



# Exploring the Diversity of Mechanisms Associated With Plant Tolerance to Virus Infection

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Tolerance is defined as an interaction in which viruses accumulate to some degree without causing significant loss of vigor or fitness to their hosts. Tolerance can be described as a stable equilibrium between the virus and its host, an interaction in which each partner not only accommodate trade-offs for survival but also receive some benefits (e.g., protection of the plant against super-infection by virulent viruses; virus invasion of meristem tissues allowing vertical transmission). This equilibrium, which would be associated with little selective pressure for the emergence of severe viral strains, is common in wild ecosystems and has important implications for the management of viral diseases in the field. Plant viruses are obligatory intracellular parasites that divert the host cellular machinery to complete their infection cycle. Hijacking/modification of plant factors can affect plant vigor and fitness. In addition, the toxic effects of viral proteins and the deployment of plant defense responses contribute to the induction of symptoms ranging in severity from tissue discoloration to malformation or tissue necrosis. The impact of viral infection is also influenced by the virulence of the specific virus strain (or strains for mixed infections), the host genotype and environmental conditions. Although plant resistance mechanisms that restrict virus accumulation or movement have received much attention, molecular mechanisms associated with tolerance are less well-understood. We review the experimental evidence that supports the concept that tolerance can be achieved by reaching the proper balance between plant defense responses and virus counter-defenses. We also discuss plant translation repression mechanisms, plant protein degradation or modification pathways and viral self-attenuation strategies that regulate the accumulation or activity of viral proteins to mitigate their impact on the host. Finally, we discuss current progress and future opportunities toward the application of various tolerance mechanisms in the field.

**Keywords:** plant–virus interactions, antiviral defenses, disease tolerance, RNA silencing, salicylic acid

## INTRODUCTION

Tolerance to biotic stresses caused by pathogens, including viruses, is well-documented in plants (Rausher, 2001; Pagan and Garcia-Arenal, 2018). Tolerance has been defined as a mitigation of the impact of virus infection irrespective of the pathogen load (Cooper and Jones, 1983). Although a significant virus load is sustained, the plant growth, yield or reproduction attributes are only minimally affected and visible symptoms are either absent or mild. Tolerance can be explained

as reaching equilibrium to allow acceptable compromises in host and virus fitness for long-term co-existence (**Figure 1**). Because viruses are intracellular obligate parasites, they require host resources to complete their infection cycle (Culver and Padmanabhan, 2007; Nagy and Pogany, 2012; Wang, 2015). Therefore, high virus fitness is at the expense of the host in symptomatic susceptible interactions. In resistant interactions, the plant fitness is preserved by preventing virus accumulation or systemic movement. In tolerant interactions, virus fitness is reduced by preventing over-accumulation of viral RNAs or by minimizing the concentration or activity of viral proteins that play a role in virulence. In turn, this limits the damage to the host. Because of their absolute dependence on their host, maintaining host fitness is also beneficial to viruses.

Plant viruses should not only be viewed as pathogens. In fact, experimental evidence documenting the beneficial impact of accommodating long-term virus infection is accumulating, especially in natural environments (Roossinck, 2011; Roossinck and Bazan, 2017). Indeed, virus infection can improve the plant resilience in sub-optimal environmental conditions, for example tolerance to drought. Virus-induced drought tolerance is associated with global reprogramming of plant gene expression, changes in hormone signaling and increased accumulation of metabolites and antioxidants (Xu et al., 2008; Westwood et al., 2013; Aguilar et al., 2017; Dastogeer et al., 2018). Interestingly, recent studies suggested that the benefits of increased drought resistance can be offset by increased virus virulence (Aguilar et al., 2017; Berges et al., 2018). Maintaining persistent virus infection can also improve the plant resistance to biotic stress including non-vector herbivory insects, other viruses, or unrelated pathogens (van Molken et al., 2012; Shapiro et al., 2013; Mascia and Gallitelli, 2016; Syller and Grupa, 2016). Thus, tolerance to virus infection does not only mitigate the impact on the host as shown in **Figure 1**, but under additional abiotic or biotic stress, it can actually enhance the host fitness. In agricultural settings, tolerance is often effective against a larger spectrum of isolates compared to resistance (Korbecka-Glinka et al., 2017). Because viruses are allowed to persist, the selection pressure for emergence of virulent strains is also reduced in tolerant cultivars compared to resistant cultivars (Rausher, 2001; Pagan and Garcia-Arenal, 2018). Thus, tolerance can be considered as an evolutionary stable defense response.

