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Genetic resistance for the sustainable control of plant virus diseases: breeding, mechanisms and durability

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Abstract Plant viruses are important agricultural pathogens, and are responsible for a significant number of commercially relevant plant diseases. There are very few efficient control measures for viral diseases, but the use of genetic resistance appears to be the most promising strategy, often conferring effective protection without additional costs or labour during the growing season, and without damaging the environment. Sources of virus resistance have been identified for most crop species, and many resistant cultivars are already commercially available and of widespread cultivation; however, much remains to be learned about genetic resistance. This review article considers three main aspects that require intense investigation. First, we review the identification of sources of resistance and how plant breeders and pathologists have focused on aspects of the breeding process particularly relevant to viruses, such as germplasm screening and the dissection of resistance phenotypes. Second, we review how molecular mechanisms controlling resistance have been unravelled, looking at case studies where resistance mechanisms are now understood in detail for each stage of the infection cycle. Third, we turn to the durability of resistance in a global context, examining factors that influence durability and how this can be predicted. We conclude with a short discussion of the technological and scientific opportunities provided by recent advances in the field.

Keywords Genetic resources · Plant breeding · Plant virus · Resistance durability · Resistance genes · Resistance mechanisms

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Introduction

Plant viruses are responsible for a significant proportion of crop diseases and are very difficult to combat due to the scarcity of effective countermeasures, placing them among the most important agricultural pathogens. Most emerging infectious diseases of plants are caused by viruses (Anderson et al. 2004), as exemplified by recent widespread epidemics of tospoviruses (Prins and Goldbach 1998) and geminiviruses (Fargette et al. 2006), outbreaks of *Plum pox virus* in stone fruit trees in the northern hemisphere, and outbreaks of *Pepino mosaic virus* in tomato crops in Europe and North America. Viral diseases can affect food quality as well as reducing yields, yet

quality is also affected by measures such as spraying with pesticides to kill off insect vectors. An alternative control strategy for viruses is the use of crop cultivars or varieties that are genetically resistant. These resistant genotypes carry a heritable trait or set of traits that are responsible for the suppression of virus multiplication or/and spread even under environmental conditions that favour virus infection in the given species. The use of genetic resistance is advantageous because it can provide effective protection with no additional cost implications for the producer during the growing season. It is also environmentally friendly and safe for the consumer. Most crop species have virus resistance traits available and in many cases cultivars with varying degrees of resistance have achieved commercial status. However, many issues concerning the use of genetic resistance for the sustainable control of viral diseases remain to be investigated. This review article is restricted to the discussion of 'natural' forms of resistance. The development and potential use of transgenic resistant varieties has been reviewed recently (Prins et al. 2008).

Breeding for resistance

The development of resistant cultivars that still produce high yields and excellent quality commodities remains a challenge for breeders (Koorneneef and Stam 2001; Strange and Scott 2005). Plant breeders and plant pathologists have traditionally approached breeding for resistance in successive steps, including (i) screening germplasm collections to identify sources of resistance and characterising their phenotypes; (ii) studying the mode of inheritance and identifying genetic markers for marker-assisted selection (MAS) (see Collard and Mackill 2008, for a comprehensive review); and (iii) introgressing resistance traits into elite cultivars and assessing performance of the new cultivars under pathogen challenge in the field (Kumar 1999). We will now consider these steps in detail, focusing on specific aspects of virus resistance.

Germplasm screening: plant and virus materials

Plant genetic diversity provides the raw material for breeding and plant improvement. Sources of resistance may already be available in the cultivar under development, but if not it can be obtained from other commercial cultivars, more distantly-related landraces and wild progenitors, and even other related species. The genetic variation for virus resistance in a single cultivar may be sufficient to develop virus-resistant lines in cross-pollinating crops, whereas self-pollinating crops tend to be more genetically uniform making such methods less productive. Incorporating further commercial cultivars in breeding programmes can be advantageous because this material has already been selected for alleles conferring high yield and quality, and even resistance to other pathogens. If further genetic diversity is required, it is possible to turn to landraces, which tend to be established, locally-grown cultivars usually consisting of a mixture of genotypes (Wintermantel et al. 1997), or wild progenitors, which may be useful sources of resistance. In some cases, resistance can be introduced from related species or genera, although this can be technically difficult and specialised techniques such as hybridisation may be necessary.

Screening methods include field exposure and inoculations under controlled conditions. Screening under field conditions is only possible in areas of high inoculum pressure, but this is an economical method for screening large germplasm collections under realistic commercial farming conditions, and provides a means to detect resistance to the virus and its vector (s). However, it is difficult to ensure homogeneous spatial and temporal distribution of the inoculum, and the presence of other pathogens and environmental variation can introduce unforeseen complexity into data interpretation. Controlled screens carried out in glasshouses or growth chambers are less representative of commercial growth conditions but they allow the amount and distribution of inoculum to be controlled and limit other sources of variation. The most appropriate choice of virus strain used for inoculation is also a crucial step: whether or not a crop shows resistance depends on both the plant and virus genotypes (Khetarpal et al. 1998). For this reason, resistance is very often strain-specific (see Fig. 1 for an example) (Harrison 2002). If data on strain diversity are available, it may be more appropriate to inoculate using the strain or strains that better represent field virus populations.

The above demonstrate that the conservation, characterisation and utilisation of both plant and virus

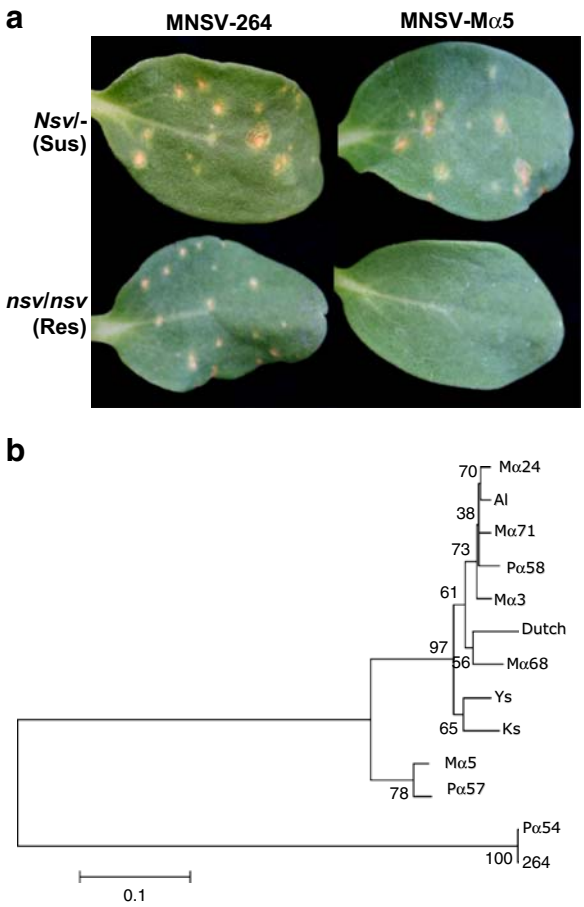

Fig. 1 Strain-specific resistance to *Melon necrotic spot virus* (MNSV) in melon (Díaz et al. 2004). **a** Cotyledons of plants of melon cvs Planters Jumbo (resistant genotype) and Tendral (susceptible genotype) inoculated with two different viral isolates. The isolate MNSV-264 can overcome resistance conferred by *nsv* (necrotic spots are indicative of a successful virus infection), whereas the isolate MNSV-α5 cannot. **b** Neighbour-Joining phylogenetic tree for the 3′-untranslated genomic regions of MNSV isolates. Isolates MNSV-264 and MNSV-α5 cluster into two different groups. The scale bars represents 0.1 nucleotide changes per nucleotide position

genetic diversity are important. Plant germplasm collections have been established in many countries and at most of the international crop research centres. Most of the world's preserved genetic resources are now in the public domain and, as a consequence of international agreements, are readily and freely available to breeders and researchers (Table 1) (Innes 1992; Babcock et al. 2007; Ferguson 2007). There are also many pathogen resources from which virus strains can be obtained (Table 1).

