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The battle for survival between viruses and their host plants

Adnane Boualem¹, Catherine Dogimont² and Abdelhafid Bendahmane¹

Evolution has equipped plants with defense mechanisms to counterattack virus infections. However, some viruses have acquired the capacity to escape these defense barriers. In their combats, plants use mechanisms such as antiviral RNA silencing that viruses fight against using silencing-repressors. Plants could also resist by mutating a host factor required by the virus to complete a particular step of its infectious cycle. Another successful mechanism of resistance is the hypersensitive response, where plants engineer R genes that recognize specifically their assailants. The recognition is followed by the triggering of a broad spectrum resistance. New understanding of such resistance mechanisms will probably help to propose new means to enhance plant resistance against viruses.

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Introduction

Plants are constantly challenged by pathogens from all kingdoms like nematodes, fungi, bacteria and viruses. To defend themselves and prevent disease, plants have evolved sophisticated and efficient mechanisms. One of the most common disease defense is the induction of a rapid localized cell death at the point of pathogen infection, called hypersensitive response (HR). The HR can be triggered by a wide variety of pathogens, including viruses, and relies mainly on dominant resistance (R) genes, which recognize pathogen-derived effector proteins. In this short review, we intend to first, provide a brief overview of severe virus-associated plant diseases

and their impact on crop production, second, to present the current state of knowledge on vectors for virus transmission, and third, to summarize recent progress in understanding plant resistance against viruses focusing on the R genes mediated dominant resistance.

Viruses and diseases

Viruses are obligate intracellular parasites absolutely dependent on the host cell machinery to multiply and spread. They are nucleic acid-based pathogens with genomes that consist of single-stranded or double-stranded RNAs or DNAs encoding few genes and usually packed into protein envelopes called the capsid. Viruses invade all forms of life and viral infection causes physiological disorders leading to diseases. Viral diseases are undoubtedly one of the most limiting factors that cause significant yield loss and continuously threaten crop production worldwide. Damages range from stunted growth, reduced vigor, decreased market esthetic values of the products and/or total yield loss. Although it's very complex to put a clear figure on the economic impact of plant diseases in agriculture, it was estimated that 15% of global crop production is lost due to pre-harvest plant disease [1] and viruses account for 47% of the plant diseases [2]. In South-East Asia, viruses such as the tungro viral disease (*Rice tungro spherical virus* and *Rice tungro bacilliform virus*), the *Rice yellow mottle virus* (RYMV) and the *Rice stripe virus* (RSV) were reported to cause yield losses of 50–100% estimated to an annual economic loss of more than US\$1.5 billion [3**]. In East and Central Africa, the *African cassava mosaic virus* (ACMV), the major constraint for cassava cultivation, was reported to cause yield losses of 47% of the production corresponding to economic loss of more than US\$2 billion [4].

Virus-transmitting vectors

An important feature shared by plant viruses is their efficient movement from host to host. This virus transmission is a vital step in the biological cycle of viruses because it ensures their maintenance, survival and spread. The virus transmission cycle involves a continuum of processes, acquisition of the virus when the vector feeds on a virus-infected plant, stable retention and transport of the virus within the vector, and inoculation of the retained virus into a new host plant during a subsequent feeding. Most plant viruses (76%) are transmitted by a diverse array of vectors including insects, nematodes and fungi. Many of these vectors are plant pests, and their association with plants

