markedly restricted in V20, associated with reduced entry into and exit from SE. This trait was attributed to the interaction of two unlinked, unidentified recessive genes. These data support the hypothesis that long-distance movement requires a set of host functions distinct from those involved in cell-to-cell movement. In another case, *Cowpea chlorotic mottle virus* (Bromoviridae) infects and moves cell-to-cell through inoculated leaves of soybeans homozygous for two recessive genes but entry into vascular tissue is restricted (75). In potato, the recessive *ra* allele, when homozygous, completely blocks vascular transport of *Potato virus A* (PVA) in graft-inoculated plants (82). Given the degree of conservation observed for some basic functions in plants, fundamental knowledge about the structure and function of plant vasculature will likely be relevant as efforts to identify these genes proceed.

In some cases, systemic movement is not prevented but delayed and reduced. In *Capsicum* genotypes homozygous for the resistance allele *pvr3*, *Pepper mottle virus* (PepMoV-FL) accumulated in inoculated leaves and moved into the stem but did not enter internal phloem for systemic movement to young tissues (77, 151, 228). Infection by a second virus, CMV, alleviated this restriction, which suggests that CMV was able to compensate for the defect in the host, either by providing a factor that facilitates movement of both viruses or alleviating the restriction by an unknown mechanism (151, 228). A similar type of resistance was described for CMV whereby virus remained localized to the lower portions of the plant (54, 156). Dufour et al. (54) showed that CMV accumulated in external but not internal phloem in the petiole of the inoculated leaf and the lower stem of the resistant genotype. Derrick & Barker (44) evaluated potato lines resistant to *Potato leafroll virus* (PLRV) and showed that the resistance was associated with an exclusion of virus from external phloem bundles, whereas virus occurred in both internal and external phloem in the susceptible line. Again, the identity of these genes in the host and their role in viral infection are unknown.

Relatively few dominant genes are known for resistance to systemic movement of plant viruses. The *Arabidopsis* RTM system is one exception. Many *A. thaliana* ecotypes support TEV replication and cell-to-cell movement in inoculated leaves but do not allow systemic movement. The loci *RTM1*, *RTM2*, and *RTM3* are required for restriction of long-distance movement of TEV (132, 212). Resistance mediated by the *RTM* genes is specific to TEV and does not involve a hypersensitive response or induction of SAR. *RTM1* and *RTM2* were isolated by map-based cloning. The deduced RTM1 protein is similar to the *Artocarpus integrifolia* lectin, jacalin. Jacalin belongs to a family of proteins with members that are implicated in defense against insects and fungi. The deduced RTM2 protein contains several domains including an N-terminal region with similarity to plant small heat shock proteins (34). Both these genes are expressed in phloem, specifically SEs,

but the mechanism by which TEV movement in this system is restricted is not understood.

DOMINANT PLANT VIRUS RESISTANCE GENES CHARACTERIZED AT THE MOLECULAR LEVEL

Most plant disease-resistance (R) genes isolated and characterized to date represent genes whose recognition of their cognate pathogens has been modeled as gene-for-gene interactions (62, 103). Under this well-known model, complementary pairs of dominant genes are defined by the host-pathogen interaction, one in the host and the other in the pathogen, whose physical interaction, direct or through intermediates, determines the outcome of the encounter (134). Following pathogen recognition, which occurs via poorly defined mechanisms, the R gene is presumed to activate a signaling cascade that coordinates plant defense responses to block pathogen spread, resulting in an incompatible interaction. Nine dominant plant virus R genes have been isolated and sequenced to date: *HRT*, *RTM1*, *RTM2, RCY1* from *Arabidopsis*; and from solanaceous hosts, *N*, *Rx1*, *Rx2*, *Sw5*, and *Tm-2²* (Table 3). Except for *RTM1* and *RTM2* discussed above, all of these cloned virus R genes share structural similarity. *HRT*, *Rx1*, *Rx2*, *RCY1*, *Sw5*, and *Tm-2²* are Class 2 R genes, proteins that contain a region of leucine-rich repeats (LRRs), a putative nucleotide binding domain (NBS), and an N-terminal putative leucine-zipper (LZ), or other coiled-coil (CC) sequences (83, 134) (Figure 2*A*). The *N* gene belongs to the Class 3 R gene family, which is similar to Class 2 but with a domain similar to the N terminus of the Toll and Interleukin 1 receptor (TIR) protein instead of the CC domain (6) (Figure 2*A*). Class 2 and Class 3 R proteins lack a transmembrane domain consistent with the intracellular location of viral avirulence factors. These genes define the plant viral pathosystems about which the most is known at the molecular and cellular levels.

Resistance to *Tobacco Mosaic Virus* in Tobacco Conferred by *N*

The *N* gene, introduced into tobacco from *Nicotiana glutinosa*, is a single dominant gene for HR to TMV that defines a classic model system for plant-virus interaction (89) and for the study of SAR (184). Below 28°C, tobacco plants carrying the *N* allele develop necrotic local lesions within 48 h at the site of TMV inoculation (89, 184). At higher temperatures, however, HR does not develop, and TMV spreads systemically throughout the plant. If a plant is initially infected at a temperature that allows systemic TMV infection and then subsequently moved to a lower temperature, a lethal systemic necrotic response is observed (47).