While many plant antiviral resistance genes (R genes) have been characterized (de Ronde et al., 2014; Miyashita and Takahashi, 2015; Sanfaçon, 2015; Hashimoto et al., 2016), the

genetic basis of tolerance is much less well-understood. However, tolerance and resistance are not necessarily mutually exclusive in the field and mechanisms that govern both outcomes can overlap significantly (Pagan and Garcia-Arenal, 2018). In fact, many defense responses genes that are activated by dominant R genes are also induced in tolerant interactions (Bengyella et al., 2015). As will be detailed below, tolerance is often explained by the balance between plant antiviral mechanisms and viral counter-defense responses.

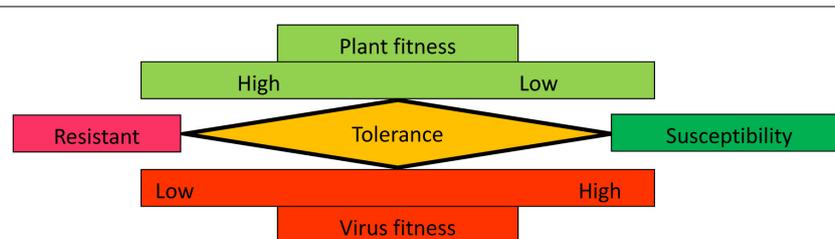
A recent review focused on plant–pathogen co-evolution in tolerant interactions (Pagan and Garcia-Arenal, 2018). In this review, we explore the molecular mechanisms that are associated with plant tolerance to virus infection. This review is not meant as an encyclopedic list of all known aspects of plant–virus interactions, rather we have selected examples that illustrate the variety of mechanisms that help attain long-term tolerance to virus infection. We also discuss current knowledge gaps as well as progress and future opportunities toward applications in the field.

## PLANT ANTIVIRAL DEFENSE AND VIRUS COUNTER-DEFENSES

The majority of plant viruses are considered generalists as they can infect a large variety of plant hosts (García-Arenal and Fraile, 2013). However, this does not mean that plants are passive in their interactions with viral pathogens. Indeed, although plants do not possess an equivalent to the animal adaptive immune system, they deploy a number of protein- and RNA-mediated defense mechanisms against viruses (Zvereva and Pooggin, 2012; Mandadi and Scholthof, 2013; Moon and Park, 2016; Gouveia et al., 2017; Nicaise, 2017; Carr et al., 2018). In turn, viruses have developed sophisticated counter-defenses to allow systemic infection of plants. The balance between plant defense responses and viral counter-defenses is finely tuned, often allowing the virus to persist without causing too much damage to its host.

### Antiviral RNA Silencing

RNA silencing is often considered the most important basal adaptive plant antiviral defense response (Moon and Park, 2016). RNA silencing is a ubiquitous gene regulation mechanism, which is based on the generation of small RNAs that guide the silencing machinery to complementary nucleic acids for transcriptional gene silencing (TGS) or post-transcriptional gene



**FIGURE 1** | Graphical representation of plant and virus fitness in resistant, tolerant, or susceptible interactions. See text for details.

silencing (PTGS) (Martinez de Alba et al., 2013). TGS results in the methylation and transcription repression of target DNAs, while PTGS operates by slicing target RNAs or repressing their translation. Plant DICER-like (DCL) proteins recognize double-stranded RNA (dsRNA) structures and process them into 21–25 nucleotides small RNA duplexes (Borges and Martienssen, 2015). One of the small RNA strands, the guiding strand, is loaded into ARGONAUTE (AGO) protein-containing RNA-induced silencing complexes (RISC) or RNA-induced transcriptional silencing complexes (RITSs) and directs these complexes to target nucleic acids in a sequence-specific manner for PTGS or TGS, respectively. In the context of antiviral RNA silencing, DCL enzymes recognize dsRNA structures present in replication intermediates produced during the replication of RNA viruses, in hairpin structures of viral RNAs, or in aberrant viral dsRNAs amplified by plant RNA-dependent RNA polymerases to produce viral-derived small interfering RNAs (vsiRNA), which are incorporated in RISC or RITS complexes (Raja et al., 2010; Martinez de Alba et al., 2013; Csorba et al., 2015; Ghoshal and Sanfaçon, 2015; Zhang C. et al., 2015; Ramesh et al., 2017). Plant microRNAs (miRNAs) are produced after processing of folded endogenous plant mRNAs derived from miRNA genes by DCL enzymes and are also highly relevant to plant–virus interactions (Martinez de Alba et al., 2013; Cui et al., 2017). As will be described below, specific miRNAs regulate the expression of genes coding for RNA silencing enzymes or other defense proteins.

