Plant defense signals: Players and pawns in plant-virus-vector interactions

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Abstract

Plant viruses face an array of host defenses. Well-studied responses that protect against viruses include effector-triggered immunity, induced resistance (such as systemic acquired resistance mediated by salicylic acid), and RNA silencing. Recent work shows that viruses are also affected by non-host resistance mechanisms; previously thought to affect only bacteria, oomycetes and fungi. However, an enduring puzzle is how viruses are inhibited by several inducible host resistance mechanisms. Many viruses have been shown to encode factors that inhibit antiviral silencing. A number of these, including the cucumoviral 2b protein, the poytviral P1/HC-Pro and, respectively, geminivirus or satellite DNA-encoded proteins such as the C2 or βC1, also inhibit defensive signaling mediated by salicylic acid and jasmonic acid. This helps to explain how viruses can, in some cases, overcome host resistance. Additionally, interference with defensive signaling provides a means for viruses to manipulate plant-insect interactions. This is important because insects, particularly aphids and whiteflies, transmit many viruses. Indeed, there is now substantial evidence that viruses can enhance their own transmission through their effects on hosts. Even more surprisingly, it appears that viruses may be able to manipulate plant interactions with beneficial insects by, for example, paying back their hosts by attracting pollinators.

199 words

Introduction: The layered nature of resistance to plant viruses

Resistance to plant viruses can take a number of forms, classifiable into innate (i.e., genetically determined resistance) or adaptive, in which the host 'learns' to recognize and respond to an invading virus. Since plants have no circulating antibodies or specialized immune cells, the only adaptive immune system they are known to possess is based on RNA silencing. In contrast to adaptive immunity provided against viruses by RNA silencing, genetically determined or innate resistance is to some extent virus- or strain-specific [1,2,3]. The least specific genetically determined resistance system is non-host resistance in which plants recognize and respond locally to relatively generic factors produced by microbial pathogens [4]. In the case of bacteria, these factors (PAMPs: pathogen-associated molecular patterns) include a conserved domain (flg22) of the protein flagellin. Flg22 perception in *Arabidopsis thaliana* is mediated by FLS2, a cell surface receptor that requires a partner kinase, BAK1 [4]. Although viruses are intracellular parasites, recent work with Arabidopsis signaling mutants has shown that several viruses (tobamoviruses and turnip crinkle virus, TCV) are inhibited in their accumulation by PAMP-triggered immunity (PTI) and that BAK1 and BKK1 (another factor required for sensing of external signals, most notably brassinosteroids) are required for this [5,6,7,8]. Based on modern interpretations [9] of a pioneering study by Fluhr and colleagues [10,11], the tobacco mosaic virus (TMV) coat protein appears to have PAMP activity, since it stimulates NADPH oxidase activity and a reactive oxygen burst in tobacco and tomato. Cucumber mosaic virus (CMV) activates PTI in Arabidopsis (with the CMV 2a RNA-directed RNA polymerase protein acting in this case as the PAMP), resulting in increased production of glucosinolates. These include aphid feeding deterrent compounds that affect interactions of the host with aphids, insects that vector CMV

[12,13]. However, it does not appear that the triggering of non-host resistance signaling by CMV induces any substantive resistance to accumulation of the virus [13]. In addition to viral proteins, viral dsRNAs can also elicit PTI, and by a mechanism distinct from RNA silencing, as shown by Niehl and co-workers [14]. Nicaise [15] recently reviewed the current status of studies of non-host resistance to viruses, and Conti and colleagues [9] have reviewed in detail the ability of viruses such as TMV to manipulate and subvert resistance mechanisms such as PTI.

In this article we discuss the genetics of resistance to plant viruses and the roles of signal chemicals in triggering induced resistance. The role of RNA silencing is discussed only briefly, since it has been reviewed extensively in the literature. In the succeeding sections of the article we describe how studies of viral subversion of RNA silencing and other resistance signaling mechanisms has revealed how viruses appear to be able to manipulate host interactions with other organisms: most notably with insect vectors. We conclude with a brief discussion of how recent discoveries in this area might inform improved plant protection strategies and improve our understanding of the coevolution of viruses, hosts and vectors.