The *N* gene was isolated by insertional mutagenesis using the activator (*Ac*) transposon system (211) and confirmed by transgenic complementation (49). Deletion- and site-directed mutagenesis indicated that the TIR, NBS, and LRR domains are all required for proper function, although their role in HR is not

TABLE 3 Naturally occurring plant virus resistance genes for which nucleotide sequences are known

Gene	Plant	Virus[a]	Resistance mechanism	Cloning method	Predicted domains	Year isolated	References
N	*N. tabacum*	TMV	Cell-to-cell movement (HR)	Transposon tagging	TIR-NBS-LRR	1994	(211)
Rx1	*S. tuberosum*	PVX	Replication	Positional cloning	CC-NBS-LRR	1999	(14)
Rx2	*S. tuberosum*	PVX	Replication	Positional cloning	CC-NBS-LRR	2000	(16)
Sw5	*S. esculentum*	TSWV	Cell-to-cell movement (HR)	Positional cloning	CC-NBS-LRR	2000	(21)
HRT	*A. thaliana*	TCV	Cell-to-cell movement (HR)	Positional cloning	LZ-NBS-LRR	2000	(38)
RTM1	*A. thaliana*	TEV	Systemic movement	Positional cloning	Jacalin like seq	2000	(34)
RTM2	*A. thaliana*	TEV	Systemic movement	Positional cloning	Jacalin like seq	2000	(212)
RCY1	*A. thaliana*	CMV	Cell-to-cell movement (HR)	Positional cloning	CC-NBS-LRR	2002	(204)
$Tm2^2$	*S. lycopersicum*	ToMV	Cell-to-cell movement (HR)	Transposon tagging	CC-NBS-LRR	2003	(116)
pvr1, $pvr1^2$ $pvr1^1$	*C. annuum*	PVY	Replication Cell-to-cell movement	Candidate approach	eIF4E	2002	(102, 186)
$mo1^1$ $mo1^2$	*L. sativa*	LMV	Replication Tolerance	Candidate approach	eIF4E	2003	(154)
sbm1	*P. sativum*	PSbMV	Replication	Candidate approach	eIF4E	2004	(67)

[a]CMV, *Cucumber mosaic virus*; LMV, *Lettuce mosaic virus*; PSbMV, *Pea seed borne mosaic virus*; PVY, *Potato virus* Y; PVX, *Potato virus* X; TCV, *Turnip crinkle virus*; ToMV, *Tomato mosaic virus*; TEV, *Tobacco etch virus*; TMV, *Tobacco mosaic virus*; TSWV, *Tomato spotted wilt virus*.

known (6, 125). Furthermore, *N* transcription is up-regulated by TMV infection (123), producing two transcripts via alternative splicing. Both translation products are necessary at an optimum ratio for resistance to be achieved (48). Transcriptional activation of several WRKY and MYB transcription factors also results from the *N*-TMV interaction (21, 220, 221).

Rar1, *SGT1*, and *EDS1*, required for signal transduction mediated by most known R genes, are also required for the *N* gene–mediated resistance in tobacco (125, 126) (Figure 2*B*). It is hypothesized that SGT1 and Rar1 associate with Hsp90 as cochaperones in the assembly or conformational regulation of N protein complexes (124). The multiprotein complex, the COP9 signalosome, which physically interacts with SGT1, is also implicated in *N* gene–mediated signaling (125). In this signaling cascade, two mitogen-activated protein kinases (MAPK), a wound-inducible protein kinase (WIPK), and SA-inducible protein kinase (SIPK) are activated (226) by an upstream MAPK kinase (MAPKK), NtMEK2 (178). Silencing WIPK, SIPK, or NtMEK2 attenuates *N* gene resistance (100) (Figure 2*B*).

Resistance to *Potato Virus X* in Potato Conferred by *Rx1* and *Rx2*

The *Rx* loci in potato, *Rx1* on chromosome V and *Rx2* on chromosome XII (181), confer resistance to PVX in the absence of necrotic cell death. *Rx*-mediated resistance results in a very rapid arrest of PVX accumulation in the initially infected cell (111). In contrast to HR-associated resistance, *Rx*-mediated resistance is active in protoplasts (1, 15, 111). When protoplasts isolated from resistant (*Rx*) and susceptible (*rx*) potato genotypes were inoculated with PVX and TMV, *Rx* protoplasts showed <100-fold less PVX RNA accumulation (15), relative to a positive control using TMV. When TMV was coinoculated with PVX, TMV RNA accumulation was also reduced to a level comparable to PVX in resistant protoplasts, demonstrating that once induced, the resistant response can target viruses other than the elicitor virus. *Rx1*, isolated from tetraploid potato by map-based cloning, encodes a 107.5-kD CC-NBS-LRR protein (14). *Rx1* and *Rx2* show the same specificity for the PVX CP (176), extremely similar nucleotide sequence, and similar linkage with resistance to *Globodera* (Table 3) (16, 76).

Transgenic experiments demonstrated that the response to PVX in *Rx*-containing genotypes can be altered depending on the mode of expression of the viral CP (14). Transgenic potato or tobacco plants expressing *Rx* show extreme resistance against PVX. When the PVX CP is constitutively expressed in the same plants, HR is observed, indicating that the amount of CP in the plant cell determines the macroscopic host response. Constitutive gain-of-function *Rx* mutants in which cell death is activated in the absence of viral CP were obtained by random mutagenesis (13). Sequence analysis revealed that most of the constitutive gain-of-function mutations occurred in or near the conserved NBS-LRR sequence motifs. It is not clear whether this phenotype is resulted from release of negative regulation by the LRR and adjacent sequences or introduction of an incompatibility between the

domains such that they are no longer held inactive (P. Moffet & G. Rairdan, personal communication). In experiments designed to determine the biochemistry of Rx function, segments of the protein were expressed independently in an elegant system where phenotypic response could be easily assayed. PVX CP-dependent HR was observed after fragments of *Rx* (CC and NBS-LRR domains) and PVX-CP were expressed transiently in *N. benthamiana* via agroinfiltration (143). These results indicate that a functional Rx protein can be reconstituted through physical interactions between domains, even when the domains are expressed in different molecules. Furthermore, PVX CP disrupted the interaction between these Rx-derived domains. The current model suggests that CP recognition induces sequential conformational changes in Rx, disrupting intramolecular interactions, thereby activating Rx-mediated signaling (143).

