The Coevolution of Plants and Viruses: Resistance and Pathogenicity

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Abstract

Virus infection may damage the plant, and plant defenses are effective against viruses; thus, it is currently assumed that plants and viruses coevolve. However, and despite huge advances in understanding the mechanisms of pathogenicity and virulence in viruses and the mechanisms of virus resistance in plants, evidence in support of this hypothesis is surprisingly scant, and refers almost only to the virus partner. Most evidence for coevolution derives from the study

of highly virulent viruses in agricultural systems, in which humans manipulate host genetic structure, what determines genetic changes in the virus population. Studies have focused on virus responses to qualitative resistance, either dominant or recessive but, even within this restricted scenario, population genetic analyses of pathogenicity and resistance factors are still scarce. Analyses of quantitative resistance or tolerance, which could be relevant for plant–virus coevolution, lag far behind. A major limitation is the lack of information on systems in which the host might evolve in response to virus infection, that is, wild hosts in natural ecosystems. It is presently unknown if, or under which circumstances, viruses do exert a selection pressure on wild plants, if qualitative resistance is a major defense strategy to viruses in nature, or even if characterized genes determining qualitative resistance to viruses did indeed evolve in response to virus infection. Here, we review evidence supporting plant–virus coevolution and point to areas in need of attention to understand the role of viruses in plant ecosystem dynamics, and the factors that determine virus emergence in crops.

ACRONYMS AND NAMES OF VIRUSES

BaMMV	*Barley mild mosaic virus*
BaYMV	*Barley yellow mosaic virus*
BCMV	*Bean common mosaic virus*
BDMV	*Bean dwarf mosaic virus*
BYDV	*Barley yellow dwarf virus*
BYMV	*Bean yellow mosaic virus*
CMV	*Cucumber mosaic virus*
CYDV	*Cereal yellow dwarf virus*
GRSV	*Groundnut ringspot virus*
LMV	*Lettuce mosaic virus*
MNSV	*Melon necrotic spot virus*
PMMoV	*Pepper mild mottle virus*
PSbMV	*Pea seed-borne mosaic virus*
PVMV	*Pepper veinal mottle virus*
PVX	*Potato virus X*
PVY	*Potato virus Y*
RRSV	*Raspberry ringspot virus*
RYMV	*Rice yellow mottle virus*
SMV	*Soybean mosaic virus*
TCSV	*Tomato chlorotic spot virus*
TCV	*Turnip crinkle virus*
TEV	*Tobacco etch virus*
TMV	*Tobacco mosaic virus*

ToMV	*Tomato mosaic virus*
TSWV	*Tomato spotted wilt virus*
TuMV	*Turnip mosaic virus*
ZYMV	*Zucchini yellow mosaic virus*

I. INTRODUCTION

Pathogens are able to infect a host and, as a result of infection, they cause damage to this host. The appropriate terminology for these two central properties of pathogens has lead to much discussion in the phytopathological literature since Vanderplank (1968) defined aggressiveness as the quantitative negative effect of a pathogen on its host and virulence as the capacity of a pathogen to infect a particular host genotype. However, in other areas of biology, including animal pathology and evolutionary biology, virulence is defined as the detrimental effect of parasite infection on host fitness (e.g., Read, 1994; Woolhouse *et al.*, 2002), that is, virulence is related to the damage that parasite infection causes to the host, and the capacity to infect a host is named infectivity (Gandon *et al.*, 2002; Tellier and Brown, 2007). In spite of other conventions in the phytopathological literature, the American Phytopathological Society defines pathogenicity as the ability of a pathogen to cause disease on a particular host (i.e., a qualitative property), and virulence as the degree of damage caused to the host (i.e., a quantitative property), assumed to be negatively correlated to host fitness (D'Arcy *et al.*, 2001). These definitions are more in line with those used by other scientists interested in the biology of hosts and pathogens, and will be used in this review, except that for gene-for-gene (GFG) and matching-allele (MA) interactions we will retain the usual terminology of avirulence/virulence genes or factors.

Because pathogen infection reduces their fitness, hosts have developed different defense strategies to avoid or limit infection and to compensate for its costs (Agnew *et al.*, 2000). In plants, the two major defense mechanisms are resistance (defined as the ability of the host to limit parasite multiplication) and tolerance (defined as the ability of the host to reduce the damage caused by parasite infection) (Clarke, 1986). Host defenses may have a negative effect on parasite fitness. Hence, hosts and parasites may modulate the dynamics and genetic structure of each other's populations, and hosts and pathogens may coevolve, defining coevolution as the process of reciprocal, adaptive genetic change in two or more species (Woolhouse *et al.*, 2002).

Woolhouse *et al.* (2002) point to three conditions that are required for host–pathogen coevolution: (1) reciprocal effects of the relevant traits of the interaction (e.g., defense and pathogenicity) on the fitness of the two species (i.e., pathogens and hosts), (2) dependence of the outcome of the

host–pathogen interaction on the combinations of host and pathogen genotypes involved, and (3) genetic variation in the relevant host and pathogen traits. If these three conditions are met, demonstrating coevolution requires in addition to show changes in genotype frequencies in both the host and the pathogen populations in the field (Woolhouse *et al.*, 2002). Although it is currently assumed that plants coevolve with their pathogens, this evidence is available for few plant–pathogen systems, and derives from analysis of the interaction of plants with bacteria, fungi, and oomycetes in their natural habitats (Burdon and Thrall, 2009; Salvaudon *et al.*, 2008). To our knowledge, analyses of genotype changes of plants and their infecting viruses in natural populations have not been reported, and there is no specific demonstration of plant–virus coevolution. However, evidence consistent with coevolution of plants and pathogens has accumulated for more than 50 years (e.g., Flor, 1971; Salvaudon *et al.*, 2008; Thompson and Burdon, 1992), deriving in a large part from agricultural systems, and this includes a considerable body of data from plant–virus interactions. In this review, we discuss the available evidence in support of coevolution in plant–virus systems; a major goal will be to pinpoint research areas in need of attention.

II. VIRUS INFECTION AND HOST DEFENSES RECIPROCALLY AFFECT THE FITNESS OF HOST AND VIRUS

Selection for resistance in plants, and for pathogenicity in viruses, would occur only if pathogenicity and resistance would negatively affect the fitness of plants and viruses, respectively. It is widely assumed that pathogen infection decreases the fitness of the infected host, that is, that pathogens are virulent, and that resistance decreases the fitness of the pathogen. However, direct evidence of these two assumptions for plants and viruses is surprisingly scarce, probably due to a limited interest till recent times of plant virologists in virulence evolution, on the one hand, and to difficulties in estimating experimentally the fitness of any organisms and linking these estimates to its evolution in nature (Kawecki and Ebert, 2004).