Identifying and dissecting resistance phenotypes

Many screens are based on the appearance of disease symptoms, but symptoms of viral diseases may be difficult to distinguish from unrelated physiological disorders. Furthermore, viral infections can be asymptomatic, a phenomenon termed tolerance by plant virologists. Thus, to distinguish infected from non-infected plants, and tolerant from resistant plants, it is essential to have an accurate, reliable and if possible rapid, convenient and inexpensive diagnostic method to monitor the presence and accumulation of viruses. Some of the methods used to analyse virus accumulation include sensitive serological tests and molecular detection techniques (Hull 2002). It is important to note that several non-genetic factors may affect the manifestation of resistance, including: (i) Differences in development rates between plants and/or accessions (*e.g.* Soler et al. 1998; Pokorny and Porubova 2006; Lunello et al. 2007). (ii) Inoculation method and dose of inoculum. Inoculation procedures vary with the virus and plant species, and should ideally achieve a 100% infection rate on susceptible plants. If the inoculum dose is too low, resistance can be overestimated; if too high, quantitative differences in resistance may remain hidden. Also, mechanical and vectored transmission may yield different results (*e.g.* Marco et al. 2003). (iii) Environmental conditions, including temperature (*e.g.* Mallor et al. 2003; Seifers et al. 2006; Kido et al. 2008). Thus, if tests for resistance are carried out under conditions that significantly differ from those that prevail in commercial fields, resistance assessments may be of little relevance.

Resistance screens therefore tend to incorporate the detection of the virus in non-inoculated leaves and also record symptom severity. These data demonstrate whether or not systemic infections occur, and show the accompanying symptoms. There also appears to be added value in determining the virus titer in inoculated and non-inoculated leaves at different times post-inoculation. This can show whether resistance involves complete or partial suppression of virus accumulation in inoculated and/or non-inoculated leaves (*e.g.* see Marco et al. 2003). Furthermore, the inoculation of protoplasts prepared from resistant plants (*e.g.* Arroyo et al. 1996; Díaz et al. 2004) can show whether or not resistance acts at the single cell level, although this type of analysis is often technically challenging.

Table 1 Public collections of genetic resources (plants and microorganisms)

Name	Acronym	Country	URL	Focus
National Plant Germplasm System (USDA)	NPGS	USA	http://www.ars-grin.gov/npgs/	Genetic diversity of plants
Tomato Genetic Resource Centre	TGRC	USA	http://tgrc.ucdavis.edu/index.aspx	Tomato germplasm
Grupo Consultivo para la Investigación Agrícola Internacional	CGIAR	USA	http://www.cgiar.org	Alliance of members, partners and international agricultural centres
International Centre for Tropical Agriculture	CIAT	Colombia	http://www.ciat.cgiar.org/index.html	Bean, cassava and forages resources
World Vegetable Centre	AVRDC	Taiwan	http://www.avrdc.org/about.html	Vegetable development and research
World Federation For Culture Collections	WFCC		http://wdcm.nig.ac.jp/hpcc.html	Culture collections in the world
LGC Standards	LGC	UK	http://www.lgcpromochem-atcc.com/	Cultures and bioproducts collections
North American Plants Collections Consortium	NAPCC	USA	http://www.ars-grin.gov/npgs/napcc.html	Botanical gardens
Nottingham *Arabidopsis* Stock Centre	NASC	UK	http://arabidopsis.info/	*Arabidopsis* stock
Escuela Técnica Superior de Ingenieros Agrónomos de Madrid	ETSIA	Spain	http://www.etsia.upm.es/DEPARTAMENTOS/biologia/documentos/GC-2000-Int.htm	Germplasm collection of crucifers
Botanic Gardens Conservation International	BGCI	England	http://www.bgci.org/	Plant conservation
Millennium Seed Bank Project	MSBP	UK	http://www.kew.org/msbp/index	Seed bank
Deutsche Sammlung Von Mikroorganismen Und Zellkulturen	DSMZ	Germany	http://www.dsmz.de/	Microorganisms, cell lines, and plant viruses collection
Cereal Knowledge Bank (CKB)	International Maize and Wheat Improvement Centre CIMMYT	Mexico	http://www.cimmyt.org/index.htm	Rice, maize and wheat scientific services
	International Rice Research Institute IRRI	Philippines	http://www.irri.org/	
National Centre For Agricultural Utilisation Research	NCAUR	USA	http://nrrl.ncaur.usda.gov/	Culture collection
United Kingdom National Culture Collection	UKNCC	UK	http://www.ukncc.co.uk/	Database of culture collection
Centro De Conservación Y Mejora de la Agrodiversidad Valenciana	COMAV	Spain	http://www.comav.upv.es/comav.html	Germplasm bank
Biodiversity International		Italy	http://www.bioversityinternational.org/	Agricultural biodiversity and germplasm collections
Common Access to Biological Resources and Information	CABRI		http://srs71.cabri.org/	Collections and biotechnological resources

Genetics of resistance

Classic analysis of resistance genetics involves crosses between resistant and susceptible lines and the characterisation of F_1, F_2 and backcross generations. This tends to be straightforward when resistance is manifested as a complete absence of the virus in resistant plants, but much more complex if resistance is partial, in which case virus titers and resistance thresholds must be determined in inoculated plants. In such complex cases, detailed characterisation of resistance phenotypes (as discussed above) can contribute significantly to correct experimental design. Resistance was a monogenic trait in 78% of the 179 host/virus combinations considered in the review by Khetarpal et al. (1998), but in the remainder it was oligogenic or polygenic. Among the monogenic examples, 51% of resistance traits

were dominant, 35% were recessive and the remainder were more complex, as incomplete dominance or dose-dependent. The analysis of polygenic resistance traits tends to be much more complex than monogenic or oligogenic traits, so researchers often focus on monogenic resistance because it can be studied and utilised more readily. This aspect of resistance breeding has been discussed in recent reviews (Khetarpal et al. 1998; Kang et al. 2005; Maule et al. 2007).