The genetics of resistance to plant viruses

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For plant viruses able to overcome non-host resistance (i.e., virulent viruses), genetic resistance systems controlled by single dominant resistance (*R*) genes, or recessive resistance (*r*) genes are the best understood [1,16,17]. *R* genes are of two types: genes that encode factors that inhibit one or more stages in the viral infection cycle, or genes encoding NLR (Nucleotide-Binding and Leucine-Rich Repeat domain) proteins [18]. The first sort are exemplified by the genes *RTM* 1-3 in *A. thaliana* that encode jacalin-repeat lectin and meprin proteins, which limit the ability of specific potyviruses to

spread systemically in the host by blocking virus exit from the vasculature [19,20]. Contrastingly, in wheat the dominant genes *Wsm1* and *Wsm2* limit the systemic movement of the potyvirids wheat streak mosaic virus and *Triticum* mosaic virus by blocking their entry into the vasculature [21]. The resistance conferred by both genes is conditional, with susceptibility to virus movement occurring above 18ºC, but the modes of action of *Wsm1* and *2* remains unknown [21]. Some plants possess genes encoding factors that directly inhibit virus replication. The best understood are *Tm-1* and *tm-1* that encode proteins that inhibit replication of specific tobamoviruses in tomato (*Solanum lycopersicum*) by binding to the 126kDa helicase/methylase/RNA silencing suppressor protein [9,17,22,23].

NLR proteins are immune sensors that trigger a broad range of local (hypersensitive response, HR) and systemic defense responses (including systemic acquired resistance, SAR) following recognition of pathogens [18]. NLR proteins confer resistance to a wide variety of pathogens or pests (bacteria, viruses, fungi, oomycetes, nematodes, aphids) but most NLR proteins recognize a specific invader species or strain [3,18]. NLRs directly or indirectly recognize 'effector' molecules delivered into host cells (in the case of most invaders) or synthesized in the host cell (in the case of viruses) by pathogens and pests [18]. For this reason, resistance controlled by NLR proteins is referred to in more recent literature as effector-triggered immunity (ETI) [18]. A broad definition of an effector is a pathogen-encoded molecule required by the invader to parasitize a host plant; in the case of viruses, which are obligate intracellular parasites, the term effector might encompass all viral proteins. ETI is more specific than non-host resistance and the evolution of new NLRs and corresponding effectors is driven by competition between hosts and those pathogens that are able to overcome non-host resistance [3,4,18].

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The best understood *r* genes that encode variants of various isoforms of the cellular eukaryotic translation initiation factors eIF4E, eIF(iso)4E and eIF4G that are required by potyviruses, bymoviruses and poleroviruses for gene expression and movement [16,24]. These viruses possess a VPg (virus protein, genome-linked) molecule covalently attached to the 5' end of the viral genomic RNA in place of a conventional cap structure. VPg molecules interact with specific initiation factors and this interaction is essential for successful infection [24,25]. The usefulness of gene editing to generate novel *r* genes was demonstrated in two important papers by Pyott et al. [26] and Chandrasekaran et al. [27]. These groups used the CRISPR/Cas9 system to modify *eIF(iso)4E* in Arabidopsis to protect against turnip mosaic virus (TuMV) in Arabidopsis [26] and in cucumber *eIF4* was modified, yielding plants protected against the potyvirids cucumber vein yellowing virus, zucchini yellow mosaic virus (ZYMV), and papaya ring spot mosaic virus [27].

Other types of pro-viral host factor can give rise to *r* genes by mutation, although how the non-mutant versions of these factors support infection is not always as clear as it is in the case of eIF4-type factors [22]. The *r* gene *rymv2* present in multiple accessions of African rice (*Oryza glaberrima*) confers durable resistance to the sobemovirus rice yellow mottle virus (RYMV) and is homologous to the *Arabidopsis* gene encoding the defense regulator CPR5 [22,28,29]. Curiously, in the case of RYMV, mutation of its Vpg sequence allows strains to overcome resistance conditioned by *rymv2*, even though this resistance does not appear to operate through disruption of viral RNA translation (*Cf.* resistance mediated by variants of eIF4-type factors) [29].

Genetic resistance to viruses is surprisingly durable; surprisingly, since viruses have high mutation rates that should accelerate evolution of resistance breaking strains.

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However, most mutations are deleterious to the small genomes of viruses and mutants may be unviable or rendered sensitive to other resistance mechanisms [30]. This may help explain why resistance genes deployed in crops to defend against viral diseases have average useful lifetimes of around 13 years, compared to 7 years for genes deployed against fungal or oomycete pathogens [31,32,33].