For animal pathogens, the effect of infection on host fitness, that is, virulence, is usually estimated as increased host mortality (Frank, 1996). This assumes that a reduction in lifespan conveys a decrease in fecundity and, hence, in fitness. But this is not obvious in many plant species, particularly domesticates, which are semelparous, that is, reproduce only once during their lives. Also, most plant pathogens do not cause an immediate increase in host mortality and their effect on host fitness depends on the pathogen life history (Barrett *et al.*, 2008). Hence, virulence on plants is most often estimated as the effect of pathogen infection on the

plant's fecundity (i.e., viable seed production) or on one of its correlates, as plant size or biomass, or even symptom severity, the most commonly used correlate of virulence (Jarozs and Davelos, 1995). However, the relationship between fecundity and biomass or symptom severity may be nonlinear and depend on both genetic and environmental factors (e.g., Pagán *et al.*, 2007; Schürch and Roy, 2004), and this relationship has been analyzed only seldom for plant viruses (Agudelo-Romero *et al.*, 2008; Pagán *et al.*, 2008). Thus, the assumption that plant viruses decrease the fitness of their hosts rests mostly on the severity of the symptoms induced by virus infection on crops, and on the effects of infection on crop productivity, what may not be relevant for plant–virus coevolution. Moreover, although several reports of experiments showing that virus infection can decrease the fitness of wild plants under controlled conditions (e.g., Friess and Maillet, 1996; Kelly, 1994; Pagán *et al.*, 2007), there is little evidence that plant viruses have any effect on plant fitness in natural ecosystems, and it has been proposed that most often viruses would be mutualistic symbionts of plants (Roossinck, 2005; Wren *et al.*, 2006). This hypothesis rests on the interesting observation that in wild hosts growing in nonagricultural ecosystems, virus infection most often does not cause any obvious symptom, at odds with what is known to occur in crops. But estimates of the effect of virus infection on wild plants fitness are presently scarce. The negative effect of virus infection on plant fitness in nature has been best documented for BYDV and CYDV on wild grasses in California (Malmstrom *et al.*, 2006; Power and Mitchell, 2004). Interestingly, virus infection, in addition to direct fitness costs, has important indirect costs as it may reduce the competitive ability of the infected plants, a phenomenon (apparent competition) that may also occur among genotypes of the same species (Pagán *et al.*, 2009). Virus infection has also been shown to increase mortality and to reduce fecundity in wild cabbage in southern England (Maskell *et al.*, 1999), and to reduce lifespan of wild pepper in its natural habitats in Mexico (our unpublished results). Other reports suggest that the effect of virus infection on the population dynamics of wild plants will vary largely according to site or population (Pallett *et al.*, 2002). On the other hand, virus infection may be beneficial for plants, as shown by an increase of tolerance to abiotic stress in virus-infected plants as compared with uninfected controls (Xu *et al.*, 2008), or by a decreased herbivory on tymovirus-infected *Kennedia rubicunda* in Australia (Gibbs, 1980). Thus, it is obvious that the effects of virus infection on plant fitness in natural ecosystems may vary largely according to the specific virus–host interaction and, probably, according to the environment, a subject that requires further attention by virologists with an interest in ecology and evolution.

For parasites, fitness is also best estimated as fecundity, that is, production of new infections per unit time (Anderson and May, 1982).

However, for plant viruses, fitness is usually estimated as within-host multiplication rates (e.g., Sacristán *et al.*, 2005) or, when different genotypes are compared, as competitive ability (e.g., Carrasco *et al.*, 2006; Elena *et al.*, 2006; Fraile *et al.*, 2010). Because resistance results in a decrease of within-host virus multiplication, it is assumed that resistance decreases virus fitness. This assumption implicitly considers that rates of between-host transmission positively correlate with rates of within-host multiplication. Indeed, for viruses transmitted by aphids, both nonpersistently and persistently, it has been shown that transmission efficiency is positively correlated with virus accumulation in source tissues (Barker and Harrison, 1986; Escriu *et al.*, 2000; Foxe and Rochow, 1975; Jiménez-Martínez and Bosque-Pérez, 2004; Pirone and Megahed, 1966). Whether or not this correlation holds for other mechanisms of horizontal transmission, or for seed transmission, remains to be analyzed.

In summary, although direct evidence is far less common than might be expected, it supports that in the case of virulent virus–plant interactions traits related to pathogenicity have a negative effect on the plant's fitness, and traits related to defense have a negative effect on the virus fitness.

III. THE OUTCOME OF PLANT–VIRUS INTERACTIONS DEPENDS ON THE PLANT AND VIRUS GENOTYPES INVOLVED

For the last 50 years, different theoretical analyses aimed at understanding and modeling host–pathogen coevolution have been published. All these analyses assume that the outcome of the host–pathogen interaction is determined by the combination of host and pathogen genotypes involved. Two major models of host–parasite interaction determining the success of infection have been proposed: the GFG and the MA models, which have been applied mostly to plant and animal systems, respectively. Genetic and molecular genetic evidence support both these models to explain plant–virus interactions (Kang *et al.*, 2005a; Maule *et al.*, 2007; Sacristán and García-Arenal, 2007).

In plant–pathogen systems, pathogenicity has been most often related and analyzed as conforming to GFG interactions, first described in the flax–flax rust system (Flor, 1955). According to this model, the interaction of specific products of the plant and pathogen genotypes determines an incompatible interaction (Fig. 1), that is, host defenses are triggered and infection is limited. Plant proteins encoded by resistance genes (R proteins) recognize corresponding proteins of the pathogen, encoded by avirulence genes (*AVR*). Recognition can be either through a direct R–AVR interaction or, more often, via multiprotein interactions, including AVR–host protein