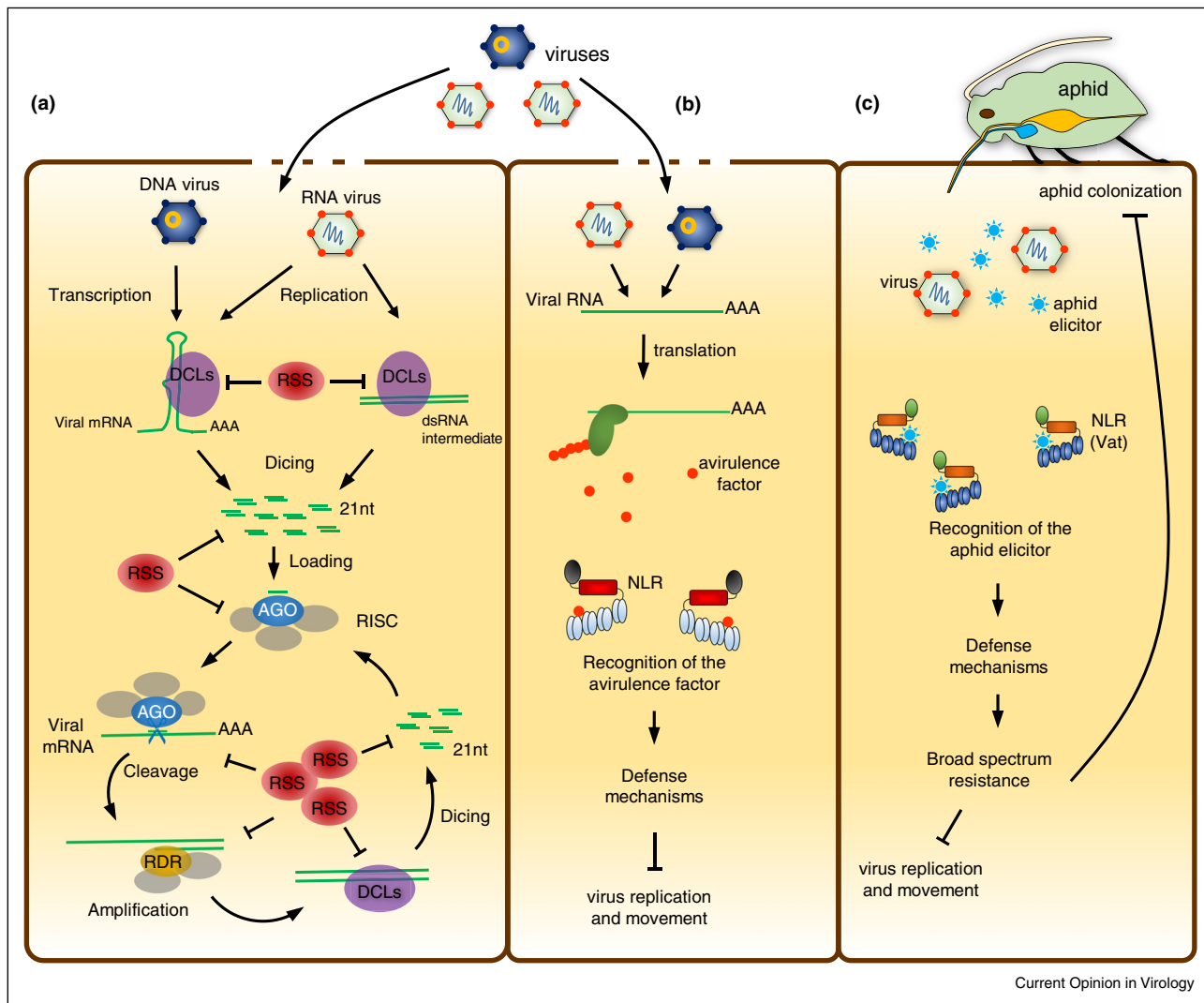
makes them ideal agents for efficient local and long-distance virus spread. By far, insects, the most common plant virus vectors, transmit the majority of described plant viruses, and of these, hemipteran insects transmit 55% of the vectored viruses [5]. In most cases, viruses of a given taxon have a specific type of insect vector. For example, viruses of the genus *Polyvirus* and *Begomovirus* are solely transmitted by aphids and whiteflies, the most economically important insect vectors, respectively.

Antiviral RNA silencing defense

Once infected, plants rely on elaborate antiviral immune arsenal to defend themselves against the invading viruses.

One of the immediate antiviral defense plant viruses encountered when invading a host is the RNA silencing (Figure 1a) [6]. RNA silencing, also called RNA interference (RNAi), is an evolutionary conserved and sequence-specific mechanism that directly defends host cells against foreign nucleic acids such as viruses and transposable elements [7]. This defense is triggered by double-stranded RNA molecules (dsRNA). Most plant viruses have RNA genomes that replicate through dsRNA intermediates by viral RNA-dependant RNA polymerases (RDRs) or contain double-stranded secondary structures. These viral dsRNAs are processed by Dicer-like (DCL) enzymes into virus-derived small RNAs (vsRNAs) that