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Signals in induced defense: Phytohormones, small RNA pathways and their convergences

Induced antiviral defense mechanisms such as SAR are activated in response to microbial or chemical stimuli; for example, following ETI/HR [34], or after exogenous treatment with a defense signal such as salicylic acid (SA) or one of its potential precursors (benzoic acid), a synthetic derivative (aspirin) or other synthetic compounds [35,36]. Since these early studies, a large number of SAR-inducing agents have been discovered [37]. In unchallenged plants, inducible defense mechanisms are inactive or active only at some low, basal level [3,37,38,39]. Such mechanisms may be costly to the plant and it therefore makes sense that they are regulated in this way [40,41]. SAR induction is dependent upon various signal molecules and phytohormones that propagate it locally and/or systemically in the plant and include SA, JA, abscisic acid (ABA), azelaic acid (AZA), glycerol-3-phosphate, and pipecolic acid [3,38,39,42,43].

Recent work has shown that SA can move through plant tissues in extracellular fluid whereas other signals involved in induction of SAR such as AZA and glycerol 3-phosphate move symplastically [44]. Symplastic signal movement occurs via plasmodesmata and, consistent with this, the plasmodesma-associated plasmodesmal-

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localizing protein 1 (PDLP1: 45) interacts with AZA [44], suggesting that PDLP1 plays a receptor-like role for this signal molecule.

RNA silencing is another inducible, but adaptive, antiviral mechanism, which in this case depends upon small RNA molecules, generated *de novo*, for its antiviral activity and for its propagation, rather than on genetically programmed biosynthesis of low molecular mass signal molecules [16,46]. However, it should be emphasized that RNA silencing does not function in isolation from SAR and can overlap with, or reinforce, other induced resistance systems (Figure 1). Examples of this include the effects of SA, ABA, gibberellins and other phytohormones, as well as transient defensive molecules such as hydrogen peroxide or nitric oxide, on the expression and/or activity of silencing factors RNA-dependent RNA polymerase 1 (RDR1) and Argonaute (AGO) [47,48,49,50,51,52,53,54,55,56]. ABA has other important effects on RNA silencing through its modulation of *AGO* transcript levels [57]. Additionally, ETI following recognition of virus infection by an NLR is associated with AGO4-mediated inhibition of translation of viral RNA [58].

Although *RDR1* gene expression is inducible by SA (as well as many other stimuli: see previous paragraph) it does not inhibit virus accumulation in infected tissue. However, it does limit the ability of certain viruses (such as TMV and potato virus Y, PVY) to invade meristematic tissue and in this way it diminishes symptom severity [49]. Thus, it performs a similar role to RDR6 in keeping meristems free of virus and in ameliorating disease, as shown using potato virus X (PVX) [59]. RDR1 also inhibits disease symptoms by viruses including PVY and TMV, regulates the levels of host mRNAs encoding proteins with known or likely roles in SA- and JA-regulated defenses in tobacco, *N. attenuata* and pepper (*Capsicum annuum*) [60,61,62,63], and RDR1 regulates cellular and organellar morphology [64]. SA-mediated resistance

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and silencing mediated by RDR1 and other factors, such as Dicer-like (DCL) 2 and 4, appear to work synergistically in the amelioration of viral disease as shown with TMV in *N. benthamiana* [49] and with citrus tristeza virus in sour orange [65]. However, work with Arabidopsis *dcl2/dcl3/dcl4* triple mutant plants showed that SA-induced resistance to viruses can occur in the absence of a functional antiviral RNA silencing system [66]. Thus, while RNA silencing can contribute to, or synergize with, SA-induced resistance, it is dispensable for effective SA-induced resistance.

Pharmacological experiments and work with transgenic plants expressing wild-type, mutant or antisense sequences derived from the gene encoding the mitochondrial enzyme alternative oxidase (AOX) showed that in tobacco (*Nicotiana tabacum*), *N. benthamiana*, and *N. glutinosa*, SA and other signals such as nitric oxide can stimulate resistance to viruses including TMV and PVX via mitochondrial retrograde signaling pathways [67,68,69,70,71,72,73,74,75] (Figure 2). Similarly, Ma and colleagues (76) found that modifying *AOX* expression in transgenic tomato (*Solanum lycopersicum*) and petunia (*Petunia hybrida*) plants could be used to enhance resistance to tomato spotted wilt virus. Disruption of mitochondrial redox in mutant Arabidopsis plants or by use of chemical inhibitors of the respiratory electron transport chain affected susceptibility to turnip crinkle virus (TCV) and CMV and SA-induced resistance [77,78]. This form of signaling involves reactive oxygen species generated in the mitochondria and is under negative regulation by AOX, which is the key enzyme of the cyanide-insensitive respiratory pathway, and potentially by other factors controlling mitochondrial redox [74,79]. It is uncertain how SA stimulates AOX-regulated retrograde signaling but candidate mechanisms include binding of SA to α-ketoglutarate dehydrogenase [42,80], or to the uncoupling

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effect of SA on mitochondrial respiration [81]. Interestingly, AOX is also implicated in resistance to a piercing-sucking insect in *N. attenuata* [82].