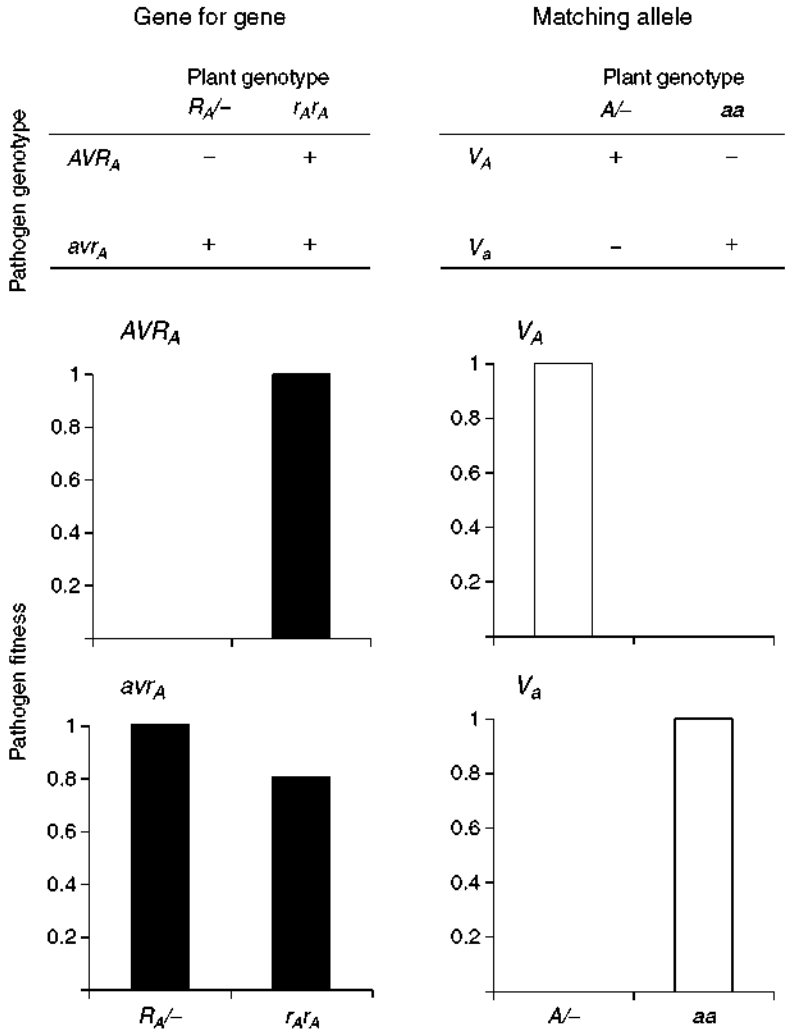

FIGURE 1 Models of host–pathogen coevolution for a diploid host and a haploid pathogen species. Left panel: gene-for-gene model. The product of the dominant resistance allele at locus A (R_A) in the host allows recognition of the product of the avirulence gene A (AVR_A) in the pathogen, triggering defenses and limiting infection (−). If the plant genotype is homozygous for the recessive susceptibility allele r_A, or the pathogen genotype has the virulence allele avr_A, the pathogen is not recognized, defenses are not triggered and infection occurs (+). In the resistant host genotype ($R_A/-$), the relative fitness of the avirulent pathogen genotype (AVR_A) is near zero, while that of the virulent one (avr_A) is considered as 1. In the susceptible host genotype (r_Ar_A), the virulent pathogen genotype has a lower relative fitness than the avirulent genotype (cost of pathogenicity). Right panel: matching-allele model.

complexes, modified/unmodified host targets of AVR, and/or adapter proteins that mediate binding, stabilize, or localize R (Friedman and Baker, 2007; Jones and Dangl, 2006; McDowell and Simon, 2006; Moffett, 2009). The recognition of AVR by the host triggers defense responses leading to limitation of multiplication and spread of the pathogen which remains localized at the infection site, and the resistance response is often associated to a hypersensitive response (HR), often involving localized host cell death. In the absence of the *AVR* allele in the pathogen or of the *R* allele in the host, the parasite is not recognized by the host, resistance is not triggered, and the host is infected, resulting in a compatible interaction. Accordingly, a key feature of the GFG model is that universal pathogenicity occurs, that is, there are pathogen genotypes able to infect all host genotypes (Agrawal and Lively, 2002).

Pathogen recognition by plant genotypes resulting in a HR was first described by Holmes (1937) for the interaction of TMV with *Nicotiana* spp. Ever since, polymorphisms for resistance to different viruses have been described in many plant species. About 51% of characterized resistance factors have a monogenic dominant inheritance, and are most often manifested as a HR (Kang *et al.*, 2005a; Khetarpal *et al.*, 1998). Twelve dominant genes conferring resistance to viruses expressed either as HR or as extreme resistance (ER; i.e., virus multiplication is limited to the initially infected cells without an apparent necrotic local lesion) have been cloned and sequenced (Table I) (Maule *et al.*, 2007; Palukaitis and Carr, 2008). All encode members of the NB–LRR class of R proteins (Dangl and Jones, 2001) that localize to the cytoplasm consistent with the lifestyle of viruses (Maule *et al.*, 2007). Viral genotypes that break down a defense response (i.e., that no longer elicit a HR or ER) have been described for many resistance factors (e.g., García-Arenal and McDonald, 2003; Janzac *et al.*, 2009), that is, there are polymorphisms in the virus population for pathogenicity. The viral *AVR* genes responsible for eliciting the defense reaction, or for resistance breaking, have been identified in many instances (García-Arenal and McDonald, 2003; Janzac *et al.*, 2009;

The product of allele *A* at a certain locus in the host genotype interacts with the product of the virulence allele V_A in the pathogen, allowing infection (+), while this interaction does not occur with the product of allele V_a, resulting in a lack of susceptibility (−) or resistance. Similarly, the product of allele *a* in the host interacts with the product of allele V_a in the pathogen, allowing infection, but not with the product of allele V_A. In a pure matching-allele model, in the host genotype *A*/− the relative fitness of the pathogen genotype with allele V_A is 1, while that of the pathogen genotype with allele V_a is 0, the opposite being true in the host genotype *aa*, and there are no fitness penalties for pathogenicity. Here alleles *A* and *a* are represented as dominant and recessive, respectively, but this is not a requirement of the model.

TABLE I Characterized genes conferring quantitative, genotype-specific resistance to viruses

	Protein	Plant species	Virus targets	AVR factor	References
Dominant genes					
Cloned					
N	TIR–NB–LRR	*Nicotiana tabacum*	Tobamoviruses	Replicase/ helicase	Padgett *et al.* (1997) and Whitham *et al.* (1994)
Rx1	CC–NB–LRR	*Solanum andigena*	PVX	Coat protein	Bendahmane *et al.* (1997, 1999)
Rx2	CC–NB–LRR	*Solanum acaule*	PVX	Coat protein	Bendahmane *et al.* (1997, 2000)
Sw-5	CC–NB–LRR	*Solanum lycopersicum*	TSWV, TCSV, GRSV	Movement protein	Bromonschenkel *et al.* (2000)
HRT	CC–NB–LRR	*Arabidopsis thaliana*	TCV	Coat protein	Cooley *et al.* (2000)
RCY1	CC–NB–LRR	*Arabidopsis thaliana*	CMV	Coat protein	Takahashi *et al.* (2002)
Y-1	TIR–NB–LRR	*Solanum tuberosum*	PVY		Vidal *et al.* (2002)
Tm-2/*Tm-2*^{2}	CC–NB–LRR	*Solanum peruvianum*	ToMV, TMV	Movement protein	Lanfermeijer *et al.* (2003, 2005), Weber and Pfitzner (1998), and Weber *et al.* (2004)

(*continued*)

TABLE I (*continued*)

	Protein	Plant species	Virus targets	AVR factor	References
Rsv1	CC–NB–LRR	*Glycine max*	SMV	P3 protein	Hajimorad *et al.* (2005) and Hayes *et al.* (2004)
RT4-4	TIR–NB–LRR	*Phaseolus vulgaris*	CMV	Replicase/ helicase	Seo *et al.* (2006)
PvVTT1	TIR–NB–LRR	*Phaseolus vulgaris*	BDMV	Nuclear shuttle protein	Garrido-Ramirez *et al.* (2000) and Seo *et al.* (2007)
RTM1	Lectin-like	*Arabidopsis thaliana*	TEV	Coat protein	Chisholm *et al.* (2000) and Decroocq *et al.* (2009)
RTM2	Small heat-shock protein	*Arabidopsis thaliana*	TEV	Coat protein	Decroocq *et al.* (2009) and Whitham *et al.* (2000)
Tm-1	TIM barrel structure	*Solanum habrochaites*	TMV, ToMV	Replicase	Ishibashi *et al.* (2007) and Meshi *et al.* (1988)
Mapped to complex loci					
Tsw		*Capsicum*	TSWV	NSs protein	Margaria *et al.* (2007)
L^1, L^2, L^3, L^4	CC–NB–LRR	*Capsicum*	Tobamovirus	Coat protein	Tomita *et al.* (2008)
I	TIR–NB–LRR	*Phaseolus vulgaris*	BCMV		Vallejos *et al.* (2006)