Resistance mechanisms

Susceptibility to a virus implies that the pathogen must be transmitted from plant to plant, and then must be capable of replication in the primary infected cells, movement to adjacent cells through plasmodesmata, colonisation of the whole plant from the initial infection foci using the vasculature, and further acquisition by vectors to reinitiate the infection cycle. Since the repertoire of viral products is very small due to the limited size of viral genomes, viruses need to recruit vector and plant factors to complete the steps of their infection cycle. Such factors must cooperate with viral products to confer susceptibility, and their absence, or their presence in a form that cannot be recognised by the corresponding viral component, may thus confer resistance. This has been termed passive resistance (Fraser 1990), as it does not require any activity by the plant. In genetic terms, host susceptibility factors would be encoded by dominant susceptibility alleles and resistance would thus be conferred by recessive resistance alleles (Fraser 1990). On the other hand, plants can also react to virus infections with extensive metabolic alterations (Culver and Padmanabhan 2007; Wise et al. 2007), which include the triggering of a range of defence mechanisms (for a recent review see Palukaitis and Carr 2008). If the virus cannot defeat such mechanisms, the plant is resistant. This kind of resistance (active resistance) is often conferred by dominant alleles (Fraser 1990).

The following sections consider case studies of passive and active resistance that have been characterised in varying amounts of detail, organised according to the stage of the viral cycle affected: plant-to-plant transmission, intracellular virus multiplication and virus translocation/accumulation (Fig. 2). We will refer to host genes that confer resistance in the host, and also to virus genes or sequences that control the virus's ability or inability to infect resistant hosts (virulence and avirulence determinants).

Resistance to plant-to-plant transmission

Primary infections are often initiated from contaminated plant propagules (normally seeds), through vector transmission from reservoir hosts, or through contact between mechanically-damaged host tissues and contaminated soil or residues from previous crops. In epidemiological terms, approximately 18% of viruses can be seed-transmitted in at least one of their hosts, whereas approximately 80% depend for transmission on vectors, mainly insects, but also nematodes, fungi and mites (Stacesmith and Hamilton 1988).

Seed transmission reflects complex and specific interactions between the virus and the combined physiology of two host plant generations (Carroll et al. 1981). Seed transmission may occur through direct embryo infection after fertilisation, or indirectly as a consequence of gametes being infected prior to fertilisation. Direct embryo infection must occur through maternal tissues, probably during a short time-window during embryo development that may be conditioned by environmental factors (Johansen et al. 1994; Wang and Maule 1994; Maule and Wang 1996; Wang et al. 1997). The infection of gametes could be determined by host factors, including those that allow the virus to infect meristematic tissues (Carroll and Mayhew 1976; Wang and Maule 1992, 1994). These two processes are not mutually exclusive, and it is likely that some viruses use both to achieve seed transmission (Maule and Wang 1996).

Resistance to seed transmission has been reported, but the underlying mechanisms have rarely been investigated in detail. One example is the resistance of barley (*Hordeum vulgare* cv. Modjo) to seed transmission of *Barley stripe mosaic virus* (BSMV), which is mediated by the recessive allele *rsm1*. The centromeric location of *rsm1* reduces the likelihood of finding markers for positional cloning because recombination is suppressed (Edwards 1995; Edwards and Steffenson 1996). Since the resistance is recessive, it may involve the loss of a functional host factor required for the replication or movement of BSMV (Zheng and Edwards 1990; Weiland and Edwards

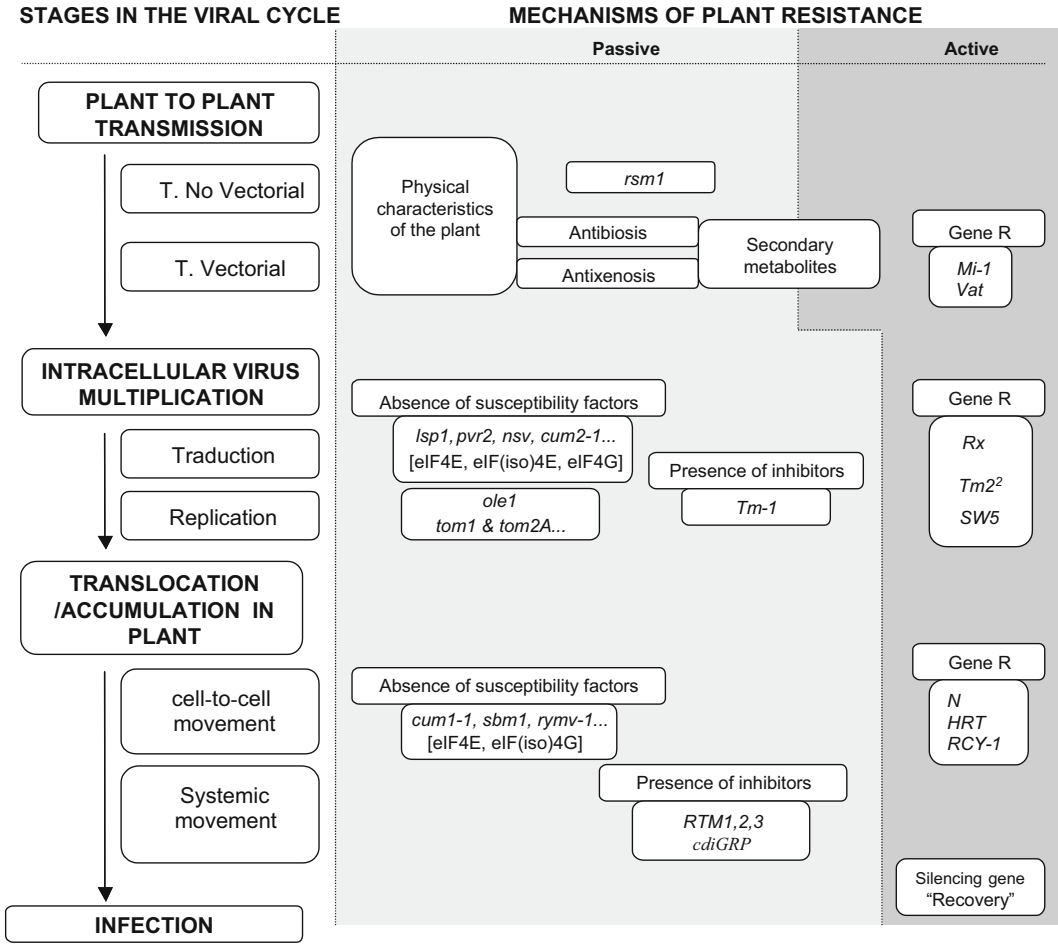

Fig. 2 Plant resistance mechanisms (active and passive) operating against viruses. Mechanisms have been organised according to the step in the viral cycle inhibited

1996). Another example is the resistance of pea (*Pisum sativum*) to seed transmission of *Pea seed-borne mosaic virus* (PSbMV), a quantitative and polygenic characteristic (Wang and Maule 1994). In this case, PSbMV is not transmitted by pollen and is detected in ovules before fertilisation. Therefore, PSbMV must infect the seeds of susceptible cultivars by directly invading immature embryos, multiplying in the embryonic tissues and persisting during seed maturation (Wang and Maule 1992, 1994). In a number of cases, it has been shown that seed transmission not only depends on embryo infection, but also on the stability of the virus in the embryo during the processes of seed formation and maturation, storage and germination (Bailiss and Offei 1990; Johansen et al. 1994).