AOX-mediated retrograde signaling does not appear to be essential for SA-induced expression pathogenesis-related (PR) proteins (defensive plant gene products discussed in the next section of this review), although it can influence their induction [72,81]. The regulatory factor NPR1 (non-expressor of pathogenesis-related protein 1) controls expression of many PR proteins in a variety of plant species [3,39]. Neither AOX-regulated SA-induced resistance to viruses, nor *AOX* gene expression itself, depends upon the activity of NPR1 [83,84]. However, several studies suggest that RDR1 influences AOX expression and the expression of RDR6, another antiviral silencing factor [51,61,63]. It has also been shown that SA-induced *RDR1* gene expression is regulated by NPR1 [85]. Taken together, these studies hint at the existence of a highly complex regulatory network that coordinates expression and/or activity of NPR1, RDRs, and AOX.

However, in some plants SA-induced resistance appears to be independent of AOX-modulated signaling. Mayers and colleagues (77) found evidence that in squash (*Cucurbita pepo*) SA induces resistance to intercellular movement of CMV by an AOX-independent mechanism. Indeed, in some plants and for certain viruses, SA itself may not be the key antiviral signal. For example, it was found that in soybean (*Glycine max*) JA is a more important determinant of resistance to the bean pod mottle virus [86] and Lozano-Duràn and colleagues [87] have suggested a role for JA in limiting geminivirus accumulation.

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Plastids are also vital components in defensive signaling because they are the sites of key stages in biosynthesis of key several defense signals [88]. They are also arenas

for signal transduction processes. Plastidic defensive signaling has effects on the permeability of plasmodesmata to virus cell-to-cell movement [89], as do several phytohormones (SA, JA and ABA) that have plastidic origins [88,90,91].

Pathogenesis-related proteins

PR proteins are plant proteins that increase dramatically in abundance following pathogen attack or certain abiotic insults [1,38,39]. PR proteins are classifiable into a range of families, based on functional and genetic characteristics [92]. Currently, there is no definitive evidence that pathogenesis-related (PR) proteins play any essential roles in induced resistance to viruses, while there is abundant evidence that they have a variety of functions in limiting the spread of cellular pathogens [1,92]. Most PR proteins are induced by SA, JA, ABA, ethylene, nitric oxide, or some combination of defense-related signals [37,38]. Probably the best candidate for an antiviral PR protein is CaPR10 from pepper (*Capsicum annuum*), which is inducible by SA, a bacteria-induced HR, as well as a variety of other stimuli. CaPR10 was proposed as an antiviral factor because it has ribonuclease activity [93, later corrected in reference 94]. CaPR10 inhibits oomycete growth on agar plates and *in vitro* it degrades TMV and cellular RNA. Including recombinant CaPR10 in the viral inoculum decreased TMV coat protein accumulation in inoculated pepper leaves [93; later corrected by 94]. These experiments do not constitute definitive evidence that PR10 plays a role *in planta*. This could be provided, for example, through *CaPR10* gene RNAi-mediated knockdown, mutation, or virus-induced gene silencing. Furthermore, since CaPR10 degrades cellular RNA, as well as viral RNA, *in vitro* [93,94] it cannot have any specificity for viral RNAs. A 2001 publication reporting that another pepper PR protein, CaPR4, conditioned cultivar-specific resistance to TMV was recently retracted [95].

Antiviral properties have also been attributed to PR3 (chitinase) and PR2a (β-1,3 glucanase) proteins from tobacco. When mixed with TMV inocula both of these two PR proteins decreased infectivity of the virus on a local lesion host [96]. Unfortunately, this is not definitive proof for an *in planta* role for these proteins in the restriction of virus replication and spread following ETI or the induction of SAR. Investigation of the potential roles of the tobacco PR proteins 1, an SA-inducible glycine-rich PR protein, and PR S (PR5, a thaumatin-like protein: [97]) by overexpression in transgenic tobacco plants showed no increase in resistance to TMV or alfalfa mosaic virus [98,99], both of which are inhibited in their multiplication in various hosts by SA [35,36,100]. Currently, therefore, although PR proteins are important in induced resistance to cellular pathogens it still remains unclear whether or not any provide a significant degree of anti-viral defense.