Recessive genes					
Cloned					
pvr2^{i} + *pvr6*	*pvr2*: eIF4E	*Capsicum annuum*	PVMV, TEV	–	Caranta *et al.* (1996) and Ruffel *et al.* (2006)
pvr1/*pvr2*^{i}	eIF4E	*Capsicum chinense*	PVMV, PVY, TEV	VPg	Charron *et al.* (2008), Kang *et al.* (2005b), and Ruffel *et al.* (2002, 2006)
nsv	eIF4E	*Cucumis melo*	MNSV	3′-UTR	Díaz *et al.* (2004) and Nieto *et al.* (2006)
rym4/5	eIF4E	*Hordeum vulgare*	BaMMV, BaYMV	VPg	Kanyuka *et al.* (2004) and Stein *et al.* (2005)
mol^{1}/*mol*^{2}	eIF4E	*Lactuca sativa*	LMV	VPg and CI	Nicaise *et al.* (2003) and Roudet-Tavert *et al.* (2007)
rymv-1	eIF(iso)4G	*Oryza sativa* and *Oryza glaberrima*	RYMV	VPg	Albar *et al.* (2003, 2006)
sbmv1^{i}	eIF4E	*Pisum sativum*	PSbMV, BYMV	VPg	Bruun-Rasmussen *et al.* (2007), Gao *et al.* (2004), and Johansen *et al.* (2001)
pot-1	eIF4E	*Solanum habrochaites*	PVY, TEV	VPg	Ruffel *et al.* (2005) and Schaad *et al.* (2000)

Kang *et al.*, 2005a; Maule *et al.*, 2007). Virtually all classes of virus-encoded protein have been shown to have the potential to be AVR factors in different plant–virus systems (e.g., Table I). Thus, monogenic dominant resistance of plants to viruses, expressed as HR or as ER, conforms to a GFG model of host–pathogen interaction.

The other major model of host–pathogen interaction is the MA model. Its key feature is that infection requires a specific match between host and parasite genes (Fig. 1). Hence, it is at odds with the GFG model since "recognition" of the pathogen by the host leads to susceptibility rather than to resistance. In a pure MA system, pathogenicity on all host genotypes (i.e., "universal pathogenicity") cannot exist, an important difference with the GFG model (Agrawal and Lively, 2002). Although data from plant–pathogen systems have been mostly analyzed under the GFG model, the MA model could better fit some types of interactions. One obvious instance is recessive resistance to plant viruses. In contrast to resistance to cellular plant pathogens, a high percentage (35%) of monogenic resistance of plants to viruses is recessive (Kang *et al.*, 2005a; Khetarpal *et al.*, 1998). Polymorphisms for recessive resistance are in fact polymorphisms for impaired susceptibility, and this type of resistance is most often expressed as immunity at the cell level (Díaz-Pendón *et al.*, 2004; Kang *et al.*, 2005a; Maule *et al.*, 2007). Several recessive resistance genes have been cloned and sequenced (Table I) (Truniger and Aranda, 2009), and in all instances they encode translation initiation factors, either eIF4E, eIF4G, or their isoforms. Polymorphisms for pathogenicity on recessive resistant host genotypes have been described for many systems, and the viral gene products responsible for the expression or the breakdown of the resistance have been identified in most cases as the viral genome-linked protein (VPg), which is thought to interact with the initiation factors for cap-independent translation to occur (Maule *et al.*, 2007; Palukaitis and Carr, 2008; Truniger and Aranda, 2009). One notable exception is the system MNSV–melon, in which the pathogenicity determinant has been mapped to the 3′-UTR of the viral genomic RNA (Díaz *et al.*, 2004). It has been proposed that interaction of the 3′-UTR of MNSV and the eIF4E is required for messenger circularization and translation (Truniger *et al.*, 2008). Thus, available information is compatible with the adequacy of the MA model to explain plant–virus interactions determined by recessive resistance systems.

Resistance to viruses in plants may also be polygenically inherited. Polygenic resistance is usually expressed as quantitative or partial resistance, in which within-host multiplication of the virus is reduced. Few QTLs for virus resistance have been mapped (Maule *et al.*, 2007), but polygenic resistance has been used in crop breeding for virus disease control, and virus genotypes overcoming these resistances have been reported (García-Arenal and McDonald, 2003; Khetarpal *et al.*, 1998).

Also, quantitative resistance of Arabidopsis to CMV depended on host–virus genotype × genotype interaction (Pagán *et al.*, 2007). Thus, there is evidence showing that the outcome of the host–virus interaction again depends on the specific plant and virus genotypes.

The other major defense strategy of plants against pathogens is tolerance. Tolerance has received considerably less attention from scientists than resistance, and its use for viral disease control has been limited by obvious difficulties of breeding for increased tolerance, as phenotype evaluation can only be done at later stages of the plant's life cycle. Also, the mechanisms of tolerance are poorly understood, but they may be related to the ability of the plant to modify its life history program upon infection (Pagán *et al.*, 2008). The genetic control of tolerance may be monogenic or, most often, polygenic (Clarke, 1986). Tolerance depends on the interacting virus and plant genotypes (Pagán *et al.*, 2008). Accordingly, virus genotypes able to overcome tolerance in crops have been described and, at least in one case, ZYMV in melon, tolerance-breaking genotypes have been shown to become prevalent in the virus population after the extensive use of tolerant varieties (Desbiez *et al.*, 2002, 2003). This was a quite unexpected finding, because as tolerance does not affect the within-host multiplication of the virus it was traditionally considered not to exert a selection pressure upon it. However, recent theoretical analyses have shown that tolerance, through reducing virulence, will select for virus genotypes with an increased within-host multiplication, as far as virulence and multiplication are linked (van den Bosch *et al.*, 2006), which may explain these observations.

In summary, no matter the type of plant defense against virus infection, there is evidence that the outcome of the plant–virus interaction depends on the interacting plant and virus genotypes, thus fulfilling this condition for plant–virus coevolution to occur.

IV. GENETIC VARIATION OF RESISTANCE AND PATHOGENICITY

For evolution to occur there must be genetic variation for the relevant trait. In the previous section we have shown that the outcome of plant–virus interactions depends on the specific plant and virus genotypes, and this is evidence for genetic variability in resistance or tolerance and pathogenicity. Analysis of the patterns of variability of plant genes determining resistance, and of the viral genes determining pathogenicity, further supports the hypothesis that plants and viruses coevolve. The available evidence derives mostly from analyses of interactions resulting in qualitative resistance, either dominant or recessive, and thus conforming to the GFG or MA models.