For vector transmission, viruses must be transmitted efficiently to a new host when the vector feeds (Hull 2002). The majority of plant viruses are transmitted by insects belonging to the order *Hemiptera*, that includes aphids (*Aphididae*), whiteflies (*Aleyrodidae*) and leafhoppers (*Cicadellidae*) (Nault 1997; Gray and Banerjee 1999). Virus transmission by insects is a highly specific process in which interactions among the virus, vector and plant must occur (Ng and Falk 2006). When sap-sucking insects feed on plants, interactions between the vector and host allow virions to be discharged into the phloem in saliva, facilitating the infection process. Resistance mechanisms acting against vectors have been historically classified as antixenosis if they influence vector behaviour in terms of feeding preference (Kogan and

Ortman 1978), or as antibiosis if they increase mortality, or reduce fitness or reproductive capacity of the vector (Smith 1989). Both types of resistance may be due to the presence of non-glandular trichomes or waxy surfaces that act as physical barriers (Sadasivam and Thayumanavan 2003), or the presence of certain secondary metabolites or deterrent compounds on leaf surfaces, vacuoles or glandular trichomes that may possess insecticidal or antifeedant properties (Singer et al. 2003) (Fig. 2). Furthermore, these metabolites may play an active role in resistance, because their synthesis can be enhanced by jasmonic acid (JA) and suppressed by salicylic acid (SA) (Traw et al. 2003; Li et al. 2004).

Genes that confer aphid resistance have been identified and mapped at least in lettuce, the genera *Malus* and *Medicago*, melon, tomato, soybean and wheat (Klingler et al. 2005; Li et al. 2007; Mensah et al. 2008; Wroblewski et al. 2007). However, only two of them have so far been cloned and characterised. (Dogimont et al. 2008; Rossi et al. 1998), both of them belonging to the nucleotide binding site leucine-rich repeat (NBS-LRR) family of resistance genes (Dangl and Jones 2001; Takken et al. 2006). The first was *Mi-1,* cloned from a wild relative of tomato (*Solanum peruvianum*) that showed high levels of resistance to root-knot nematodes (*Meloidogyne arenaria, M. incognita,* and *M. javanica*) (Gilbert and McGuire 1956; Rossi et al. 1998), to the whitefly *Bemisia tabaci* (Milligan et al. 1998) and to the aphid *Macrosiphum euphorbiae* (Blackman and Eastop 2000). *Mi-1* is constitutively expressed in roots and leaves, and the resistance that it confers against nematodes is associated with a hypersensitive response (HR) (Dropkin 1969; Kaloshian et al. 1995; Lopez-Perez et al. 2006), while for whiteflies and aphids it appears to inhibit their feeding, fecundity and survival on leaves of mature plants (Kaloshian et al. 2000; Pascual et al. 2000; Martinez de Ilarduya et al. 2003). The SA signalling pathway is an important component of *Mi-1*-mediated resistance (Thompson and Goggin 2006; Bhattarai et al. 2007).

The second NBS-LRR resistance gene is *Vat*, which confers resistance to *Aphys gossypii* and to viruses that are non-persistently transmitted by this vector in melon (Pitrat and Lecoq 1980). Using a map-based cloning strategy and functional analysis in transgenic melon plants, Dogimont et al. (2008) demonstrated that a single gene encoding a coiled-coil (CC)-NBS-LRR protein confers both functions. Recognition of an aphid gene product by *Vat* probably triggers the plant's responses, preventing aphid feeding, reducing fecundity and survival and inhibiting non-specific antiviral responses (Dogimont et al. 2008).

Resistance to intracellular virus multiplication

About 80% of plant viruses have single-stranded, positive-sense RNA genomes. Their cellular replication cycle begins with genome desencapsidation (normally in the cytosol) followed by synthesis of viral proteins from viral mRNAs with the help of the host cell machinery, and then replication of the viral genome (Buck 1999; Noueiry and Ahlquist 2003). Genome sequencing has shown that all positive-strand RNA viruses share common features (Haseloff et al. 1984), indicating common replication and gene regulation strategies (Buck 1996). Indeed, several cellular proteins recently identified as host factors involved in viral translation and replication may be shared by members of different plant virus genera (Tomita et al. 2003; Serva and Nagy 2006).

Host susceptibility factors have been identified in model species like *Saccharomyces cerevisiae* and *Arabidopsis thaliana* through the analysis of large mutagenised populations (for a review see Diaz-Pendon et al. 2004). Findings using artificially induced mutations might be helpful for understanding the mechanism of viral infection, and also have the potential to be translated to crop plants. At least two phylogenetically diverse plant RNA viruses, *Brome mosaic virus* (BMV) and *Tomato bushy stunt virus* (TBSV), are able to replicate in yeast (Janda and Ahlquist 1993; Panavas and Nagy 2003), allowing powerful yeast resources to be used in genome-wide mutant screens (Kushner et al. 2003; Nagy and Pogany 2006). For example, it has been shown that a yeast protein integral to the endoplasmic reticulum (OLE1) is required for BMV replication. This protein is a Δ9 fatty acid desaturase, so loss of function causes a change in the cell membrane composition that blocks viral replication (Lee et al. 2001). On the other hand, the analysis of *A. thaliana* mutants *tom1* and *tom2A* showed that *Tobacco mosaic virus* (TMV) replication is blocked in protoplasts of mutant plants. Tom1 and Tom2A are transmembrane proteins that localise to the tonoplast, interact with each other and