Experiments using virus-induced gene silencing (VIGS) showed that *Rx*-mediated resistance does not require EDS1 (164) and RAR1. Bieri et al., however, have shown that silencing Rar1 actually reduces the levels of Rx (18). Therefore, Rar1 is likely a cochaperone required to varying degrees by different R proteins (P. Moffet, personal communication). Silencing of tobacco MAP kinase kinase kinase (MAPKKK) interferes with the function of the *Rx* gene (99, 100). Similar to results described above for the *N* gene, silencing SGT1 also compromised *Rx*-mediated resistance (165), and HSP90 is required, presumably acting as a cochaperone to stabilize Rx (129) (Figure 2*B*).

Resistance to *Tomato spotted wilt virus* in Tomato Conferred by *Sw-5*

Economic considerations have promoted the goal of TSWV-resistant tomato varieties in plant breeding programs for nearly 70 years. Early genetic studies reported five genes, *Sw-1*^{a}, *Sw-1*^{b}, *sw-2*, *sw-3*, and *sw-5*, from two species, *Solanum pimpinellifolium* and *Solanum lycopersicum* (60, 90), all of which were overcome quickly. *Sw-5*, introgressed from *Solanum peruvianum* into tomato, has demonstrated broad and stable resistance (183, 200). In resistant genotypes, local necrotic lesions develop on inoculated tissue, and systemic movement of the virus is restricted. The *Sw-5* locus was isolated by positional cloning and sequenced, revealing that the resistance allele encodes a CC-NBS-LRR R protein. *Sw-5* is remarkably similar to the tomato *Mi* gene for nematode resistance with the exception of four heptad amphipathic leucine zippers at the N terminus (21). This pronounced similarity suggests that *Sw-5* and *Mi* may share a common signal transduction pathway. *Sw-5* and its paralogs were mapped to tomato chromosome 9 and chromosome 12 with other fungal, viral, and bacterial R genes. A comparative analysis with the genus *Capsicum*, which is considerably diverged from *Solanum* within the tribe Solanae, indicated that paralog position was largely conserved between these genera (94). In *Capsicum*, monogenic dominant TSWV resistance conferred by *Tsw* showed identical resistance phenotype and strain-specificity to *Sw5*, but no cross-hybridization with *Sw5* was detected. When resistance-breaking TSWV

strains were analyzed, avirulence determinants mapped to different subgenomic RNAs (94).

Resistance to *Tomato mosaic virus* in Tomato Conferred by *Tm2²*

Tm2², the second tobamovirus R gene isolated, is one of the three R genes, *Tm1*, *Tm2*, and *Tm2²*, used widely in tomato breeding to control *Tomato mosaic virus* (ToMV) (81, 166). The *Tm1* gene from *S. hirsutum* confers extreme resistance and was mapped to chromosome 2. *Tm2* and *Tm2²*, considered to be alleles from *S. peruvianum*, are located close to the centromere of chromosome 7 (81). *Tm2²*, considered the more durable of the two alleles, was isolated by transposon tagging and encodes an 861 amino acid CC-NBS-LRR protein (116). The predicted protein from the susceptible allele *tm2* also encodes a CC-NBS-LRR protein that appears comparable in most respects to the protein encoded by the resistance allele. Analysis of the nucleotide sequence of resistance-breaking virus isolates indicated that the MP protein is the avirulence factor in this resistance system (24, 210). However, different mutations are required to overcome *Tm2* and *Tm2²*.

Resistance to *Turnip crinkle virus* in *Arabidopsis* Conferred by *HRT*

A single dominant gene, *HRT*, was identified for HR resistance to TCV (41). *HRT* is located on chromosome 5 and encodes a CC-NBS-LRR protein with striking similarity to the *RPP8* gene family for resistance to the oomycete *Peronospora parasitica* (38). Despite very high sequence similarity, *HRT* and *RPP8* specifically control only their cognate pathogens. Analysis of resistance in *HRT*-expressing transgenic plants indicated that *HRT* is necessary but generally insufficient for resistance. About 90% of the *HRT*-transformed Col-0 plants developed HR and expressed *PR-1* after TCV infection yet remained susceptible to TCV. Full resistance to TCV required both *HRT* and a recessive allele *rrt* (38). Later experiments demonstrated that the *HRT*-/*rrt*-mediated response is dependent on *EDS1* and independent of *RAR1* and *SGT1* (31). In this system, TCV CP is the avirulence determinant recognized by *HRT* (38). A host protein, TIP (TCV interacting protein) that belongs to the NAC family of transcriptional activators is known to interact with TCV CP. Although the relevance of this interaction to the mechanism of resistance remains unclear, this interaction apparently functions to keep TIP out of the nucleus (179).