Most viruses encode a viral suppressor of silencing (VSR) to counteract the plant antiviral RNA silencing. Characterized VSRs show tremendous diversity in their protein sequence and mode of actions (Csorba et al., 2015). VSRs can block RNA silencing by inhibiting the initiation/spread of RNA silencing (e.g., by binding small RNAs and sequestering them away from the silencing complexes), by affecting the assembly/stability/function of silencing complexes (e.g., by destabilizing or inhibiting AGO proteins) or by redirecting silencing complexes in the regulation of host defense genes (e.g., by inducing the transcription of endogenous miRNAs that down-regulate key plant silencing factor genes) (Csorba et al., 2015; Wiczorek and Obrepalska-Stepelowska, 2015). VSRs can specifically disrupt PTGS or TGS or can simultaneously affect both. Interestingly, some VSRs function by interacting with endogenous plant suppressors of silencing and/or by activating their transcription (Trinks et al., 2005; Endres et al., 2010; Yong Chung et al., 2014). Finally, it should be noted that some viruses encode more than one VSR (Lu et al., 2004) and that some VSRs can target multiple steps of RNA silencing (Csorba et al., 2015).

## Salicylic Acid-Mediated Defense Responses

Salicylic acid (SA) is a key signal molecule in plants that mediates defense responses associated with basal innate immunity and with inducible immunity directed by antiviral dominant R genes (Mandadi and Scholthof, 2013; Gouveia et al., 2017; Carr et al., 2018). Basal innate immunity associated with bacterial and fungal infection depends on surface-associated

receptors that recognize conserved microbe/pathogen-associated molecular patterns (M/PAMPs) and induce a cascade of events leading to PAMP-triggered immunity (PTI) (Jones and Dangl, 2006). In the case of virus infection, the presence of intracellular dsRNAs has been shown to trigger the PTI response in plants independently of the RNA silencing pathway (Niehl et al., 2016). PTI is accompanied with SA accumulation, and triggers a cascade of events, including an oxidative burst, activation of mitogen-activated kinases and induced expression of defense genes (e.g., pathogenesis-related or PR proteins) (Bigeard et al., 2015).

The second line of SA-mediated defense responses is often referred to as the effector-triggered defense (ETI). ETI requires the recognition of pathogen avirulent proteins, also termed effectors, by plant intracellular receptors, which are encoded by dominant R genes (Jones and Dangl, 2006). Most known antiviral dominant R genes encode proteins with nucleotide-binding leucine-rich repeats (NB-LRR) that share similarities with R genes directed at fungal and bacterial pathogens (Moon and Park, 2016; Gouveia et al., 2017). The ETI defense response is similar to PTI in its nature, but is more acute. ETI is generally associated with a local hypersensitive reaction (HR), which causes rapid cell death and the formation of visible necrotic lesions on inoculated leaves, and with the subsequent establishment of systemic acquired resistance (Moon and Park, 2016; Gouveia et al., 2017).

Several plant viruses have been shown to suppress the oxidative burst and the expression of defense genes associated with PTI or ETI (Hussain et al., 2007; Mubin et al., 2010; Zvereva et al., 2016; Nicaise and Candresse, 2017). A replicase protein of tobacco mosaic virus promotes the degradation of ATF2, a plant NAC transcription factor, which regulates the expression of PTI-responsive genes (Wang X. et al., 2009). Similarly, interaction between the turnip crinkle virus coat protein (CP) and TIP, another NAC transcription factor was correlated with the inhibition of innate immune defense responses (Donze et al., 2014). Finally, the P6 protein from cauliflower mosaic virus (CaMV) suppresses SA-signaling in part by modulating the expression and sub-cellular localization of NPR1 (NON-EXPRESSOR OF PATHOGENESIS-RELATED1), a transcriptional activator of downstream SA-responsive genes (Love et al., 2012).