also with the helicase domain of the viral replicase (Yamanaka et al. 2002; Tsujimoto et al. 2003). Screening a collection of *A. thaliana* mutants also identified *lsp1,* in which the replication and/or gene expression of the TEV and *Turnip mosaic virus* (TuMV) genomes is blocked. *Lsp1* encodes the eukaryotic translation initiation factor (iso)4E (eIF [iso]4E) (Lellis et al. 2002), which belongs to the eIF4E family of translation factors, recently shown to be susceptibility factors for many different plant viruses (Robaglia and Caranta 2006). Mutations in genes of this family confer resistance against viruses of the family *Potyviridae*, whose genomes characteristically possess a 3′-poly(A) tail and a covalently bound virus-encoded protein (VPg) at the 5′-end. The VPg cistron encodes an avirulence determinant in several potyvirus/host combinations (Borgstrom and Johansen 2001; Moury et al. 2004; Ayme et al. 2006; Robaglia and Caranta 2006) and eIF4E/VPg interactions (Charron et al. 2008; Wittmann et al. 1997; Schaad et al. 2000; Leonard et al. 2000, 2002, 2004; Kang et al. 2005; Robaglia and Caranta 2006) appear to correlate with virus infectivity (Charron et al. 2008; Leonard et al. 2000). However, the molecular mechanisms underlying potyvirus resistance mediated by eIF4E remain elusive. As the main role of eIF4E in cellular mRNA translation consists of binding the cap structure at the 5′ mRNA end, promoting its recruitment by the translational machinery, it has been suggested that the VPg protein may act as a cap substitute such that the VPg/eIF4E-specific interaction might be necessary for translational initiation on virus genomic RNA. Nevertheless, recent evidence suggests that the role of eIF4E in the potyvirus cycle might be distinct from its physiological function in cellular mRNA translation (German-Retana et al. 2008). Alternative roles for eIF4E include mediating genome circularisation for virus RNA replication, intracellular virus transport and cell-to-cell virus trafficking, among others (Gao et al. 2004b; German-Retana et al. 2008; Robaglia and Caranta 2006). Resistance mediated by eIF4E is not restricted to potyviruses, as reports have shown similar phenomena in the genera *Bymovirus* (Kanyuka et al. 2005; Stein et al. 2005), *Cucumovirus* (Yoshii et al. 2004), *Sobemovirus* (Albar et al. 2006) and *Carmovirus* (Nieto et al. 2006). Indeed, the molecular mechanism of resistance to *Melon necrotic spot virus* (MNSV) has been characterised in detail. Resistance to MNSV in melon is controlled by the *nsv* gene (Coudriet et al. 1981), which acts at the single-cell level (Diaz et al. 2004). Nieto et al. (2006) characterised the *nsv* locus, demonstrating that it encodes melon eIF4E and that a single amino acid change is sufficient to confer resistance to MNSV (Nieto et al. 2006). Recently, it has been shown that MNSV contains a short sequence at the 3′-end of its genomic RNA that functions as a cap-independent translational enhancer (3′-CITE). Sequences of the 3′-CITE differ among virulent (MNSV-264) and avirulent (MNSV-α5) strains, and determine whether or not MNSV can infect melons carrying the eIF4E resistance allele. This suggests that the translational initiation complex depends upon an efficient interaction between eIF4E and the viral 3′-CITE, and that resistance occurs when this interaction is inefficient (Fig. 3) (Truniger et al. 2008).

Dominant resistance may also operate at the single-cell level (Fig. 2). Two different resistance mechanisms have been identified so far for dominant resistance alleles, one corresponding to the presence of inhibitors of virus replication, and the other reflecting a resistance response controlled by NBS-LRR genes. In cowpea, a dominant trait that blocks *Cowpea mosaic virus* multiplication in resistant protoplasts works by inhibiting viral polyprotein processing (Ponz et al. 1988). It has recently been shown that the tomato dominant resistance gene *Tm-1* encodes an 80-kDa polypeptide ($p80^{GCR237}$) of unknown function that is able to inhibit the replication of *Tomato mosaic virus* (ToMV) both *in vitro* and *in vivo*. In this case, the inhibition of replication seems to be mediated by $p80^{GCR237}$ binding to replication proteins before the formation of the replication complex linked to the cell membrane (Ishibashi et al. 2007). However, most extensively studied examples of dominant resistance correspond to genes encoding CC-NBS-LRR proteins that control resistance responses. Some of these examples include *Tm-2*^{2}, which confers extreme resistance to ToMV in tomato and tobacco (Weber et al. 1993; Lanfermeijer et al. 2003, 2004), and *Rx*, which confers extreme resistance to most *Potato virus X* (PVX) strains in potato (Bendahmane et al. 1997, 1999). Analysis carried out in resistant protoplasts showed that Rx-mediated resistance is elicited by the PVX coat protein and is effective against unrelated viruses such as CMV (Köhm et al. 1993; Bendahmane et al. 1995). The interaction between PVX CP and Rx has been studied

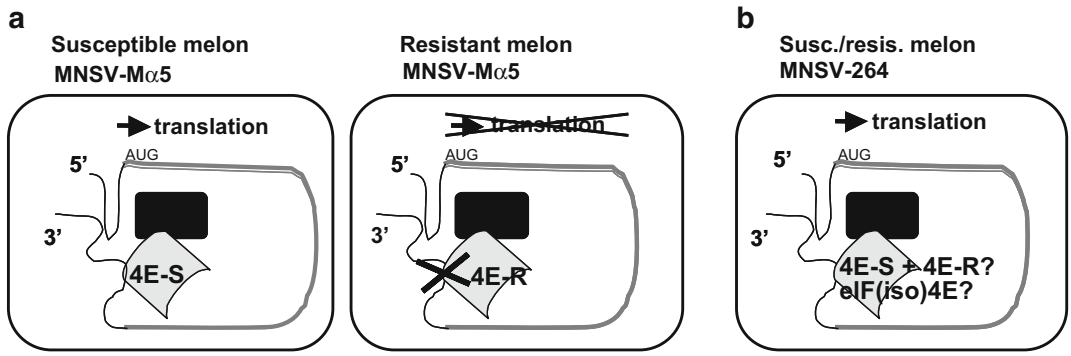

Fig. 3 Model for the molecular mechanism of resistance to *Melon necrotic spot virus* (MNSV) controlled by *nsv* (Nieto et al. 2006; Truniger et al. 2008). **a** Translation initiation of MNSV-Mα5 (avirulent isolate) in susceptible or resistant melon cells: an efficient interaction between a segment of the viral genomic RNA and the melon eukaryotic translation initiation factor 4E (*i.e. nsv*) (*Cm*-eIF4ES) from susceptible genotypes leads to the formation of the translation initiation complex and translation of viral RNA. In contrast, inefficient interaction between viral RNA and *Cm*-eIF4E from resistant genotypes bocks the assembly of the translation initiation complex and, therefore, translation of the viral RNA cannot occur. **b** Viral RNA of MNSV-264 (virulent isolate) might interact with *Cm*-eIF4E from susceptible or resistant genotypes; alternatively, it might not require Cm-eIF4E for its cap-independent translation

in potato (Bendahmane et al. 1995) and *N. benthamiana* (Moffett et al. 2002), the latter study showing that the LRR and CC domains undergo physical intramolecular interactions; when both domains are provided independently, their interaction reconstitutes the function of the complete protein as it generates an elicitor-specific HR in the presence of CP and, hence, virus suppression (Moffett et al. 2002). The intramolecular interaction involving the Rx CC domain appears to be context-specific and may initiate signalling (Rairdan and Moffett 2006). Recently, it has been shown that there are regions in the CC domain that interact with Ran GTPase (RanGAP2), modulating the interaction between CC and NB-LRR or vice-versa (Rairdan and Moffett 2006; Sacco et al. 2007; Tameling and Baulcombe 2007; Rairdan et al. 2008). However, it is still unknown whether CP interacts directly with the product of the *Rx* gene or whether additional partners are required; moreover, much has to be learned to fully understand the precise mechanism by which virus resistance is actually executed.