A. Variability of resistance and pathogenicity under the gene-for-gene model

GFG interactions between plant and pathogens have been much analyzed and, in recent years, knowledge on the structure of R and AVR proteins, on their molecular variation and on the mechanisms underlying recognition, has made enormous progress. This is also the case for GFG plant–virus interactions. However, evidence supporting plant–virus coevolution is sparse, comes from different pathosystems, and detailed analyses of the variation of R and AVR in the same system are lacking.

1. *R*-gene variability

Most molecularly characterized genes that determine dominant qualitative resistance to viruses are involved in GFG-like plant–virus interactions and resistance is expressed as either an ER or a HR. Exceptions to this include the Arabidopsis genes *RTM1* and *RTM2*, which confer resistance to systemic colonization by TEV, and the tomato gene *Tm1* that encodes an inhibitor of ToMV replication (Chisholm *et al.*, 2000; Ishibashi *et al.*, 2007; Whitham *et al.*, 2000). All resistance genes that determine an ER or HR reaction upon virus inoculation encode proteins (R proteins) that contain nucleotide-binding site (NB) and leucine-rich repeat (LRR) domains, with either TIR or CC domains at their N-terminal regions (Table I). No function other than resistance is known for this protein class, and many copies of NB–LRR protein-encoding genes occur in plant genomes (Dangl and Jones, 2001; Friedman and Baker, 2007).

Most NB–LRR *R* genes to plant pathogens occur in complex loci, formed by tightly linked homologous genes (Hulbert *et al.*, 2001). This is also the case for *R* genes targeting different viruses in different plant species, for instance, the *N* gene of resistance to TMV in *Nicotiana tabacum* (Whitham *et al.*, 1994), the *Rx1* and *Rx2* genes of resistance to PVX in *Solanum tuberosum* and *S. acaule* (Bendahmane *et al.*, 1999, 2000), the *HRT* gene of resistance to TCV in *Arabidopsis thaliana* (Dempsey *et al.*, 1997; McDowell *et al.*, 1998), the *Y-1* gene of resistance to PVY in *S. tuberosum* (Vidal *et al.*, 2002), the *Rsv1* gene of resistance to SMV in soybean (Hayes *et al.*, 2004), or the *L* gene of resistance to tobamoviruses in *Capsicum* spp. (Tomita *et al.*, 2008). Often, resistance genes to viruses in complex loci are allelic or tightly linked to resistance genes against other pathogens or herbivores, as is the case for *Rx2* and *Gpa3* (*Globodera pallida*) and *R1* (*Phytophthora infestans*) in potato or *HRT* and *RPP8* (*Hyaloperonospora parasitica*) in Arabidopsis (Bendahmane *et al.*, 2000; Cooley *et al.*, 2000). Duplications and recombination through unequal crossover seem to be a major mechanism in the evolution of *R* genes and a way to generate new specificities (Friedman and Baker, 2007). Indeed, reported mutation rates at *R* genes are high; thus, the frequency of reversion to susceptibility to

TMV in an *Nn* population of tobacco is ~1/2000 (Whitham *et al.*, 1994), which is better explained by unequal crossing over causing deletions between repetitive sequences than by point mutations, considering the spontaneous rate of nucleotide substitutions in eukaryotes (Drake *et al.*, 1998). Recombination may occur between linked genes within complex loci (e.g., Hayes *et al.*, 2004; Whitham *et al.*, 1994) or between unlinked disease resistance genes, as shown for *Rx1*, *Rx2*, and *Gpa2*, which locate at different chromosomes in the potato genome (Bendahmane *et al.*, 2000). It has been shown that virus infection promotes recombination in the host plant genome with transgeneration effects (Kovalchuk *et al.*, 2003; Molinier *et al.*, 2006). Hence, the appearance of new recognition specificities through recombination in *R* genes could be favored by infection and play an important part in plant–virus coevolution (Friedman and Baker, 2007), a hypothesis to be analyzed.

In addition to recombination, point mutation is another major source of genetic variation in *R* genes. Evidence for diversifying selection, compatible with plant–pathogen coevolution, has been reported for *R* genes conferring resistance to cellular plant pathogens (e.g., Allen *et al.*, 2004; Dodds *et al.*, 2006; Mauricio *et al.*, 2003; Parniske *et al.*, 1997; Rose *et al.*, 2004; Wang *et al.*, 1998). Diversifying selection affects mostly the LRR domain, which is associated to specificity of recognition in R. Diversifying selection has not been demonstrated for *R* genes to viruses, but characterization of the single-gene locus alleles *lptm2*/*Tm2*^{2} of *S. peruvianum*, and *Tm2* of *S. habrochaites*, in which alleles *Tm2* and *Tm2*^{2} confer resistance to different genotypes of ToMV, showed that the resistance alleles differ from one another and from the susceptibility allele *lptm2* by a reduced number of mostly nonsynonymous nucleotide changes (Lanfermeijer *et al.*, 2003, 2005).

Under the GFG model of host–pathogen coevolution, fitness costs of resistance and pathogenicity are required for stable polymorphism at these traits to occur in host and pathogen populations (Fig. 1). Costs of resistance have been much reviewed (Bergelson and Purrington, 1996; Bergelson *et al.*, 2001; Brown, 2003; Mauricio, 1998): evidence is controversial and there is none for any resistance factor to viruses. However, there is indirect evidence that resistance may be costly: artificial evolution of *Rx* by introducing random point mutations in the LRR domain resulted in the appearance of variants with new specificities, which showed enlarged recognition of PVX genotypes or even of distantly related viruses (Farnham and Baulcombe, 2006). Since alleles with these enlarged recognition abilities do not occur in nature, these results suggest that fitness penalties constrain the evolution of *R* genes.

Conclusions on adaptive evolution of R proteins should consider several traits that show that interactions under the GFG model are certainly more complex than originally considered. On the one hand,

the process of plant–pathogen recognition itself may involve other proteins than R and AVR, so that recognition of AVR is indirect involving multiprotein complexes. Indirect recognition may be more common than direct R–AVR interaction, and it has been shown to occur in all characterized plant–virus systems (Caplan *et al.*, 2008a,b; Jeong *et al.*, 2008; Ren *et al.*, 2000; Tameling and Baulcombe, 2007). It has been proposed that the mode of R–AVR recognition, direct or indirect, will affect the evolution of *R* and *AVR*, indirect recognition resulting in balancing selection in *AVR* and *R* (Van der Hoorn *et al.*, 2002), but evidence in support of this hypothesis is scant, and there is none from plant–virus systems. Also, *R* genes often determine the unspecific recognition of different virus species within the same genus, rather than specific recognition of viral genotypes, for example, the *Sw5* of *S. lycopersicum* determines resistance against different tospoviruses, the *I* gene of *Phaseolus vulgaris* determines resistance to different potyviruses, while the *N* gene of *Nicotiana* determines resistance to different tobamovirus (Bromonschenkel *et al.*, 2000; Fisher and Kyle, 1994; Padgett and Beachy, 1993). Thus, it is not known which species within these genera exerted a selection on the host plant leading to the appearance of resistance, or if resistance to other virus species is due to shared structures in AVR or just coincidental. Last, resistance/susceptibility alleles may be more complex than originally considered from inheritance analyses, and rather than resulting from variations in single-gene loci, be due to rearrangements resulting in gain/loss of several cistrons encoding NB–LRR proteins, as shown for *Rsv1* (Hayes *et al.*, 2004) or as proposed to explain the evolution of the *L* locus within the genus *Capsicum* (Tomita *et al.*, 2008). How all these traits of GFG systems would affect selection pressures of viruses on plants and, hence, the evolution of *R* genes, remains to be explored, but certainly should be considered both when analyzing evidence apparently in support of plant–virus coevolution and when developing theoretical models of host–pathogen coevolution.