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Increased SA biosynthesis is associated with resistance but it can occur during compatible plant-pathogen responses

There is ample evidence that SA is required for basal and induced resistance to a number of viruses. This has been established through two approaches. Firstly, the use of plants expressing *nahG* (bacterial salicylate hydroxylase) transgenes; these transgenic plants cannot accumulate SA at normal levels [101]. The second approach has used mutant plants that lack functional copies of genes encoding enzymes that catalyze steps in SA biosynthesis [102].

SA can be synthesized from compounds derived either from the phenylpropanoid pathway, potentially via hydroxylation of benzoate or *o*-coumarate [102,103,104,105,106] or via the shikimate pathway from chorismate [102,107]. Some plants such as soybean can biosynthesize SA utilizing carbon backbones drawn

291 from either pathway [108]. Despite many years of research there are still unanswered
292 questions regarding SA biosynthesis. For example, plants such as Arabidopsis that
293 utilize the shikimate pathway for most (but not all: 109) SA biosynthesis utilize a
294 similar approach to bacteria in that the conversion of chorismate to SA is a two step
295 process, comprising conversion of chorismate to isochorismate catalyzed by
296 isochorismate synthase (ICS) and conversion of isochorismate to SA and pyruvate by
297 isochorismate pyruvate lyase (IPL) [102]. Arabidopsis possesses two ICS isoenzymes
298 (AtICS1 and 2) that possess similar levels of activity but of which only one, AtICS1,
299 is expressed at high levels and only the AtICS1 gene is responsive to pathogens and to
300 SA [85,110]. Neither AtICS1 or 2 possesses IPL activity and no IPL has yet been
301 detected in plants [see further discussion see [110] and references therein]. Thus,
302 although it is clear that Arabidopsis is dependent upon the shikimate pathway for
303 production of most if not all of its SA, it remains unclear how the conversion of
304 chorismate to SA is achieved. There are also important unknowns for SA biosynthesis
305 *via* the phenylpropanoid pathway. Although activity of enzymes with potential to link
306 the phenylpropanoid pathway to production of SA (e.g., benzoic hydroxylase and SA
307 aldehyde synthase) have been discovered in tobacco [104,111], it does not appear that
308 detailed characterization of these enzymes or their corresponding genes has been done
309 [112].

310 Although increased SA biosynthesis occurs during defense responses, some viruses
311 induce increased SA accumulation without apparently causing any inhibition of
312 infection. This is seen in compatible interactions involving potyviruses and CMV
313 [52,113,114,115,116]. Pre-treatment of plants with SA can inhibit infection by these
314 viruses. So presumably CMV and potyviruses have already replicated to high levels
315 before they trigger SA accumulation. In the case of potyviruses, the potyviral HC-Pro

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can act as the trigger that stimulates hosts to produce SA [117]. This is curious since the same factor allows potyviruses to evade SA-induced resistance [118]. For CMV, the 2b primes, but does not trigger, increased SA biosynthesis [52,116]. The CMV 2b protein also allows the virus to evade SA-induced inhibition of CMV accumulation in inoculated tissues [69,116]. The ability of a virus to trigger SA accumulation and yet evade its antiviral effects may be important in the manipulation of plant-insect interactions (see later sections). Currently it is not known how compatible viruses (i.e. those that do not trigger ETI) induce increased SA biosynthesis in susceptible hosts.

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Viruses fight back: The effects of viral counter-defense factors on defensive signaling

Viruses are able to defeat one or more types of antiviral resistance. This first became apparent during early work on viral RNA silencing suppressor proteins. For example, viral counter-defense factors, some with known RNA silencing suppressor activity, such as the CMV 2b protein [52,69] and the multifunctional P1/HC-Pro proteins of potyviruses [118,119], the begomovirus C2 protein [87] and the geminiviral β-satellite DNA gene product βC1 [121,122], interfere in various ways with signaling pathways mediated by SA, JA, or both signals, further suggesting a connection. In the case of the CMV 2b protein, specific domains have been identified that are responsible for interference with SA-induced resistance [116].

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A recent paper suggested that the CMV 2b protein acts directly on JA-mediated signaling by binding to JAZ proteins [122]. However, the 2b protein also affects miRNA-regulated gene expression, which is known to impact on JA-mediated signaling [60,123], making it likely that this viral counter-defense protein has more than one way of interfering with this signaling pathway. Recently, it was shown that

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PTI is inhibited by the coat protein of the potyvirus plum pox virus [124]. Ethylene signaling is disrupted by the potyviral NIa protein [125] and this, like many of the other effects of viral gene products on phytohormone signaling described here, may have important effects not only on counteracting antiviral resistance, but also on the interactions of infected host plants with the insect vectors that transmit plant viruses.