## Dominant or Recessive Antiviral Resistance Genes That Do Not Depend on SA Signaling

Some characterized dominant R genes do not encode proteins with signature NB-LRR sequences and do not induce ETI-like defense responses (Gouveia et al., 2017). These R genes limit virus infection using different mechanisms. For example, a protein encoded by the tomato *Tm-1* gene binds to the tomato mosaic virus replication proteins and inhibits viral RNA replication (Ishibashi and Ishikawa, 2014). Finally, there are many characterized plant recessive resistance genes that correspond to mutations of plant factors that are essential to the virus infection cycle, most often translation factors, such as

eIF4E or eIF4G (Truniger and Aranda, 2009; Sanfaçon, 2015; Hashimoto et al., 2016).

## Role of Plant Hormones in Antiviral Defenses and Cross-Talks Between Defense Mechanisms

In addition to RNA silencing and SA-mediated defenses, signaling pathways controlled by various plant hormones influence plant antiviral responses (reviewed in Robert-Seilaniantz et al., 2011; Mandadi and Scholthof, 2013; Alazem and Lin, 2015; Carr et al., 2018). Jasmonic acid (JA) and ethylene (Et) are normally associated with defense mechanisms that operate against necrotrophic pathogens (JA and Et) and insect pests (JA) and have antagonistic effects on SA signaling and associated defense responses. Abscisic acid (ABA) regulates plant development and modulates the response to environmental stresses. ABA also has antagonistic effects on the SA- and JA/Et-pathways. Multiple levels of cross-talk among the SA-, JA-, ABA-signaling pathways and RNA silencing highlight complex regulatory mechanisms of host defense responses that are manipulated by viruses to their advantage. For example, some VSRs interfere not only with antiviral RNA silencing but also with the SA-, JA- or Et-pathways, in some cases down-regulating plant defense responses to promote their transmission by insect vectors (Ji and Ding, 2001; Geri et al., 2004; Lozano-Duran et al., 2011; Love et al., 2012; Westwood et al., 2014; Zvereva et al., 2016; Wu et al., 2017; Poque et al., 2018). SA was also recently shown to regulate cross-talks between gibberellin synthesis/signaling (involved in plant development) and the induction of miRNAs targeting plant defense genes (Kriznik et al., 2017). Finally, primary plant metabolism pathways (synthesis of carbohydrates, lipids, or amino acids) have been shown to impact plant defense responses (Bolton, 2009; Rojas et al., 2014). For example, sugars are both essential energy resources for the activation of defense responses and regulators of these responses (Bolouri Moghaddam and Van den Ende, 2012).

## SYMPTOM DETERMINANTS IN PLANT-VIRUS INTERACTIONS

### Fitness Costs of Activating the Plant ETI or PTI Defense Responses

Expression of defense genes during ETI or PTI is associated with fitness costs. As mentioned above, mounting the defense response requires energy resources, which are diverted at the expense of plant growth and development. Indeed, constitutive overexpression of R genes or other defense genes often causes pleiotropic effects on plant development (Heil and Baldwin, 2002; Tian et al., 2003; Yang and Hua, 2004; Yi and Richards, 2007). Induction of defense hormones can also result in reduced plant growth (Huot et al., 2014; Havko et al., 2016; Guo et al., 2018). Thus, the activation of SA-dependent defense responses is likely one of the factors contributing to the dwarfing phenotypes observed in many plant–virus interactions.

Plants down-regulate the expression of R genes or associated defense genes in the absence of pathogen pressure using either dedicated repressor genes or miRNA-mediated RNA silencing. For example, the *Arabidopsis thaliana* *BONZAI1* (*BONI*) gene down-regulates the expression of the R-like gene *SNC1* (Yang and Hua, 2004). Plant miRNAs have been identified that target characterized R genes or R-like genes with signature NB-LRR sequences (He et al., 2008; Zhai et al., 2011; Li et al., 2012; Shivaprasad et al., 2012; Deng et al., 2018). These miRNAs often target conserved regions of R or R-like genes resulting in the production of secondary siRNAs, which in turn down-regulate a larger number of related genes based on sequence similarities (Zhai et al., 2011; Li et al., 2012; Shivaprasad et al., 2012; Boccara et al., 2014). Following virus infection, the miRNA-mediated repression of R and R-like genes is released and the plant defense is upregulated (Shivaprasad et al., 2012). This may be an indirect consequence of the inhibition of plant RNA silencing by VSRs. Indeed, elevated expression of the R-like gene *SNC1* is observed in plants expressing VSRs (Yi and Richards, 2007). Similarly, tobacco plants expressing the potyvirus HC-Pro VSR display enhanced resistance to various pathogens, including several viruses (Pruss et al., 2004; Jovel et al., 2011). As a counter-defense, some plant viruses regulate the expression of specific miRNAs that target R or R-like genes (e.g., miR1885 induced by turnip mosaic virus) (He et al., 2008), or other defense genes (miR164a that targets NAC transcription factors implicated in regulating cell death) (Bazzini et al., 2009).