Resistance to *Cucumber mosaic virus* in *Arabidopsis* Conferred by *RCY1*

Extensive examination of 12 *Arabidopsis* ecotypes identified a CMV-Y-resistant ecotype, C24 (201). The resistance response of C24 includes suppression of virus multiplication to a low level, the formation of necrotic lesions at the primary site

of virus infection, and restriction of virus to the inoculated leaves. This resistance response in C24 is controlled by a single dominant *RCY1* (resistance to cucumber mosaic virus strain Y) gene. The analysis of a series of chimeric viruses constructed from the avirulent isolate CMV-Y and the virulent isolate CMV-B2 revealed that the coat protein of CMV-Y serves as the avirulent determinant of resistance in C24 (204). The *RCY1* gene has been mapped in *Arabidopsis* within the MRC-5 region on chromosome 5, in which nine other defined resistance genes (*RAC3*, *RPS4*, *HRT*, *TTR1*, and five distinct *RPP* loci) are located (204). Fine mapping and sequence comparison of this region from C24 and a CMV-Y susceptible C24 mutant identified the *RCY1* gene encoding 104-kDa CC-NBS-LRR type protein. RCY1 is allelic to the resistance gene *RPP8* against *Peronospora parasitica* in the ecotype Lansberg erecta and *HRT* against TCV in the ecotype Dijon-17. The *RCY1*-conferred resistance requires both salicylic acid and ethylene signaling but not jasmonic acid signaling (202, 203).

RECESSIVE PLANT VIRUS RESISTANCE GENES CHARACTERIZED AT THE MOLECULAR LEVEL

Despite notable progress towards defining the elements that comprise dominant R gene-mediated defense responses in plants, little is known about the nature of plant susceptibility to disease. Owing to the relatively small number of proteins they encode, viruses completely depend on the host factors to complete their life cycle (2, 213). Typical plant viruses encode 4 to 10 proteins that coordinate the complex biochemistry and intermolecular interactions required for viral infection cycles. Studying recessive virus resistance provides a unique opportunity to reveal host factors required for susceptibility and mechanisms of pathogenesis of the pathogen. Recent findings have confirmed early theoretical predictions (described above) that mutations of some host factors will result in recessively inherited resistance to plant viruses. The identification and characterization of host factors in which mutations interrupt viral pathogenesis will provide a new opportunity for understanding viral pathogenesis itself, as well as host responses; this is an approach that has been unavailable to date in the study of dominant resistance. Whether as a consequence of the economic importance of the Potyviridae, the relative prevalence of recessive resistance to this group of viruses, and/or the relative ease with which these viruses can be experimentally manipulated, studies of recessive R genes to date have focused largely on this viral family.

Several host genes whose mutations impair the infection cycle of plant viruses, including BCTV, CMV, TEV, TuMV, TMV, TGMV, and TCV, have been identified and characterized in *Arabidopsis* (Table 2). The translation initiation factor *eIF4E* has been identified repeatedly as a naturally occurring recessively inherited resistance locus in pepper *pvr1* (102, 186), lettuce *mo1* (154), and pea *sbm1* (67) and has been implicated in barley as a candidate for *rym4/5* (167) (Table 3). The eIF4E isoform eIF(iso)4E also has been implicated in *Arabidopsis* and pepper resistance

(102, 121). The role of eIF4E and eIF(iso)4E in the potyvirus infection cycle is not known. However, the negative effects of mutations in these host factors on the infectivity of various potyviruses in various host plants imply that the effect of these host factors upon potyvirus infection cycle is probably conserved. The common feature linking *pvr1/2*, *sbm1*, and *mo1* is that the viral avirulence determinants map to a specific region in the VPg, the protein covalently linked to the 5′ end of the viral RNA and perhaps mimicking the m^7G cap of eukaryotic mRNAs (19, 104, 105, 148). In eukaryotic cells, eIF4E binds to the m^7G cap as the first step in recruiting mRNA into the translational preinitiation complex. A similar role for eIF4E might be predicted when potyvirus infects plant cells (102). Although eIF4E has never been shown to bind VPg in infection, VPg or its precursor VPg-Pro interacted with eIF4E or eIF(iso)4E in yeast two-hybrid and in vitro pull-down assays (102, 122, 190, 217).

In the 1950s, *pvr1* and *pvr2* in pepper (*Capsicum annuum* and *C. chinense*) were initially considered allelic but then two loci were distinguished because of differences in resistance spectra. The allele formerly known as $pvr2^1$ is effective only against PVY-0, and $pvr2^2$ is effective against both PVY-0 and PVY-1. The allele *pvr1* was relatively broad in effect, controlling TEV, PepMoV, and PVY) (115). We now know that only one locus is involved, *pvr1*, at which at least three resistance alleles and two susceptibility alleles occur (186). Point mutations in eIF4E that fall near critical positions for cap-binding function abolish interaction with TEV VPg and determine the range of isolates across three potyviral species that are controlled (102). Two of these alleles when homozygous block accumulation of the virus in protoplasts (43, 150). The narrower spectrum allele retards movement of the virus through the plant but has no effect at the protoplast level (5). In a fourth case, *Pepper veinal mottle virus*, it appears eIF4E and probably eIF(iso)4E must be mutated to control the virus (102).

In lettuce, $mo1^1$ and $mo1^2$ control common isolates of LMV. In the homozygous state, $mo1^1$ confers resistance, i.e., absence of LMV accumulation; $mo1^2$ results in reduced LMV accumulation and lack of symptoms (180). As observed in pepper, allelic variants of eIF4E, $Ls\text{-}eIF4E^0$, $Ls\text{-}eIF4E^1$, and $Ls\text{-}eIF4E^2$ contained point mutations that result in predicted amino acid substitutions near the cap-binding pocket of the protein (154).

In pea, *sbm1* confers resistance to PSbMV pathotypes P1 and P4 as described above, now known to be a consequence of mutations in an eIF4E homolog (67). Transient expression of susceptible-eIF4E in a resistant background complemented PSbMV infection by supporting both virus multiplication in primary target cells and cell-to-cell movement. Processes that account for cell-to-cell movement are not well understood, and therefore it is difficult to speculate on a plausible role for eIF4E in virus movement. Nevertheless, in both the pepper and pea systems, variants at an eIF4E locus result in inhibition of movement, as well as extreme resistance. Again, point mutations in the resistant eIF4E allele are located in and around the cap-binding pocket. Similar to pvr1, cap-binding ability of the eIF4E protein is abolished in the resistant eIF4E variant. Recently, *rym4/5* for resistance to BaYMV in barley has also been shown to encode eIF4E (215). In contrast

to dominant R genes where resistance to the same or closely related pathogens generally do not occur in syntenic positions, a recessive potyvirus R gene *pot1* from tomato was mapped to a collinear position with pepper gene *pvr2* (163). These results indicate that recessive R genes are highly conserved. Evidence to date indicates that, for the most part, dominant and recessive R genes may not be related mechanistically and evolutionarily.