2. *AVR*-gene variability

The first AVR factor identified in a plant pathogen was the capsid protein (CP) of TMV, which elicits the HR defense response triggered by the N' resistance gene in *Nicotiana* spp. (Knorr and Dawson, 1988; Saito *et al.*, 1987). Since then, it has been shown that many other virus-encoded proteins may act as an AVR factor on different R proteins (see Table I). For example, within the genus *Tobamovirus*, the CP of TMV is the AVR factor for N'; the p50 helicase domain of the RNA-dependent polymerase (RdRp) of TMV is the AVR for the *N* gene in *Nicotiana*, and the movement protein of ToMV is the AVR for *Tm2* and $Tm2^2$ in tomato (Meshi *et al.*, 1989; Padgett *et al.*, 1997; Weber and Pfitzner, 1998). Within the *Potyvirus* genus, the NIa protease of PVY is the AVR factor for *Ry* in potato

(Mestre *et al.*, 2003), the P3 protein of SMV elicits *Rsv1* in soybean (Hajimorad *et al.*, 2005), or the cylindrical inclusion helicase of TuMV elicits *TuRB01* of *Brassica* (Jenner *et al.*, 2000). Within the *Cucumovirus* genus the CP of CMV is the AVR for *RCY1* in *Arabidopsis* and the 2a protein for *RT4-4* in *Phaseolus* (Seo *et al.*, 2006; Takahashi *et al.*, 2002). Further examples can be found in Kang *et al.* (2005a) or Maule *et al.* (2007). Because it is necessary that virus-encoded proteins interact with host factors for completion of the virus life-cycle within the infected host, they can be considered as pathogenicity effectors, as is the case for AVR factors of cellular plant pathogens (Jones and Dangl, 2006).

While AVR of cellular plant pathogens may avoid recognition by R through a large array of mechanisms including point mutations, recombination and even the deletion of AVR itself (Friedman and Baker, 2007; Sacristán and García-Arenal, 2007), obviously this cannot be the case for plant viruses, which have small genomes encoding multifunctional proteins. Changes in recognition of viral AVR by R proteins depend on one to few amino acid substitutions (Harrison, 2002; Maule *et al.*, 2007). For many R factors only one or few *avr* genotypes have been reported, with no evidence of diversifying selection on *AVR/avr*. Thus, virulence on *N* is extremely rare, occurring only in tobamovirus species with a restricted geographical distribution (García-Arenal and McDonald, 2003). Similarly, although pathogenicity on *Rx* is due to mutations at two positions in PVX CP (Goulden *et al.*, 1993), in nature only one strain, PVX-HB, with limited distribution, has been reported with these mutations and phenotype (see García-Arenal and McDonald, 2003). On the other hand, different mutations in the CP of TMV led to breakage of *N'*-mediated resistance in tobacco. In an elegant series of papers, Culver and colleagues have analyzed a large set of TMV CP variants, obtained by site-directed mutagenesis, that totally or partly overcame *N'*-mediated resistance, and determined that the maintenance of the CP three-dimensional structure is essential for *N'* elicitation (see Culver, 2002). Similarly, field isolates of PMMoV that overcome partially or totally L^3 resistance in pepper, inducing systemic necroses or mosaics, respectively, differ from the AVR genotype in few nucleotide substitutions resulting in different amino acid changes in the CP that may destabilize its three-dimensional structure. Interestingly, although different resistance-breaking genotypes have been characterized, CP mutations resulting in resistance breakage occur only in certain combinations, and the different resistance-breaking genotypes have different geographical distributions, having been reported either in the Mediterranean or in Japan (Berzal-Herranz *et al.*, 1995; Hamada *et al.*, 2002, 2007; Tsuda *et al.*, 1998), which suggests that only certain evolutionary pathways may lead to pathogenicity on L^3. Also, in TSWV different genotypes virulent on pepper carrying the resistance gene *Tsw* have been reported in different areas of the Mediterranean basin, and most of the

few nucleotide substitutions in the *AVR* gene encoding Nss protein resulted in amino acid substitutions (Margaria *et al.*, 2007).

Limited polymorphism in resistance-breaking genotypes suggests that there are fitness penalties associated with increased pathogenicity. Although experimental estimates of putative costs of pathogenicity are few, evidence for these costs derives from several systems. Thus, there is evidence for selection against PVX CP mutants pathogenic on *Rx* (Goulden *et al.*, 1993), and no field isolate of PVY has been reported to overcome *Ry* in potato, although resistance-breaking mutants in the NIa protein were obtained experimentally (Mestre *et al.*, 2003). Also, fitness penalties could relate to functions other than virus multiplication: RRSV strains overcoming *Irr* resistance in raspberry had a decreased transmission both by nematodes and through the seed in alternate hosts (Hanada and Harrison, 1977; Murant *et al.*, 1968). TuMV genotypes overcoming *TuRB01* resistance in rape were outcompeted by avirulent ones in susceptible hosts. Assays were done with engineered *avr* mutants with no second-site mutations, thus providing evidence for a cost due to a pleiotropic effect of the *avr* mutation (Jenner *et al.*, 2002a). Fitness costs have also been reported for TuMV mutants overcoming a second resistance gene, *TuRB04* (Jenner *et al.*, 2002b). At odds with other reports, the data in Jenner *et al.* (2002a,b) allow us to estimate the fitness of virulent mutants relative to avirulent ones, which shows values of about 0.50 (Sacristán and García-Arenal, 2007). Similarly, competition experiments among field PMMoV isolates virulent or avirulent on L^3 resistance in pepper also showed high differences in relative fitness; the fitness of *avr* isolates being on average 0.47 relative to that of *AVR* isolates (Fraile *et al.*, 2010). Interestingly, evidence for fitness penalties was also provided by the dynamics of *avr*/*AVR* genotypes of pepper-infecting tobamoviruses in the field, as compared with the relative acreage of the different *L* alleles deployed over a period of more than 20 years (Fraile *et al.*, 2010); to our knowledge, the only long term analysis of avr/AVR dynamics for a plant–virus system.