Necrotic responses associated with HR are generally thought to play a role in restricting virus movement. However, HR is not always efficient at restricting viruses and cells outside of the cell death zone of local necrotic lesions can harbor infectious virus (Lukan et al., 2018). In some pathosystems, induction of HR is either weak or delayed and does not prevent the systemic spread of viruses. Instead, this can result in runaway HR leading to systemic lethal necrosis (Moffett, 2009; Pallas and Garcia, 2011; Mandadi and Scholthof, 2013; Künstler et al., 2016).

### Impact of Viral Infection on Plant Organelles

In susceptible plants, virus infection can cause profound reorganization of host cells, by altering the structure and integrity of intracellular membranes and organelles (Laliberte and Sanfaçon, 2010). A common symptom of virus infection is chlorosis, often expressed as yellow mosaic symptoms on the leaves. Chlorotic symptoms have been correlated with virus-induced changes in the number or size of chloroplasts, or with structural alterations: invaginations of chloroplast membranes, formation of tubular stromules, changes in the number or appearance of grana or starch grains (Li et al., 2016; Zhao et al., 2016; Bhattacharyya and Chakraborty, 2017). In addition, biotic stress including viral infection has been reported to cause global repression of plant photosynthetic genes (Bilgin et al., 2010). The chloroplast is a key player in the deployment of plant defense responses with SA, JA,

and reactive oxygen species being produced in the chloroplast (Dempsey et al., 2011; Kangasjarvi et al., 2012; Li et al., 2016; Zhao et al., 2016; Bhattacharyya and Chakraborty, 2017). It was recently shown that ETI-dependent activation of MPK3/MPK6 (mitogen-activated kinases) inhibits photosynthesis which in turn leads to the accumulation of reactive oxygen species required for the HR (Su et al., 2018). Specific interactions between viral and chloroplast proteins can also interfere with the normal functioning of the chloroplast (Zhao et al., 2016).

Replication of RNA viruses requires association with and extensive modification of intracellular membranes derived most often from the endoplasmic reticulum (ER), but also from chloroplasts, peroxisomes or vacuoles, depending on the specific plant–virus interaction (Laliberte and Sanfaçon, 2010; Jin et al., 2018). Cell-to-cell movement of some viruses also require modification of ER membranes. The ER is an important organelle that orchestrates post-translational modifications and folding of cellular proteins destined to the secretory system. Alterations of the ER structure caused by virus infection and the vigorous ER-associated synthesis of viral proteins can cause severe ER stress, which if not mitigated, can lead to programmed cell death (Zhang and Wang, 2012; Verchot, 2016a). Most often, viral integral membrane proteins are responsible for the ER modifications. In some cases, these viral proteins act as viroporins, creating aqueous pores in the membranes and affecting their integrity (Nieva et al., 2012; Sanfaçon, 2013). In addition, viral movement proteins (MPs) interact with and modify the plasmodesmata that connect plant cells to promote virus cell-to-cell movement, a process which can disrupt the natural movement of nutrients and signal molecules between cells (Harries and Ding, 2011). Alterations of the actin and tubulin intracellular transport networks are also common consequences of plant virus infection (Niehl et al., 2013; Pitzalis and Heinlein, 2017).

## Toxic Effects of Viral Proteins

In addition to the gross alterations in sub-cellular structures described above, a large network of interactions between plant and virus proteins has been characterized (Wang, 2015; Nagy, 2016). In fact, hub viral proteins may interact with a large number of host proteins. For example, the tombusvirus p33 replication protein has more than 100 known plant protein interaction partners (Nagy, 2016). Although, it is beyond the scope of this review to describe each known protein-protein interaction, it is important to note that many of these interactions affect the host physiology profoundly, which can lead to visual symptoms and/or impact the host general fitness (reviewed in Culver and Padmanabhan, 2007; Mandadi and Scholthof, 2013).