Resistance to virus translocation and colonisation of whole plants

Once a virus has multiplied successfully in primary infected cells, it must spread to adjacent mesophyll cells through plasmodesmata, and then to phloem parenchyma and companion cells in what has been called cell-to-cell or local movement. Since further replication occurs in each of these infected cells, large numbers of virus particles are eventually loaded into phloem sieve elements where they are translocated over long distances through the vascular system. The majority of plant viruses encode movement proteins (MP) that bind to and unfold single-stranded RNAs to increase the size exclusion limit of plasmodesmata in mature leaves, thereby facilitating the intercellular translocation of viral nucleic acids (Citovsky and Zambryski 1991; Lucas 2006). MPs are required for cell-to-cell movement, in some cases together with additional accessory proteins and, at least for some viruses, also for systemic movement (Carrington et al. 1996; Waigmann 2004). Different host factors also appear to be required for cell-to-cell and systemic movement (Scholthof 2005). As for other steps of the infection cycle, these factors tend to be essential for susceptibility and their absence or modification may confer resistance. Although there are little data available on these factors, the recent discovery of proteins integral to plasmodesmata may shed some light on this phenomenon (Bayer et al. 2006; Thomas et al. 2008; Maule 2008).

Genetic screens of *A. thaliana* have shown that the *cum1-1* and *cum2-1* alleles restrict the cell-to-cell movement of CMV and of CMV and TCV, respectively (Yoshii et al. 1998). Through positional cloning, it was found that the corresponding genes encode eukaryotic translation initiation factors 4E and 4G, respectively (Yoshii et al. 2004). In the case of

cum1-1, CMV replication at the single-cell level occurs normally, but expression of the CMV MP does not occur because there is no productive interaction between eIF4E and the MP mRNA, thus preventing cell-to-cell movement of the virus (Yoshii et al. 2004). Additionally, the pea *sbm1* gene that controls susceptibility to PSbMV (Gao et al. 2004a) also encodes eIF4E and facilitates cell-to-cell movement of the virus. In this case, the precise mechanism of inhibition of virus movement is unclear (Gao et al. 2004b), although it is probably different to that operating in the *cum1-1* resistance to CMV, because PSbMV does not have a MP expressed from a separate subgenomic RNA like CMV.

Long-distance viral movement is still poorly understood because of its complexity and the difficulty in dissecting the process, so very few host genes involved in its control have been identified (Whitham and Wang 2004; Scholthof 2005). No susceptibility factors required for long-distance movement have yet been identified, although host factors that can suppress it have been characterised (Fig. 2). For example, Ueki and Citovsky (2002) have shown in *N. tabacum* a chemically-inducible, glycine-rich protein (cdiGRP) that can inhibit the accumulation of *Turnip vein clearing virus* (TVCV) by obstructing the escape of virions from the phloem. Similarly, screen of *A. thaliana* mutants for their susceptibility to the colonisation of whole plants by TEV revealed at least three loci, *RTM1*, *RTM2* and *RTM3*, involved in the restriction of TEV long-distance movement. These genes are also involved in the systemic movement of other potyviruses such as *Lettuce mosaic virus* (LMV) and *Plum pox virus* (PPV) (Revers et al. 2003; Decroocq et al. 2006). *RTM1* encodes a jacalin-like protein and *RTM2* encodes a small heat shock protein (Mahajan et al. 1998; Chisholm et al. 2000; Whitham et al. 2000), both expressed in phloem tissue (Chisholm et al. 2001). *RTM3* has yet to be functionally characterised, and the molecular basis of their ability to suppress potyvirus long distance movement remains unknown.

Inducible resistance mediated by a variety of mechanisms can also operate at the level of long-distance movement. Thus, several genes encoding NBS-LRR proteins mediate resistance responses that result in the confinement of viruses to initial infection foci or to initially-infected leaves. Examples include the *A. thaliana RCY-1* and *HRT* genes, which confer resistance to CMV-Y and TCV, respectively (Takahashi and Ehara 1994). In both cases, the avirulence determinant is the virus CP (Takahashi et al. 2001, 2002). RCY1-conferred resistance requires both SA and ethylene but not JA signalling (Takahashi et al. 2001, 2004; Sekine et al. 2006), whereas HRT-conferred resistance requires the upregulation of PR-1, and the response is dependent on SA but not ethylene or JA (Dempsey et al. 1997; Cooley et al. 2000; Kachroo et al. 2000). Resistance mediated by the *N* gene from *N. glutinosa*, which confers resistance to TMV, also belongs to this group. *N* was the first virus resistance gene to be cloned (Whitham et al. 1994) and validated by transgenic complementation experiments (Dinesh-Kumar et al. 1995). *N* encodes a cytoplasmic protein with Toll/interleukin-1 receptor (TIR)-NBS-LRR domains, all of which are required for viral recognition and/or signalling in the resistance response (Whitham et al. 1994; Baker et al. 1997; Dinesh-Kumar and Baker 2000; Liu et al. 2002). The avirulence determinant for the *N* gene is the C-terminal region of the viral replicase (Padgett and Beachy 1993), whose helicase domain (p50) interacts specifically with N's TIR domain (Ueda et al. 2006). Recently, it has been identified that the association of p50 and the TIR domain of the N to form an active immune complex is mediated by an N receptor-interacting protein (NRIP1), which is a functional rhodanese sulfurtransferase that normally localises to the chloroplasts (Caplan et al. 2008). TMV infection of *N*-carrying plants is associated with the upregulation of N, which modulates the formation of two gene products expressed through differential splicing and required in an appropriate ratio for their activity (Dinesh-Kumar and Baker 2000; Levy et al. 2004). After recognition of the virus, N signalling activates a defence response through a kinase cascade involving SA, ethylene and JA. In addition to specific intermolecular interactions, this leads to programmed cell death and a HR (Soosaar et al. 2005; Caplan and Dinesh-Kumar 2006). Despite the recent elucidation of recognition and signalling pathways mediated by genes encoding NBS-LRR proteins, the molecular processes that NBS-LRR proteins induce to prevent virus accumulation remain largely unknown. Significantly, recent evidence suggests that these proteins may engage RNA interference (RNAi) components of the host cell machinery (see below) for the specific

translational repression of viral transcripts (P. Moffett, personal communication).

In addition to its potential role in virus resistance mediated by NBS-LRR genes, RNAi, also known as RNA silencing, has a fundamental role in other types of resistance. Recent evidence indicates that RNAi-based resistance to viruses and other pathogens in plants is part of a matrix of interrelated pathways initiated by double-stranded (ds) RNAs, and mediated by several types of small RNAs and a cascade of enzymatic processes, also involved in plant development and stress responses (Vazquez 2006; Ding and Voinnet 2007). RNAi defends plants against viruses by targeting and destroying virus-derived RNAs using small interfering RNAs (siRNAs) as a guide, in a sequence-specific manner (Ding and Voinnet 2007). Perhaps the most evident role of RNAi in natural virus resistance is in the phenomenon known as 'recovery', a type of resistance to virus colonisation of whole plants which involves the initial development of typical infection symptoms, frequently with dark green islands (Moore and MacDiarmid 2006), followed by attenuation or elimination of the symptoms and reduction of virus titers in emerging leaves (Baulcombe 2004). For example, *N. clevelandii* plants inoculated with *Tobacco black ring virus* (TBRV) show severe initial symptoms on the inoculated and first systemic leaves but neither symptoms nor virus accumulation in upper leaves, and recovered leaves are resistant to a subsequent infection with the same virus or with viruses carrying homologous sequences (Ratcliff et al. 1997). Similar phenomena have been described for tobravirus and caulimovirus infections (Covey et al. 1997; Ratcliff et al. 1999). Symptom recovery can be dissociated from the reduced virus titers, but is always correlated with RNAi (Jovel et al. 2007). As for other resistance phenomena described in this review, the molecular basis of recovery and the precise role of RNAi in this process are still largely unknown.