Consistent evidence for pathogenicity-associated fitness penalties in plant viruses contrasts strikingly with the conflicting results for fungi and oomycetes (Sacristán and García-Arenal, 2007) and may be highly relevant for the analysis of the durability of the resistance of crops to viruses.

B. Variability of resistance and pathogenicity under the matching-allele model

Recessive resistance (i.e., lack of susceptibility) to plant viruses may be best interpreted under the MA model. Mutations leading to resistance can be countered by mutations in the virus, thus restoring compatibility on the mutated host gene. All evidence on the structure of VPg proteins and

on the mutations resulting in overcoming recessive resistance strongly suggest a direct interaction between the eIF4E/eIF(iso)4G and the VPg, required for infection (Charron *et al.*, 2008; Hebrard *et al.*, 2008; Truniger and Aranda, 2009). Although interest in recessive resistance is more recent than on dominant resistance, and fewer pathosystems have been analyzed in detail for the variation of either the resistance or the pathogenicity determinants, they have provided the best evidence so far for plant–virus coevolution.

The system for which more information is available is the pepper–PVY interaction determined by the *pvr2* locus of *Capsicum*, encoding eIF4E, and the virus VPg. In the only large-scale survey of the variation of a gene encoding resistance to a virus, Charron *et al.* (2008) have reported 10 *pvr2* alleles in a worldwide survey of accessions of *Capsicum annuum*. The most common allele, with a 0.4 frequency, $pvr2^{+}$, determines susceptibility to PVY and to another pepper-infecting potyvirus, TEV, while alleles $pvr2^{1}$–$pvr2^{9}$, determine resistance, with different specificities toward different PVY and TEV genotypes. *pvr2* alleles conferring resistance differ from $pvr2^{+}$ by 1–4 amino acid substitutions at nine positions in two domains of eIF4E, polymorphic sites being located in the surface of the protein, and there is evidence for diversifying selection at these domains. Amino acid substitutions resulting in resistance impair the physical interaction of eIF4E and the VPg of incompatible virus genotypes. On the virus side, up to 11 amino acid changes in the central region of PVY VPg have been described to determine pathogenicity on resistance alleles of *pvr2*, and, again, there is evidence that positive selection on these sites leads to diversification of the VPg. Overcoming one *pvr2* allele does, or does not, confer pathogenicity on other alleles, pending on the specific mutations (Ayme *et al.*, 2007; Moury *et al.*, 2004), as corresponds to a MA interaction. Thus, data on the pepper/PVY system provides evidence that the direct interaction *pvr2*/VPg drives the coevolution between resistance and pathogenicity leading to diversifying selection at both genes.

The MA model predicts that polymorphisms for pathogenicity and resistance will be maintained by negative frequency-dependent selection, with no need of resistance or pathogenicity costs (Fig. 1) (Agrawal and Lively, 2002). It has been argued that pure GFG and MA models are extremes of a continuum, in the inside of which the MA model should be modified to admit partial infection, that is, the parasite infects, but reproduces less effectively, and the host suffers less intensely from parasitism than in a "full infection." Within this continuum, costs of resistance and pathogenicity would exist as a function of the degree of success of partial infection (Agrawal and Lively, 2002; Parker, 1994). Functional assay of the 10 eIF4E variants in yeast failed to detect differences in the efficiency of cap-dependent mRNA translation (Charron *et al.*, 2008), strongly suggesting that there is no fitness penalty for PVY resistance,

although this may not be universal for eIF4E-mediated resistance to potyviruses (e.g., Kang *et al.*, 2005a). The relative fitness of different VPg mutants overcoming allele $pvr2^3$ was analyzed in pepper genotypes homozygous either for $pvr2^3$ or for the susceptibility allele $pvr2^+$, and in the susceptible host *Nicotiana clevelandii*. The various pathogenic PVY genotypes differed in fitness in all three hosts, but some of them were as fit in susceptible pepper and *N. clevelandii* plants as the nonpathogenic wild type (Ayme *et al.*, 2006). Again, in this respect the *pvr2*/PVY system corresponds to a modified MA model.

Another well-characterized system is the rice–RYMV interaction. Recessive resistance in rice to RYMV is conferred by *rymv1*, encoding eIF(iso)4G (Albar *et al.*, 2006). Different mutations in RYMV VPg determine pathogenicity on the different resistance alleles at *rymv1*. Mutations at five amino acid positions in the central region of the VPg are involved in overcoming *rymv1–2*, and there is evidence of diversifying selection at these positions (Pinel-Galzi *et al.*, 2007). A high percentage (~17%) of field isolates of RYMV from Africa were pathogenic on either allele *rymv1–2* or *rymv1–3*, and fewer (~5%) on both (Traoré *et al.*, 2006). No fitness penalty for pathogenicity on *rymv1–2* was found in passage competition experiments with nonpathogenic genotypes (Sorho *et al.*, 2005).

V. COSTS OF PATHOGENICITY AND RESISTANCE DURABILITY

The use of resistance bred into cultivars is a preferred strategy for the control of infectious diseases of plants. However, the advantages of resistance for the control of plant pathogens are countered by the common short life of the resistant variety, as the protection conferred by the resistance factor may be lost due to the increase in frequency of resistance-breaking genotypes in the pathogen's population (Kang *et al.*, 2005a; Khetarpal *et al.*, 1998; Maule *et al.*, 2007). Hence, a major interest in the study of plant–pathogen coevolution is to understand the factors that lead to resistance breakage, and to predict the durability of the protection conferred by resistance factors. As resistance durability, by definition (Johnson, 1979), can only be known *a posteriori*, this is rather a difficult task.

It has long been observed that, on average, the life of resistance factors deployed against viruses is considerably longer than that deployed against cellular plant pathogens. Thus, the life of resistance factors deployed against fungi and oomycetes was of 7.3 years (average for 27 host–pathogen systems from data in McDonald and Linde, 2002), while for viruses it was of 12.8 years (average for 25 host–pathogen systems from data in García-Arenal and McDonald, 2003) (Fig. 2). While earlier analyses identified the inheritance and mechanisms of the resistance as a