Figure 1



Mechanisms of plant resistance to viruses. (a) Antiviral RNA silencing in plants and its suppression by virus-encoded RNA silencing suppressors (RSSs). RNA silencing is initiated by the recognition of viral dsRNAs or partially double strand hairpin RNAs, which are processed to vsRNAs. (b) NLR-mediated plant resistance. Following entry into a host cell, viral effectors are expressed from the virus genome. Specific plant NLR genes interact (directly or indirectly) with these effectors to trigger virus resistance. (c) Model for *Vat*-mediated resistance involving separate recognition and response phases. In the *A. gossypii* resistant plant, the *Vat*-NLR recognizes an elicitor molecule from the aphid. This recognition phase induces local resistance mechanisms that inhibit aphid colonization and replication and movement of viruses transmitted by the same aphid.

are uploaded into the RNA-induced silencing complex (RISC) and used to guide the silencing of the viral genome [8–10]. The antiviral RNA silencing response acts against all RNA and DNA viruses, but since DNA viruses do not replicate through dsRNA intermediates, precursors of vsRNAs could potentially be formed by antisense transcription, RDR activity or from secondary structures of viral RNAs (Figure 1a) [11,12]. To resist virus infections locally and systemically, plants generate secondary vsRNAs, the mobile silencing signal that spreads from the site of initiation to the surrounding tissues and over long distances via the plasmodesmata and the phloem. This non-cell autonomous process primes RNA silencing in non-infected cells and depends on host RDRs proteins [13,14].

To escape the antiviral RNA silencing defense, almost all types of plant viruses have evolved RNA silencing suppressors (RSSs). Although, RSSs are highly diverse in sequence, structure and involved in a number of basic viral functions (replication, movement and encapsidation), their modes of action can be classified into three classes: first, binding to dsRNA resulting in inhibition of vsRNA production by DCL proteins; second, sequestration of sRNA duplexes and interfering with RISC assembly and cell-to-cell movement of vsRNA; and third, direct targeting of effectors or processing factors leading to their inhibition or destabilization (Figure 1a) [15**–19]. Because of the central role of RNA silencing in plant development, defense and adaptation to stress, specific strategies have been developed by the host to neutralize the effects of RSSs and stimulate the defense reactions [10]. Among the counter-counterdefense responses, the plant hosts use resistance (R) proteins to guard the integrity of RNA silencing components and to either directly or indirectly recognize RSSs and finally induce hypersensitive response (HR) [20–23].

Hypersensitive response

One common feature of the host immune resistance is the rapid induction of programmed cell death at the site of pathogen invasion and at the immediately surrounding cells. This symptomatic manifestation is called Hypersensitive Response (HR) [24]. The HR is triggered by a wide variety of pathogens, including viruses, to prevent pathogen spread in the plant [24]. Hypersensitive reactions are initiated by the recognition of the pathogen-encoded avirulence factor (Avr) by the plant host R genes (Figure 1b) [25*]. The Avr/R protein interactions may trigger a mitogen-activated protein kinase (MAPK) signaling cascade and lead to a fast accumulation of reactive oxygen species (ROS) and defense hormones, salicylic acid (SA) and jasmonic acid (JA). At the cellular level, HR is associated with calcium ion influx, callose deposition at the plasmodesmata, modification of the membrane permeability and a drastic transcriptional reprogramming

leading to the expression of Pathogenesis Related (PR) genes [26–29].

Although, the HR cell death and the resistance response are closely associated, increasing evidence shows that these two defense components can be physiologically, genetically and temporally uncoupled. Among the supporting examples, the interaction of the potato *Rx1* resistance gene with the *Potato virus X* (PVX) capsid protein (CP) inhibits PVX replication independently of the CP-triggered HR cell death [30**].

The vast majority of the cloned dominant R genes encode nucleotide-binding leucine-rich repeat (NB-LRRs or NLRs) proteins that recognize the Avr factor through a ‘gene-for-gene’ interaction (Table 1) [31]. NLR genes usually confer narrow resistance spectrum, restricted to a single pathogen and usually to a limited number of strains. Irrespective of the pathogen they perceive, canonical plant NLRs proteins consist of trimodular domains: first, the N-terminal Toll-interleukine-1 receptor (TIR) or coiled-coil (CC) domains that define the two main classes of R proteins: TIR-NLRs or CC-NLRs, (ii) the central nucleotide binding (NB) domain and (iii) the leucine-rich repeat (LRR) domain at the C-terminal end [25*,32,33**,34]. Strong genetic evidence supports that the LRR domain determines the pathogen recognition specificity and that this domain is under diversifying selection pressure to evolve new pathogen recognition specificity [33**,35**,36].