Virus-induced changes in phytohormone signaling – roles in host and vector manipulation

Do virus-induced alterations in plant defensive signaling and metabolism in susceptible hosts serve any purpose beyond directly aiding viruses to replicate and spread? A growing body of data, in particular from studies of viruses vectored by whiteflies and aphids, indicates that viruses influence the efficiency of insect-mediated virus transmission, facilitate mutualistic relationships between viruses and their insect vectors, and might even condition 'pay-backs' to susceptible hosts.

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Transmission of viruses by insects with probing stylets (such as aphids and whiteflies) can be classified as non-persistent or persistent [126,127,128,129]. Non-persistently transmitted viruses like CMV or potyviruses are acquired and transmitted rapidly (periods of seconds) when the vectors feed on the epidermal cells of plants [130,131]. In non-persistent transmission, virus particles are loosely bound to the probing mouthparts (stylets) of the insect and are not internalized [25,127,128,129,132]. Persistently-transmitted viruses are internalized by the insect (such vectors include whiteflies, aphids, planthoppers, leafhoppers, or thrips) and require extended feeding times (hours) and penetration of the phloem for acquisition of the virus. A further period is required for virus particles to reach the insect salivary glands, at which point the insect becomes competent for virus transmission [25,128,132,133]. Most

persistently-transmitted plant viruses do not replicate within insect vectors; viruses that do replicate in insect vectors possess negative-sense or double-stranded RNA genomes [25]. Such viruses are able to modify gene expression in their insect vector/hosts [134,135], which is a potential pathway for virus-mediated behavioral modification. A striking example of direct manipulation of insect behavior by a plant virus that replicates in its vector is provided by tomato spotted wilt virus, which changes the feeding activity of male thrips (*Frankliniella occidentalis*) so as to maximize the likelihood of inoculation of virus into leaf cells [136]. Intriguingly, there are examples of persistently and non-persistently transmitted viruses that directly affect vector behavior, although they do not replicate in insects. Once acquired by males of its vector whitefly, *Bemisia tabaci*, cucurbit chlorotic yellows virus alters feeding behavior, although it resides in the foregut without replicating [137]. Aphids that have acquired barley yellow dwarf virus or potato leafroll virus, neither of which replicate in these insects, exhibit modified responses to plant volatile cues that steer them preferentially towards uninfected host plants [138,139]. Despite these puzzling examples of direct manipulation of insect vectors by viruses that (as far as we know) express their genes only in plants, vector manipulation by the majority of viruses has to occur indirectly, i.e. by altering host plants with respect to their defenses, nutritional properties and or the visual, tactile or olfactory cues they present to insects.

There appears to be mutualism between plant viruses and their vectors in cases in which virus infection improves host quality for vector colonization. This will benefit the vector through improved survival and reproduction, which is likely to benefit the virus by increasing the likelihood of transmission. For example, geminivirus-infected plants support larger populations of *B. tabaci* than uninfected plants, as seen in

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cassava infected by begomoviruses that cause cassava mosaic disease [140]. An important mechanism by which geminiviruses improve host quality is by selectively suppressing and stimulating specific plant defense pathways to facilitate increased infestation and minimize the resistance of plants to whiteflies. This is a fine balancing act. Whitefly feeding stimulates SA biosynthesis and consequent defensive signaling, which suppresses many JA-stimulated anti-insect responses [141,142]. However, this is a potentially serious challenge for whitefly-transmitted viruses, since stimulation of SA-mediated defensive signaling engenders SAR, which will inhibit infection by viruses, including geminiviruses [1,39,143]. Consistent with this, prior feeding by whiteflies on tobacco and tomato renders the plants less susceptible to subsequent inoculation with the begomovirus tomato yellow leaf curl China virus (TYLCCNV) by *B. tabaci* [144]. Geminiviruses have evolved a number of ways to inhibit JA-responsive gene expression with up-regulating SA-mediated virus resistance. The TYLCCNV βC1 pathogenicity factor/silencing suppressor encoded by its β-satellite DNA inhibits JA-regulated gene expression and decreases terpenoid production via inhibition of the MYC2 transcription factor activity; effects that enhance performance of whiteflies on infected plants [72,120,121,145]. The multifunctional C2/L2 protein of the geminivirus tomato yellow leaf curl Sardinia virus, disrupts defensive signaling (including JA-mediated signaling) by deregulation of turnover of proteins of hormone perception complexes [87].