COEVOLUTION OF VIRUS RESISTANCE AND VIRAL AVIRULENCE GENES

Avirulence genes in plant pathogens have been defined by their requirement for disease resistance in hosts containing corresponding R genes (62, 103). Plant viruses evolve very rapidly owing to very short replication cycles, large numbers of genomes within each cell across many cells per host, and many hosts. For RNA viruses, the absence of a proofreading function in viral replicases may result in mutation rates as high as 10^4 per replication cycle per base (52). Viral genetic variation can result from several major genetic processes including mutation, recombination, and the acquisition of additional genomic sequence. As a consequence, resistance-breaking viral genotypes are known for most host resistance, especially for genes showing HR. Avirulence determinants are typically identified by creating chimeric clones derived from viral genotypes with contrasting virulence and then testing for infectivity. Once an avirulence domain is identified, site-directed mutagenesis allows identification of specific point mutations responsible for virulence. Table 4 lists R genes and corresponding viral avirulence factors identified to date.

Virtually any part of the viral genome can define an avirulence determinant. With respect to R genes that confer HR, avirulence factors include viral RNA polymerase subunits, movement protein, and CP. Several potyviral avirulence genes have been identified for dominant R genes that do not show HR. The CI and P3 proteins of *Turnip mosaic virus* serve as avirulence determinants for the *Brassica napus* R genes, *TuRBO1* and *TuRBO4/5* (96–98), while SMV HC-Pro and P3 are involved in overcoming *Rsv1* in soybean (57).

In contrast to the case for dominant genes where many different viral components have been identified as avirulence determinants, a pronounced trend is apparent viral factors that serve as the determinant for pathogenicity in resistance systems controlled by recessively inherited R genes. Of nine R gene studies to date, seven identify potyviral VPg as the pathogenicity determinant for recessive resistance, although the systems in question show diverse resistance phenotypes: *Capsicum pvr1/pvr1*^{2} resistance to PVY is cellular (148), tobacco *va* resistance impairs the cell-to-cell movement (155), and *Nicandra physaloides* and *Solanum commersonii* affect long-distance movement (177). The eighth study, also focused on a potyviral system, PsbMV/pea, identified the P3-6K1 cistron as the pathogenicity determinant (101). Only one study to date has focused outside the Potyviridae. In this case, the 3′ untranslated region of the carmovirus *Melon necrotic spot virus* (MNSV) genomic RNA defined the location of the viral determinant in the

TABLE 4 Viral avirulence determinants and their corresponding plant resistance genes

Plant	Resistance gene	Virus[a]	Avirulence gene	Reported mesistance mechanism	Resistance-breaking change	References
Arabidopsis	*HRT*	TCV	Coat protein	HR	Not available	(157, 218)
	RCY1	CMV	Coat protein	HR	Not available	(204)
Bean	*Bdm*	BDMV	BV1 protein	HR	Not available	(69)
Brassica napus	*TuRBO1*, *TuRBO1b*	TuMV	CI	HR	Single aa	(96)
	TuRBO3	TuMV	P3		Single aa	(98)
	TuRBO4,	TuMV	P3	Replication	Single aa	(97)
	TuRBO5		CI	HR	Single aa	
C. amaranticolor		CaMV	Gene VI product		Not available	(109, 191)
Cowpea		CMV	2a polymerase	HR	Single aa	(108)
Cucumis melo L.	*nsv*	MNSV	3′ portion of MNSV genome	Replication	3′ UTR	(45)
Lettuce	$mo1^1$	LMV	3′ half of genome	Replication	Not available	(178)
	$mo1^2$			movement		
Nicandra physaloides		PVA-M	62 K and VPg	Systemic movement	Four aa	(177)
Pea	*sbm-1*	PSbMV	VPg	Replication	Not available	(105)
	sbm-2	PSbMV	P3 and 6K1 cistron		Not avialable	(101)

Pepper	*L*^{1}, *L*^{2}, *L*^{3}	TMV	Coat protein	HR	Not available	(17, 40, 72)
	pvr1^1	PVY	VPg	Movement	Single aa	(148)
	pvr1^2			Replication		
Potato	*Nb*	PVX	25 K movement protein	HR	Single aa	(133)
	Nx	PVX	Coat protein	HR	Single aa	(189)
	Rx1, *Rx2*	PVX	Coat protein	Replication/HR	Two aa	(15)
	Ry	PVX	NIa protease	Replication	Not known	(140)
Tobacco	*N′*	ToMV	Coat protein	HR	Single aa	(110, 187)
Tobacco	*N*	TMV	Replicase (helicase domain)	HR	Several aa	(162)
	va	PVY	VPg	Cell-to-cell	Single aa	(155)
N. clevelandii		TBSV	P22 movement protein	Cell-to-cell movement	Not available	(35, 192)
Tomato	*Tm-1*	ToMV	Replicase	Replication	Two aa	(138)
	Tm-2, *Tm-2*^{2}	ToMV	30 kD movement protein	HR	Two aa	(139, 210)
	pot-1	PVY	VPg		Single aa	(148)
	Sw-5	TSWV	M RNA	HR	Mutiple aa	(87)
Soybean	*Rsv1*	SMV	HC-Pro and P3 cistron			(57)