Resistance durability

The biological scenario of plant resistance breakdown by viruses

Johnson (1981) defined durable resistance as one that remains effective while used extensively in agriculture for a long time in an environment conducive to the disease. Assuming that the virus population is totally avirulent when a new form of resistance is exploited by growers, the breakdown of the resistance involves three steps that need to be fulfilled by the virus population (Fig. 4). The first step is the appearance of virulent variants in the initially avirulent viral population. As soon as these variants appear, they compete with the

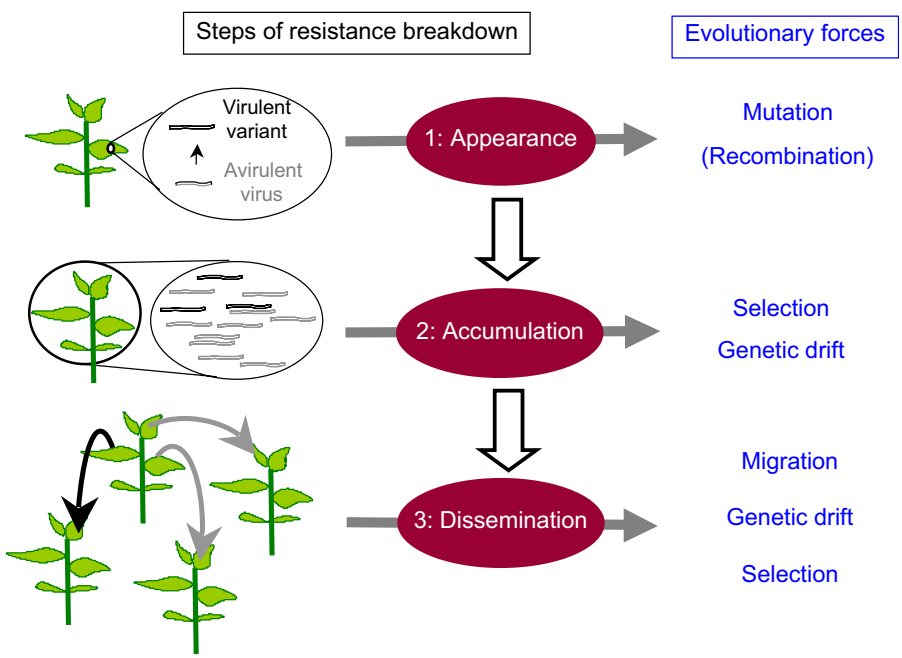

Fig. 4 Evolutionary forces involved in the breakdown of virus resistance in plants

avirulent viral population for accumulation in infected plant cells and whole plants. Only if they are competitive enough, will they multiply enough in these plants (step 2) and have the opportunity to spread to other plants in the crop (step 3) allowing epidemics to develop in resistance-carrying plants. It is generally accepted that if all these steps are carried out efficiently by virulent strains of the virus, then resistance will break down; if not, the resistance will be durable.

Different evolutionary forces govern these steps (Fig. 4). The first step usually involves a small number of nucleotide substitutions (often one or two) in the so-called avirulence gene encoded by the viral genome. Virus avirulence genes corresponding to approximately 30 plant resistance genes or alleles have been identified (Harrison 2002). In almost all cases, these nucleotide substitutions correspond to putative amino acid substitutions. Consequently, it is generally assumed that the avirulence factor is not the nucleic acid by itself but the protein it encodes. Convincing evidence has been produced for this (Moury et al. 2004; Schirmer et al. 2005; Charron et al. 2008; Chiba et al. 2008), although non-coding regions of the virus genome have been shown to be the avirulence factor for at least two resistances (Díaz et al. 2004; Szittya and Burgyan 2001). In theory, when nucleotide substitutions at different positions in the viral genome are required for virulence, recombination or reassortment between two (or more) avirulent virus isolates could also generate a novel virulent strain.

The second step depends predominantly on two evolutionary forces: differential selection between virulent and avirulent variants and genetic drift during the infection process. Because viral genes are often multifunctional, even a limited number of nucleotide changes may have strong pleiotropic effects. Mutations responsible for gains of virulence also frequently induce fitness costs to the virus in plants devoid of the corresponding resistance. This was shown in several instances (Agudelo-Romero et al. 2008; Goulden et al. 1993; Lanfermeijer et al. 2003; Jenner et al. 2002; Desbiez et al. 2003; Ayme et al. 2006) although other examples suggest that virulent strains can be at least as fit as avirulent ones (Chain et al. 2007; Sorho et al. 2005). However, in these latter examples, it was not determined whether mutations outside the virulence factor also contributed to fitness variations. Genetic drift is active during virus infections (French and Stenger 2003; Sacristán et al. 2003) and can result in the spatial segregation of virus strains within plants (Dietrich and Maiss 2003; Jridi et al. 2006) affecting in turn the future dissemination of these variants between plants and the probabilities of extinction or emergence of virulent strains (Moury et al. 2007).

The third step of resistance-breaking is probably the most complex since three different evolutionary forces can shape the virus population: (i) spatial dissemination (migration) of viruses between plants, (ii) genetic drift during transmission events and (iii) selection imposed by virus vectors.

Factors that influence the durability of plant resistance to viruses

According to Johnson's (1981) definition, the durability of resistances can be measured only *a posteriori* after their large-scale deployment. Predicting the durability of resistance at the beginning of breeding programmes therefore represents a major challenge and relies on knowledge of the factors that can influence such durability.

Nature of plant resistance No clear association has been observed between the genetics of virus resistance and its durability. On the contrary, a barely significant overall association was identified between resistance phenotype and durability, although no particular category of resistance was found more durable than any other (García-Arenal and McDonald 2003). 'Extreme resistances', *i.e.* dominant resistances that reduce virus multiplication at the single-cell (protoplast) level and do not induce HR in inoculated tissues, appear particularly durable (Barker and Harrison 1984; Köhm et al. 1993; Bendahmane et al. 1995; Hajimorad and Hill 2001). However, few examples of this form of resistance have been characterised so general rules cannot be derived as yet from these observations.

Based upon data obtained predominantly from plant resistance to fungi, polygenic resistance is often presumed to be more durable than monogenic resistance (Turkensteen 1993; Lindhout 2002; Chen et al. 2003; Schurnbusch et al. 2004). Such complex resistance traits are less amenable to experimental analysis than monogenic and oligogenic traits, but at least one study showed that quantitative trait loci (QTL) with minor effects on resistance can considerably increase the durability of a major resistance gene (Palloix et al. 2009).