Manipulation of defensive signaling by geminiviruses can have some remarkably subtle outcomes. Modifying of the balance between the SA- and JA-dependent signal transduction pathways by the begomovirus tomato yellow leaf curl virus (TYLCV) enhanced the performance of its *B. tabaci* vector on tomato plants, while decreasing that of a non-vector herbivore, a spider mite [146]. Arguably, the virus might be

427 providing a further payback to its whitefly vector by decreasing competition by other
428 herbivores. But how does inhibiting defenses against whiteflies aid the geminiviruses
429 themselves? Rates of acquisition and transmission of these persistently transmitted
430 viruses are enhanced if whitefly vectors are encouraged to settle and engage in
431 extended phloem feeding. Thus, virus-whitefly mutualism can also allow for
432 increased reproduction of the insects, further increasing the size of the pool vectors
433 available to transmit the virus.

434 Engendering settlement of vectors is also advantageous for viruses that are
435 transmitted by aphids in a persistent manner. Aphid-transmitted RNA viruses such as
436 luteovirids also require prolonged feeding by their vectors from the phloem for virus
437 acquisition [127,128,147]. Eigenbrode and colleagues showed that plant emitted
438 volatiles play an important role in attracting aphids to settle for prolonged periods on
439 plants infected with barley yellow dwarf virus and potato leafroll virus [147,148].

440 **Indirect viral manipulation of vector behavior is complex and may be an arena**
441 **for virus-host-aphid co-evolution**

442 With respect to viruses transmitted by aphids in the non-persistent manner, earlier
443 work focused on the role of visual cues in attracting aphids to infected plants
444 [149,150]. But an increasing body of data suggests that in some [151,152], but not all
445 [153], cases changes in volatile compound emission caused by infection of plants with
446 non-persistently viruses such as CMV may initially cause aphids (*Myzus persicae* or
447 *Aphis gossypii*) to be drawn to feed on CMV-infected plants. In cucurbits and
448 Arabidopsis CMV also induces the biosynthesis by the host of substances that are
449 distasteful to aphids [13,151]. The results of work with CMV-cucurbit-aphid models
450 [151,152] and with the CMV-Arabidopsis-aphid model [13], suggest that CMV is

able to manipulate plant volatiles to attract vectors, but limit aphid feeding to maximize acquisition of the virus and encourage the aphids to leave using anti-feeding compounds [151,152]. However, as discussed by Mauck [154] and Groen and colleagues [12], the relationships between virus-infected plants and vectors are not always so obviously conducive to virus transmission.

For example, the ability of CMV to induce aphid feeding deterrence in Arabidopsis is strain specific; the Fny strain induces glucosinolate production and feeding deterrence, but the LS strain has no effect on aphid feeding behavior in this host [13,155]. Although the Fny strain of CMV induces feeding deterrence on Arabidopsis, it inhibits aphid resistance in tobacco [156]. A number of potyviruses (TuMV, PVY, ZYMV) inhibit plant host defenses or increase palatability or nutritional value to aphids [125,157,158,159,160]. The amelioration of aphid resistance by virus infection is unlikely to increase the rate of aphid-mediated transmission of these non-persistently transmitted viruses and, indeed, may slow it down.

It has been suggested that this host plant and virus strain pleiotropy in virus-induced effects on aphid infestation might be beneficial to the virus and its vectors [12,13]. Specifically, in the case of a broad host-range virus like CMV, if infection *always* induced feeding deterrence to aphids, this might cause local extinction of vector populations and in the long term be damaging to the virus. However, if some hosts become more tolerant of aphid infestation following infection, these plants may serve as refuges for the virus and its vectors, especially when environmental conditions are not conducive to transmission [12,13]. However, another hypothesis is that this pleiotropy in virus-induced changes in the host-aphid interaction phenotype reflects the degree to which a virus strain and its host plant have co-evolved. Thus, it is suggested, a well-adapted strain of a non-persistently transmitted virus will tend to

induce changes in host metabolism that will encourage migration of viruliferous aphids and, for a persistently transmitted virus, virus infection will increase the hospitality of the host to aphids [154,161]. Currently, it is difficult to determine which of these hypotheses is the most likely and this is likely to be an area of active and exciting research in the future.