[a]BYMV, *Bean yellow mosaic virus*; CaMV, *Cauliflower mosaic virus*; CMV, *Cucumber mosaic virus*; LMV, *Lettuce mosaic virus*; MNSV, *Melon necrotic spot virus*; PSbMV, *Pea seed borne mosaic virus*; PVA-M, *Potato virus* A strain M; PVY, *Potato virus* Y; PVX, *Potato virus* X; TBSV, *Tomato bush stunt virus*; TCV, *Turnip crinkle virus*; TuMV, *Turnip mosic virus*; ToMV, *Tomato mosaic virus*; TMV, *Tobacco mosaic virus*; TVMV, *Tobacco vein mottling virus*; TSWV, *Tomato spotted wilt virus*; SMV, *Soybean mosaic virus*.

interaction of MNSV with melon (45). In the eight cases where the viral elicitor is protein, host recognition of these viral proteins that serve as pathogenicity determinants is altered by amino acid substitutions that do not appear to significantly compromise the function of the protein in pathogenesis. For other microbial pathogens, there often appears to be a fitness penalty association with mutations from avirulence to virulence (128). Although this type of fitness/avirulence tradeoff has not been noted generally for plant viruses, there are specific examples where this occurs. Isolates of ToMV capable of overcoming $Tm2^2$ gene were found to multiply poorly on resistant plants (116). If the $Tm2^2$ resistant protein targets a domain of the viral MP such that this protein is mutated to overcome resistance, these mutations could result in diminished fitness.

DURABLE RESISTANCE AND VIRUS RESISTANCE BREEDING

Assessment of success for investment in control of crop loss via plant breeding depends upon how long the resistance will last and the intensity of cultivation during this period. The term durable resistance has been defined as resistance that has remained effective through a relatively long period of time although resistant crop varieties are widely cultivated in an environment favorable for disease development. This term is useful primarily for retrospective assessment when applied to naturally occurring R genes. At present, our understanding of the relevant biology does not allow for predictive estimations. Nevertheless, there are dramatic differences between R genes with respect to durability when deployed in agriculture, even if some attempt is made to compensate for differences in deployment intensity. Despite the perception that monogenic dominant resistance is inherently unstable, some R genes remain useful for several decades or more (Table 5). The dominant *I* gene for resistance to BCMV and a number of other viruses in *Phaseolus vulgaris* has been deployed in snab bean breeding since the early 1930s (114). Although isolates that result in systemic necrosis have appeared, no pathotypes of any of the viruses controlled by the *I* gene can overcome resistance and cause mosaic disease. Although the necrotic response can be more destructive than mosaic, the gene is still very widely deployed because it eliminates seed transmission of the viruses in question. In theory, recessive resistance may be more durable than dominant resistance (64), and there are cases in both monocots and dicots where recessive R genes have been widely deployed for 50 years or more. This hypothesis, however, has not been assessed definitively to date.

There is also considerable speculation that resistance or tolerance governed by a series of different genes, each with incremental possibly overlapping effect (horizontal resistance), will be more durable than resistance governed by genes with major effect (vertical resistance). The extent to which genes that contrast with respect to vertical versus horizontal resistance actually involve different mechanisms is still unresolved. Results from several nonviral systems suggest that defeated "major" genes may still define resistance QTL. If resistance or tolerance is due to a composite effect from several overlapping R genes or mechanisms, then a

TABLE 5 Examples and reported mechanisms of durable resistance genes to plant viruses

Resistance genes	Host	Virus	Reported mechanisms	Selected references
Tm-2²	Tomato	ToMV	Impaired fitness	(116)
Sw-5	Tomato	TSWV	Multiple aa changes	(21)
sbm1 + sbm2	Soybean	SMV	Multiple aa changes	(86)
TuRB03 + TuRBO4	Turnip	TuMV	Multiple aa changes	(97)
N	Tobacco	TMV	Multiple aa changes	(161, 162)
Rx	Potato	PVX	Replication	(1, 119)
Ry	Potato	PVY	Replication	(86)
pvr1	Pepper	PVY, TEV	Replication	(150)
I	Common bean	BCMV	Replication	(114)
Tu	Lettuce	TuMV	Unknown	(227)

BCMV; *Bean common mosaic virus*, PVY; *Potato virus* Y, PVX; *Potato virus* X, *Tobacco etch virus*; TEV, TuMV; *Turnip mosaic virus*, ToMV; *Tomato mosaic virus*, TMV; *Tobacco mosaic virus*, TSWV; *Tomato spotted wilt virus*, SMV; *Soybean mosaic virus*.

resistance-breaking virus would have to acquire multiple mutations to diminish or overcome the effect. As mentioned above, relatively few studies have focused on this type of polygenically inherited resistant or tolerant response to plant viruses, and even fewer cases exist where this type of resistance has been transferred into crop varieties. One example is provided in pea where genotypes homozygous for two recessive R genes, *sbm1* and *sbm2*, have shown particularly durable resistance to PSbMV (86).

Although the mechanisms that govern resistance durability remain largely unknown, durability of the *Tm2²* gene might be explained by the reduced fitness of avirulence gene mutation, as described above (116). Many virus R genes that operate at the cellular level appear to confer very durable resistance, e.g., *Rx* and *Ry* in potato, *pvr1* in pepper (7, 15, 111). If avirulent viruses have very limited or no chance to replicate in infected hosts, the chance of virulence arising in a viral population would diminish. For both dominant and recessive R genes, durability will certainly be a consequence of viral population dynamics, the nature and frequency of mutations required for shifts in pathogenicity, and changes in the frequency of virulent isolates, among other factors.