NLRs proteins function as molecular switches, shifting between a constitutively inactive ‘off’ conformation and an active ‘on’ state after the recognition of the pathogen. To prevent unnecessary activation of the NLR-mediated responses, intramolecular interactions between the LRR domain folded back across the NB domain and the N-terminal dimerization, TIR or CC, domain maintain the NLRs proteins into the inactive ‘off’ mode [37**]. Recent studies on the potato *Rx1* gene that encodes a CC-NB-LRR protein and mediates resistance to PVX demonstrate that intramolecular CC-NB and NB-LRR domain interactions keep *Rx1* protein in an inactive state [38**,39–41].

The translation of the pathogen recognition into an efficient resistance response is attributed to the NB domain [42]. Within this domain, the P-loop and the MHD motifs are essential for the NLR function. Substitutions in the P-loop inactivate the NLRs proteins whereas mutations of the aspartic acid (D) in the MHD motif render many NLRs proteins autoactive initiating the resistance response in the absence of pathogen or avirulence protein [38**,43].

R gene-mediated resistance to aphid infestation and aphid-transmitted viruses

Aphids are the major virus-transmitting pests of plants. Besides vectoring numerous devastating viruses, aphids

Table 1

NLRs genes cloned for a dominant resistance against plant viruses

Plant species	R gene (NLR type)	Virus recognized	Avirulence factor	References	
<i>Nicotiana glutinosa</i>	<i>N</i> (TIR-NLR)	TMV	p50	[49**]	
<i>Solanum tuberosum</i>	<i>Rx1</i> (CC-NLR)	PVX	CP	[30**]	
	<i>Rx2</i> (CC-NLR)	PVX	CP	[50]	
	<i>Y-1</i> (TIR-NLR)	PVY	Unknown	[51]	
	<i>HRT</i> (CC-NLR)	TCV	CP	[52]	
<i>Arabidopsis thaliana</i>	<i>RCY1</i> (CC-NLR)	CMV	CP	[53]	
	<i>Sw5b</i> (CC-NLR)	TSWV	NSm	[54]	
<i>Solanum peruvianum</i>	<i>Tm-2</i> (CC-NLR)	TMV, ToMV	30 kDa MP	[55,56]	
<i>Glycine max</i>	<i>Rsv1</i> (CC-NLR)	SMV	P3 + HC-Pro	[57,20]	
<i>Phaseolus vulgaris</i>	<i>I</i> (TIR-NLR)	BCMV, BNMV, BICMV, AzMV, CABMV, PWV, SMV, ThPV, WMV, ZYMV	Unknown	[58]	
	<i>PvVTT1</i> (TIR-NLR)	BDMV	BV1 (NSP)	[59]	
	<i>PvCMR1</i> (TIR-NLR)	CMV	2a	[60]	
	<i>Ctv</i> (CC-NLR)	CTV	Unknown	[61,62]	
	<i>Poncirus trifoliata</i>	<i>L¹⁻⁴</i> (CC-NLR)	TMV, ToMV, TMGMV, BPeMV, PaMMV, ObPV, PMMoV	CP	[63]
		<i>BcTuR3</i> (TIR-NLR)	TuMV	Unknown	[64]
<i>Brassica rapa</i>	<i>TuRB07</i> (CC-NLR)	TuMV	Unknown	[65]	
<i>Vigna mungo</i>	<i>CYR1</i> (CC-NLR)	MYMV	CP	[66]	
<i>Cucumis melo</i>	<i>Pvr¹⁻²</i> (TIR-NLR)	PRSV	Unknown	[34]	
	<i>Vat</i> (CC-NLR)		Unknown	[33**]	