Future prospects

Induced resistance and its manipulation have now been studied for many years. The objectives of this research are to devise methods to control virus infection in crops and to increase our fundamental understanding of plant defense and plant-virus interactions. In recent years these studies have also provided insights into how defense signaling networks and defense signal molecules intersect with host-vector interactions and virus transmission [12,162]. This work could result in improved control of insect pests, including vectors, for example by manipulation of emission of insect-attracting volatiles. Such approaches have previously yielded important results for integrated pests management, such as the push-pull intercropping systems used to protect maize [163] and may lay the groundwork for future attempts to modify crops to repel vectors [see 164]. Recent, exciting work on the large-scale effects on vector gene expression of feeding on virus-infected versus healthy plants [165,166] could help identify new insect and plant targets for inhibition of insect-mediated virus transmission. Similarly, increased knowledge of how volatiles affect vector choice or even the preferences of beneficial insects such as biocontrol agents [167] and pollinators [168] could be used to enhance both protection and productivity, respectively. The attraction of beneficial insects to susceptible, infected plants could represent a payback to hosts, with viruses enhancing the survival and reproduction of susceptible hosts. This could have important impacts on the co-evolution of hosts and

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viruses and, it has been argued, inhibit the evolution of plants resistant to viruses [168].

In summary, it is conceivable that studies of induced resistance and defensive signaling may lead to integrated methods to improve resistance, decreased virus transmission and foster interactions with beneficial insects, which may not only protect crops but also increase their productivity. Improved understanding of viral manipulation of plant defense will also provide insights into the co-evolution of viruses, their host plants and vectors, and other plant-interacting organisms.

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Acknowledgements Support for our work was provided by the Republic of Korea Rural Development Agency (grant number PJ012426), the UK Biotechnological and Biological Sciences Research Council (SCPRID grant number BB/J011762/1, and GCRF grant number BB/P023223/1) and the Leverhulme Trust (Grants F/09 741F and RPG-2012-667).

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Figure 1. A simplified overview of how antiviral RNA silencing (**a**) overlaps with NPR1-dependent, salicylic acid-induced defense gene activation (including up-regulation of *RDR1* gene expression [85]) (**b**) and NPR1-independent antiviral resistance (**c**) including those dependent upon mitochondrial signaling phenomena (see Figure 2) known to occur in Arabidopsis and tobacco and those operating by unknown signaling mechanisms [77]. Abbreviations: AGO, Argonaute proteins; DCLs, dicer-like endoribonucleases; DS RNA. Double-stranded RNA structures, for example, distinct secondary structures in viral RNAs or occurring during viral replication; siRNAs, short (21-14nt) interfering RNA molecules generated by DCLs; NPR1, non-expressor of PR proteins 1, a master regulator of many aspects of gene expression changes triggered by salicylic acid and other defensive phytohormones such as jasmonic acid; PR proteins, pathogenesis-related proteins, several of which are known to have defensive properties against oomycete, fungal and bacterial pathogens [73]; RDR1, an RNA-dependent RNA polymerase that is inducible by a wide range of defensive signals [50,60,85,169] and which functions in amplification ('amplification loop') of RNA silencing through *de novo* generation of DS RNA substrates for DCLs. Dashed arrows indicate known effects of various factors in resistance. It is becoming apparent that several defensive phytohormone pathways (e.g. abscisic acid [47,57] and gibberellins [48]) affect components of RNA silencing, but salicylic acid is focused on here for simplicity.

Figure 2. Reactive oxygen species (ROS) are generated in mitochondria as by-products of respiratory electron transport chain activity. Although potentially toxic, ROS can also act as signals via interaction with hypothetical redox-sensing proteins leading to retrograde signaling and changes in nuclear gene expression associated antiviral resistance [74,170]. In plant mitochondria, ROS accumulation is negatively regulated by the enzyme alternative oxidase (AOX) and a number of other systems [170]. AOX does this by using excess reducing power accumulating in the mitochondrial ubiquinone (coenzyme Q) pool to catalyze reduction of oxygen to

1099 water without concomitant ATP generation [170]. Use of transgenic plants that have
1100 modified AOX levels or that express mutant AOX proteins, combined with studies
1101 using viral vectors carrying *AOX*-derived sequences to disrupt AOX activity or
1102 expression [67,71,171] indicate that AOX also regulates the induction of antiviral
1103 resistance by salicylic acid and nitric oxide, which induce transient increases in ROS
1104 through, respectively, uncoupling and/or inhibition of α-ketoglutarate dehydrogenase
1105 [42,80], and inhibition of respiratory electron transport [74,81,172].
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Highlights

- Plants possess multiple antiviral defenses.
- Many of these depend on biosynthesis of signal chemicals
- Plant viruses have evolved counter-defense factors
- Viral proteins including counter-defense factors can affect host-insect interactions
- Manipulation of host-insect interactions may facilitate virus transmission