Intrinsic virus traits The size of virus populations and their capacity for dissemination in the agro-ecosystem can also affect resistance durability. The virus population size directly affects the probability of virulent strains arising, and this depends on the number and distribution of host plants and on the capacity of the virus to accumulate in these host plants, which varies greatly among different viruses. Viruses can be subjected to population bottlenecks at certain steps of their infection cycles, which may cause the extinction of many variants and reduce the probability of novel virulent strains emerging. Differences in dissemination capacity among virus species are not known with precision, but can be inferred from knowledge of the vectors involved in virus transmission and the potential spread of viruses in seeds or in material used for vegetative propagation. Notably, air-borne vectors can disseminate viruses over greater distances than soil-borne ones and persistent viruses can be disseminated over greater distances than non-persistent ones. The number of vector species and their prevalence are also important. These parameters, together with the frequency of 'sexual reproduction', *i.e.* recombination or reassortment, in virus populations were incorporated into a semi-quantitative compound index called 'evolutionary potential' (EP; García-Arenal and McDonald 2003), which has been shown to correlate with resistance durability: the greater the EP, the lower the durability of resistance. When virulence is associated with a fitness cost in plants lacking the resistance gene, fitness could be recovered through secondary mutations (Sanjuán et al. 2004, 2005) or, perhaps more rapidly, by recombination or reassortment, thus contributing to the emergence of virulent strains. The link between recombination/reassortment and resistance durability is not straightforward, since neither process has been shown to be involved directly in the generation of virulent strains or the frequency of recombinants or reassortants has been shown to differ between virulent and avirulent isolates (Elena and Sanjuán 2007). However, this might underlie the emergence of TSWV virulence towards the resistance conferred by the nucleocapsid gene of TSWV in transgenic tobacco plants (Qiu and Moyer 1999; Hoffmann et al. 2001).

Different resistance genes targeting the same virus tend to differ in durability. By definition, the EP of viruses cannot account for these differences. In this respect, knowledge derived from the identification of virulence genes and mutations could help predict resistance durability more accurately. In almost all cases, these nucleotide substitutions correspond to putative amino acid substitutions. Harrison (2002) showed that the number of amino acid substitutions required for virulence was linked to resistance durability. In some instances, a single mutation was sufficient to turn an avirulent strain into a resistance-breaking strain (*i.e.* PVX; Malcuit et al. 1999), this being associated with a low resistance durability. However, when two or more substitutions were necessary, durability was generally high (Bendahmane et al. 1995). The comparison of *Tm-2* and *Tm-2*^{2} illustrates this very well, as pointed out by Harrison (2002), in that even extremely similar resistance genes show great differences in durability.

Environmental and anthropic factors The prevalence of viral diseases and the durability of disease resistance can be strongly influenced by the frequency and geographic distribution of host plants and/or vector populations, the physical environment (*e.g.* climate, soil quality) as well as human decisions (choice of crop species and genotypes) and behaviour (trade or introduction of infected plants or seeds). Such decisions can increase virus population sizes, reduce the impact of population bottlenecks and increase the likelihood of dissemination in the agro-ecosystem. They could also affect the probability of individual plants becoming infected with different virus isolates, promoting recombination or reassortment. Insect vectors are particularly affected by climate variations (Canto et al. 2009) and can also be transported for long distances by human agricultural activity. The recent worldwide expansion of thrips (*Frankliniella occidentalis*) and whiteflies (*B. tabaci*) has facilitated the spread of particularly damaging plant viruses and, in the case of thrips, certainly influenced TSWV resistance-breaking in pepper (Margaria et al. 2004).

Conclusions and prospects

Work carried out over the last decade looking at the molecular basis of disease resistance and how it can be exploited has helped in the development of new

scientific and technological approaches, some of which are summarised briefly below.

Resistance screening: high throughput methodologies Most sources of resistance to plant viruses have been discovered in phenotype-driven screens, but vast germplasm resources remain to be explored. Maximum efficiency in the exploitation of unexplored genetic resources requires high-throughput screening. The cloning and genetic engineering of viral genomes provides a means to create viral strains labelled with markers that may facilitate screening and phenotypic analysis. For example, Whitham et al. (1999) developed a selectable TEV strain which expressed a herbicide resistance gene; this facilitated the efficient identification of either gain-of-susceptibility or loss-of-susceptibility mutants in large collections of *Arabidopsis*-mutagenised plants. This approach could be most beneficial when coupled with the use of devices designed to inoculate large numbers of plants efficiently (Chemo et al. 2000).

Sources of resistance: quantitative trait loci Phenotypic screens often reveal quantitative resistance traits which are usually polygenic. Breeders and pathologists tend to disregard such traits as they are more difficult to handle than monogenic and oligogenic ones. However, the isolation of QTL may simplify the analysis of quantitative resistance and allow the development of resistant varieties, making QTL a vast and untapped supply of new resistance alleles. Before QTL can be used routinely, a number of challenges remain to be addressed including the improvement of diagnostic assays used for QTL detection, and the identification of genetic markers for MAS (Maule et al. 2007).

Translational genetics: genetic screens for alleles defective in conferring susceptibility As discussed above, much of the molecular data on virus resistance and susceptibility has been generated using model species as experimental systems, and the corresponding host factors (targets) must then be studied in crops for application in the field. For this purpose, a number or research activities are required, including the development of tools for high-throughput genotypic screenings (*e.g.* by EcoTILLING (Nieto et al. 2006)), the accumulation of genome data for important crop species, and the generation of platforms for the efficient genetic analysis of large collections of mutagenised lines (*e.g.* by TILLING (Targeted Induced Local Lesions IN Genomes)) (Oleykowsky et al. 1998; Slade et al. 2005).

Resistance durability: predictors The quest for resistance durability predictors for breeders and growers relies largely on our knowledge of the biological mechanisms of resistance-breaking, and our ability to estimate precisely the durability of the resistance genes that have already been used. Even though evolutionary mechanisms accounting for the entire process of resistance breakdown have been identified (Fig. 4), their effects on virus populations are particularly difficult to quantify accurately and their impact on plant viruses is poorly understood. This data gap could be narrowed by large-scale epidemiological studies, which may allow the prevalence, incidence, genetic diversity and structure of virulent and avirulent virus populations to be estimated. Given the complexity of the mechanisms involved, assessing the risks of resistance-breaking and defining strategies to combine resistances with additional control methods will be difficult to achieve using purely experimental approaches. Mathematical modelling would be extremely helpful in this respect.

Resistance management: transfer of knowledge to end-users Various outputs can be expected from models developed to predict the durability of resistance: the relative importance of, and the interplay between, various mechanisms that operate during resistance-breaking, comparative durabilities of different resistance genes and mechanisms, the identification of resistance durability predictors and the establishment of integrated strategies to avoid resistance breakdown. It is clearly very important that predicted outputs that can be modulated by human activity and have a critical impact on resistance durability are understood by farmers and other potential end-users.

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