CC, coiled-coil; TIR, Toll/interleukin 1 receptor; CP, Coat Protein; MP, Movement Protein; NSP, Nuclear Shuttle Protein; AzMV, *Azuki mosaic virus*; BCMV, *Bean common mosaic virus*; BDMV, *Bean dwarf mosaic virus*; BICMV, *Blackeye cowpea mosaic virus*; BNMV, *Bean necrotic mosaic virus*; BPeMV, *Bell pepper mottle virus*; CABMV, *Cowpea aphid-borne mosaic virus*; CMV, *Cucumber mosaic virus*; CTV, *Citrus tristeza virus*; MYMV, *Mungbean yellow mosaic virus*; ObPV, *Obuda pepper virus*; PaMMV, *Paprika mild mottle virus*; PMMoV, *Pepper mild mottle virus*; PRSV, *Papaya ringspot virus*; PVX, *Potato virus X*; PVY, *Potato virus Y*; PWV, *Passionfruit woodiness virus*; SMV, *Soybean mosaic virus*; TCV, *Turnip crinkle virus*; ThPV, *Thailand passiflora virus*; TMGMV, *Tobacco mild green mosaic virus*; TMV, *Tobacco mosaic virus*; ToMV, *Tomato mosaic virus*; TSWV, *Tomato spotted wilt virus*; TuMV, *Turnip mosaic virus*; WMV, *Watermelon mosaic virus*; ZYMV, *Zucchini yellow mosaic virus*.

also affect plant health by directly feeding on phloem sap [5,44]. Recently, the isolation of the dominant *Virus aphid transmission (Vat)* gene from melon, *Cucumis melo*, provides novel insights into the double resistance to the aphid, *Aphis gossypii*, infestation and *A. gossypii*-vectored viruses [33**]. The *Vat* gene encodes a NLR protein with an unusual conserved LRR repeat [33**]. *Vat* confers resistance to the aphid-transmitted *Cucumber mosaic virus (CMV)* and to several aphid-transmitted potyviruses, although these viruses have very distinct infection strategies [45]. These viruses are vectored within the saliva of *A. gossypii* and the *Vat*-mediated virus resistance is observed only if host plants harboring *Vat* gene are infected by an avirulent strain of *A. gossypii*. When plants are infected mechanically or by another aphid species, virus infection occurs on either the *Vat* resistant and non-*Vat* susceptible plants [33**]. The *Vat* gene example is an elegant illustration of the two-steps process, a specific recognition of an aphid, *A. gossypii*, and a triggered broad-spectrum resistance that blocks virus infection (Figure 1c). However, questions regarding the identity of the aphid avirulence factors necessary to induce the *Vat*-mediated resistance still unresolved.

Conclusions and perspectives

Nowadays, virus disease management consists mainly in agricultural practices such as the destruction of infected plants, the eradication of plants reservoir and the use of

pesticide to limit the population of vectors. Another powerful mean to control virus infection is the use of disease resistant genes in breeding programs. Unfortunately R genes do not exist against all the devastating viruses and when available their introgression in high yielding varieties is tedious. Among the hurdles, the difficulty to cross elite lines with non-cultivated plants and the linkage drag of unwanted loci that reduce the agronomic fitness of the crop. Moreover, R genes are in many cases overcome by resistant breaking strains.

In the post genomic era, one would expect to use gene editing tools to design a resistance gene against an important viral function. Such function should have stringent constraint so that its mutation probably affects the fitness of the virus. Until recently this was a dream. The development of tools such as the TALENs (Transcription Activator-Like Effector Nucleases) and the CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) have opened wide the possibility to engineer a new generation of resistance genes. In this scenario, plant virologist will bring new insight on how the virus highjacks the plant machinery to identify key viral protein domains that the virus can not easily modify. In the case of active resistance, molecular biologist will modify existing R genes so that new virus variant will be recognized by the host plant and eradicated by the plant immune system. In the case of passive resistance,

induced mutation in a plant gene will create plant protein that will not penalize the plant growth but in the same time is not recognized by the virus as a host factor.

The current progress in gene editing will no doubt boost the development of genetic engineering of R genes. If we succeed in engineering such R genes, such approach is likely to provide a high level of protection, and because they are on the basis of a plant's own defense arsenal, they are likely to provide durable resistance as well. The pioneer work on in artificial evolution of R genes in the pathosystem *Rx*-Potex virus has set the ground for such work. *Rx* mutants, with enhanced recognition of *Rx*-resistant breaking strains of PVX or other viruses such as *Poplar mosaic virus* (PopMV) [46^{••},47^{*}], were identified. Similarly, for recessive resistance, induced mutations in translational initiation factor such as *elF4E* have led to *Potato virus Y* (PVY) resistance in tomato [48^{*}].

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