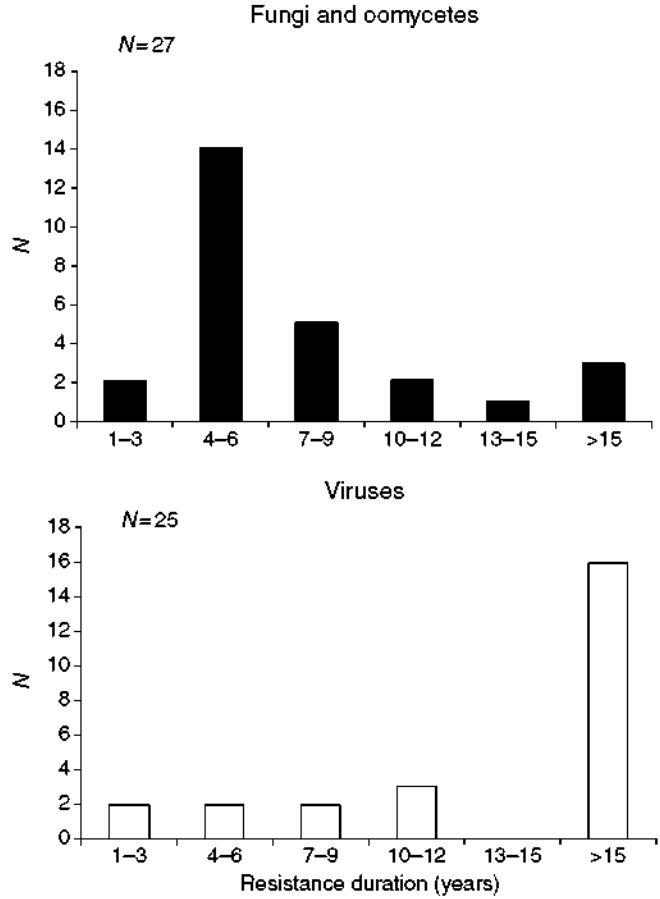

FIGURE 2 Duration of resistance factors bred into crops. The distribution of the effective duration of resistance factors to fungi and oomycetes over 27 pathosystems, or to viruses over 25 pathosystems is shown. Mean duration of resistance was 7.3 ± 4.0 and 12.8 ± 4.9 years (mean ± standard deviation) to fungi and oomycetes and to viruses, respectively. Median duration values were 4–6 and over 15 years for resistance to fungi and oomycetes and to viruses, respectively. Data are from García-Arenal and McDonald (2003) and McDonald and Linde (2002).

major factor in its durability (Fraser, 1990), the capacity of the virus to evolve as a factor determining resistance durability received more attention later on. Thus, the appearance of resistance-breaking virus genotypes on 10 monogenic dominant resistance factors was partially related to the number of amino acid substitutions required to convert the avirulence factor into a virulent one (Harrison, 2002). The analysis of the effective life of 50 resistance factors (including monogenic dominant, monogenic

recessive, and polygenic) in relation to a compound risk index based on life history traits affecting the evolutionary potential of the virus, indicated a relationship between evolutionary potential and resistance durability (García-Arenal and McDonald, 2003). While this analysis suggested a broad relationship between the evolutionary potential of the virus and resistance durability, it failed to explain why different resistance factors deployed to control the same virus species in the same or in different host species often had different effective lives. Janzac *et al.* (2009) have re-examined the relationship between virus evolvability and resistance durability, not finding a relationship between the risk index proposed by García-Arenal and McDonald (2003) and resistance duration for a set of 14 dominant and 5 recessive monogenic resistance factors in 20 pathosystems. They neither found a relationship between the nucleotide diversity of the genes encoding for the avirulence factors in the different virus species considered. However, they found a significant association between the evolutionary constraints on avirulence, measured as a relationship between nucleotide substitutions at nonsynonymous and synonymous sites (d_N/d_S ratios) and resistance durability. While in both studies association and correlation between virus factors and resistance durability was always weak, regardless of statistical signification, it was clearly determined that the inheritance of the resistance was not a factor in its durability (García-Arenal and McDonald, 2003; Janzac *et al.*, 2009).

Thus, current evidence points to the evolvability of the avirulence factor itself as a predictor to the durability of a resistance factor. For many analyzed pathosystems, resistance-breaking virus isolates have been reported to occur in the field without becoming prevalent in the virus population (García-Arenal and McDonald, 2003; Janzac *et al.*, 2009). Hence, all evidence suggests that the cost of pathogenicity may be a major determinant of the durability of a resistance. It is important to consider that functional constraints on protein evolution, as uncovered by the d_N/d_S ratio, would explain only in part the costs of pathogenicity. This cost, that is, the selection against unnecessary avirulence in the absence of resistance, will depend also on other evolutionary factors, some of which will be determined by intrinsic traits of the small genomes of viruses. An example would be constraints to recombination due to multifunctionality of genes, or due to epistatic interaction both within and among genes (Escriu *et al.*, 2007; Lefeuvre *et al.*, 2007; Martin *et al.*, 2005; Sanjuán *et al.*, 2004). Other factors will be related to the virus life history rather than to the virus genome structure. This will be the case for effective population size or gene and genome flow between viral populations. Thus, the relationship between costs of pathogenicity and resistance durability is complex, and much in need of further study.

VI. CONCLUDING REMARKS

Although it is currently assumed that plants and viruses coevolve, evidence in support of this hypothesis is quite weak. A major conclusion of this review is that research in several areas related to plant–virus coevolution is badly needed and should be encouraged.

A major limitation of current knowledge is that most data taken as evidence for plant–virus coevolution derive from the analysis of highly virulent viruses infecting crops, and is mostly limited to the virus side, that is, to the evolution of the virus population in response to the use of resistance factors in the crop directed at controlling virus-induced diseases. Few data are available on the evolution of the host in response to virus infection. The occurrence in crops and their wild relatives of resistance factors effective against viruses is usually taken as evidence of virus–host coevolution, but those factors could have evolved under the pressure of other pathogens or herbivores. It has been proposed that diversification of identified virus taxa, which are those infecting crops, occurred after the expansion of agriculture, and was driven by agriculture-associated ecological changes (Fargette *et al.*, 2008; Gibbs *et al.*, 2008). Little is known of virus–plant interactions in wild ecosystems, or on whether these interactions are pathogenic or mutualistic. There is an urgent need of studies on the occurrence of viruses in wild plants and on the effect of virus infection on wild plant fitness. Such studies are a prerequisite to analyze plant–virus coevolution and put it in a similar ground to current knowledge on the coevolution of plants and cellular pathogens, which has been carried on for decades.

In recent years, huge progress has been achieved in understanding the molecular aspects of plant–virus interactions, as determined by both dominant and recessive resistance (Moffett, 2009; Truniger and Aranda, 2009). Other defense mechanisms, such as quantitative resistance or tolerance, have received little attention. Population genetic analyses of resistance and pathogenicity factors are still scarce, and more effort is needed also in this area. Notably, there are few instances of the joint analysis of resistance and pathogenicity in the same plant–virus system, which is a drawback to derive general conclusions. Analyses such as those published for the pepper–PVY and rice–RYMV systems are in urgent need for GFG-like interactions.

Current knowledge on the molecular mechanisms underlying virus recognition by plants, defense reactions, and pathogenicity factors should be considered by scientists involved in theoretical analyses on host–pathogen coevolution. Ecological and epidemiological factors are currently being incorporated into theoretical models (e.g., Tellier and Brown, 2007, 2009), but this is not yet the case for mechanistic aspects

such as broad recognition of groups of taxa (i.e., reduced specificity of recognition) or recognition involving multiprotein complexes. Theoreticians should also consider the peculiarities of viruses as pathogens and as evolving entities, for instance how would high pathogenicity costs resulting from limited evolvability affect current models of host–pathogen coevolution.

If the analysis of plant–pathogen coevolution is a promising area of research, with deep academic and applied consequences, this is even more so for the specific case of plant–virus coevolution, a field still in its infancy. We hope that this review will contribute to drive the attention of scientists to this most interesting field.

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