CONCLUSIONS AND PROSPECTS

Dramatic advances have occurred in the past decade on several fronts in the study of genetics of resistance to plant viruses. The advent of genomic and bioinformatic approaches, increased understanding of host responses at the organismal and cellular levels, the clarification of the degree of conservation observed in plant-viral systems, and our increasingly sophisticated ability to precisely manipulate

host and viral genes and genomes have all contributed to significant shifts in our understanding of the structure and function of genetic resources for plant virus resistance. Nonetheless, our knowledge of plant genetic variability relevant to viral interactions remains far from comprehensive. To date, research efforts have focused disproportionately on a few viral and plant families, with strong bias toward viruses with RNA genomes that infect dicots and host responses that show monogenic control. Continued evaluation of plant genetic diversity with respect to interactions with viruses is needed, as is characterization of the inheritance of contrasting responses in diverse host species.

A striking area of progress has been the identification at the molecular level of a number of viral R genes from a wide array of plants. In contrast to early speculation that mutations that result in resistance would occur in many different types of genes, these studies to date have shown a remarkable degree of conservation evident in both monocot and dicot hosts for both dominant and recessive resistance. The extent to which this will remain true is unknown as more comprehensive information drawn from diverse host-pathogens interactions accumulates. The trends resolved to date, however, are very clear. In plant viral resistance showing dominant inheritance, most of the genes isolated and characterized to date fall into a series of related categories that involve proteins containing NBS-LRR domains, similar to those that control a wide array of other plant pathogens. In recessively inherited resistance, 7 of 9 examples known to date affect loci that encode 1 of 2 isoforms of the eukaryotic translation factor eIF4E. The degree of conservation observed will clearly accelerate the pace of gene discovery via candidate gene approaches, e.g., the *bc-u*, *bc-1*, *bc-2*, and *bc-3* system in *Phaseolus vulgaris* and other systems in which one or more recessive loci are involved in resistance to RNA viruses. These systems represent clear opportunities to examine the extent to which eIF4E-related sequences may serve as candidates for diverse recessive R genes.

Given this observation of striking overall conservation among many R genes identified to date, how these genes actually function to produce resistance becomes very compelling because insights drawn from one system are likely to be broadly applicable. Equally compelling, and perhaps of considerably more applied significance, will be research directions that aim to elucidate the sources of specificity in these interactions.

Progress has lagged in the identification of R genes that control plant viruses with genomes comprised of DNA, and that contribute to quantitatively inherited (polygenically controlled) viral resistance or tolerance. One promising area of current activity is the identification of host proteins that interact with viral genes or gene products during infection. This work is primarily aimed at understanding mechanisms of viral infection and pathogenesis, rather than viral resistance and has exploded with the advent of such techniques as yeast two- and three-hybrid assays and those that canvas for specific protein-protein interactions. Numerous proteins identified this way using viral gene products as bait have relevance to the viral life cycles and pathogenicity, even in viral systems about which relatively little is known. An important limitation to these studies is the degree to which an interaction identified in yeast or in vitro can be demonstrated in planta. The next

generation of candidate genes for viral R genes and QTL will undoubtedly come from these studies.

A major discovery of the past decade resulting from these types of studies with profound implications in virology, plant biology, and biotechnology is gene silencing and its role in pathogenesis and resistance. In addition to elucidating central aspects of cellular metabolism with profound effects on gene expression and regulation, these studies have allowed for the development of vectors, based on viral genomes, most notably the tobravirus *Tobacco rattle virus*, for viral-induced gene silencing (VIGS) (10, 125). These tools provide the basis for powerful genetic approaches through which genes are identified by the phenotypes produced when they are silenced. This approach, known as reverse genetics, is becoming increasingly important in projects involving high-throughput functional genomic analyses of plant genomes.

Despite landmark advances over the past 15 years with respect to both fundamental understanding of the structure and, to some extent function, of plant viral R genes, and major milestones in their applications in agriculture, much remains to be done. With expanding agricultural monocultures, particularly in the developing world, have come rising threats from viral pathogens for which the necessary resistance resources are not known. Although virus resistance was among the first objectives addressed by transgenic crops in the United States, the ways in which mutations in plant genes interfere with viral infection and biology of resistance specificity and durability are still poorly understood. Elucidation of the mechanisms by which broadly effective and durable host-resistant responses can be induced by a wide array of plants, and the ways in which these responses may be deployed in agriculture will surely be a major focus of investigation for the future.

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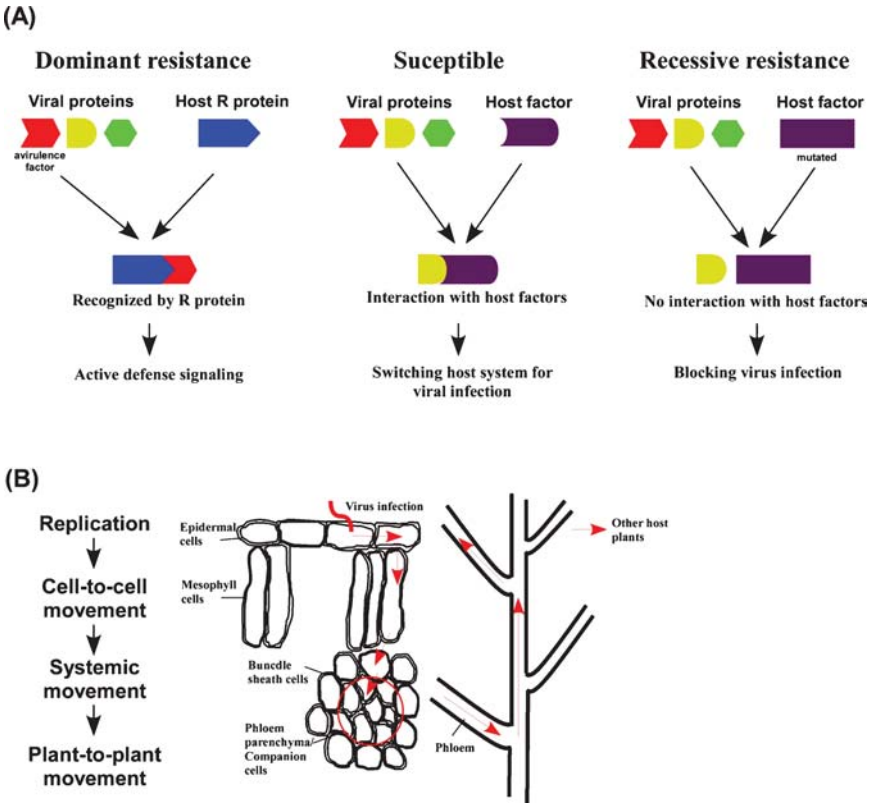

Figure 1 (*A*) Possible virus resistance mechanisms showing dominant or recessive inheritance contrasted with a susceptible interaction. (*B*) Stages of a viral infection cycle with points of potential host interference identified as resistance targets.

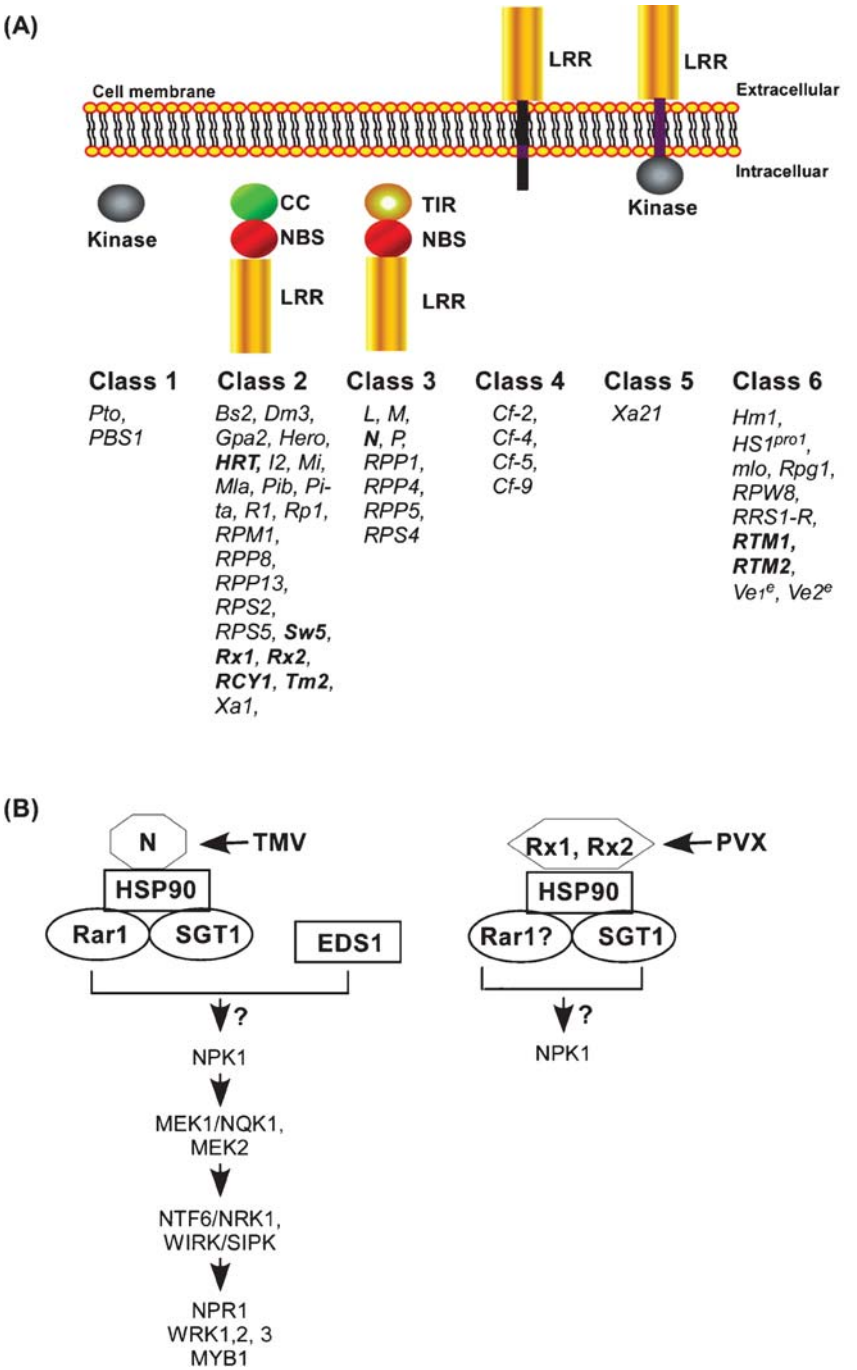

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Figure 2 (*A*) Structure and location of the six main classes of plant disease resistance proteins. Virus resistance genes are indicated in bold letters. Classes 1–5 are defined based on combinations of a limited number of structural motifs. Class 6 includes R proteins that do not fit into classes 1–5. LRR, leucine-rich repeat; NBS, predicted nucleotide binding site; CC, predicted coiled coil domain; TIR, Toll and interleukin 1 receptor domain. (*B*) Downstream components of virus resistance genes. Left panel is modified from (124). Question marks indicate unknown signaling steps.

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CONTENTS