Although many viral proteins contribute to virulence, VSRs are often virulence factors and symptom determinants. VSRs were first discovered in the context of synergistic interactions between two plant viruses. The potyvirus HC-Pro protein was shown to assist a potexvirus with counter-defense responses to the plant antiviral RNA silencing, resulting in increased

symptom severity (Anandalakshmi et al., 1998). The virulence properties of VSRs may be partly due to the increased virus accumulation that follows the inhibition of the plant antiviral RNA silencing. However, symptom severity is not always correlated with the level of genomic viral RNA accumulation (Pagan et al., 2007). For example, a chimeric potato virus X expressing the potyvirus HC-Pro VSR accumulates to lower levels than the native virus in infected plants but causes more severe symptoms (Aguilar et al., 2015). Several VSRs are also recognized as elicitors of dominant R genes and trigger necrotic defense responses (Li et al., 1999; Wang et al., 2015). Because RNA silencing is a ubiquitous gene regulation mechanism in plants, VSRs may disturb not only antiviral RNA silencing pathways but also other aspects of the plant metabolism and development that are regulated by RNA silencing. As mentioned above, VSRs can impact the expression, stability or activity of AGO proteins, in particular AGO1 which is required for miRNA-mediated regulation of plant gene expression. Thus, ectopic expression of VSRs in transgenic lines can cause phenotypic changes, similar to symptoms induced during virus infection or to those observed in AGO1-deficient mutants (Zhang et al., 2006; Bortolamiol et al., 2007; Varallyay and Havelda, 2013). Similarly, many VSRs such as the tombusvirus p19 protein have been shown to sequester not only vsiRNAs but also plant siRNAs or miRNAs (Chapman et al., 2004; Wu et al., 2010; Pertermann et al., 2018). Interestingly, recent reports suggest that p19 sequesters vsiRNAs more efficiently than miRNAs and that miRNA binding may only occur early in infection when the concentration of vsiRNAs is still low (Kontra et al., 2016; Pertermann et al., 2018). Thus, the regulation of this VSR activity is fine-tuned during virus infection perhaps to mitigate its impact on the host physiology.

## Viral siRNAs Directed at Plant Genes

Reports on how viruses use vsiRNAs to modulate the expression of plant genes are emerging. *In silico* analysis, and in some cases further functional validation, revealed many plant mRNA targets of vsiRNA in several plant–virus interactions (Qi et al., 2009; Miozzi et al., 2013; Stare et al., 2015; Wang et al., 2016a; Moyo et al., 2017; Xu and Zhou, 2017). Perhaps not surprisingly, several targeted transcripts encode proteins related to host stress responses and signal transduction. For example, vsiRNA of cotton leaf curl Multan virus were shown to target a gene encoding a MYB transcription factor that restrict virus accumulation (Wang et al., 2016a). Targeting of plant genes by vsiRNAs can also cause visual symptoms. Infection of cucumber mosaic virus together with the associated satellite Y RNA causes yellowing of leaves in *Nicotiana tabacum*. This was correlated with the down-regulation of a gene involved in chlorophyll biosynthesis (*Chll*) which is targeted by small RNAs derived from the satellite RNA (Shimura et al., 2011; Smith et al., 2011). Similarly, downregulation of *Nicotiana benthamiana* eukaryotic translation initiation factor (NbeIF4A) was shown to be associated with the stunting phenotype of *N. benthamiana* plants infected with rice stripe virus (Shi et al., 2015).

## PREVALENCE OF TOLERANCE IN WILD ECOSYSTEMS AND IMPACT OF ENVIRONMENTAL FACTORS

### Long-Term Mutually Beneficial Co-existence Defines Many Plant–Virus Interactions in Natural Environments

Plant viruses were first discovered because of their impact on economically important crops and as a consequence they have been described as pathogens for many years. However, plant–virus interactions are much more complex in natural environments. Metagenomic studies have revealed that virus infection is common in natural ecological settings with 60–70% of plants infected with one or several viruses (Roossinck et al., 2015). Interestingly, virus-infected plants are normally asymptomatic in wild environments (Roossinck, 2014). In fact, the point has been made that large-scale crop monocultures in agricultural settings and the consequent loss of biodiversity has contributed to the emergence of severe plant virus diseases (Roossinck, 2015; Roossinck and Garcia-Arenal, 2015). In natural settings, generalist viruses would be favored. Accommodating a wider host range usually results in reduced virulence, in part because of selection pressures to evade or counteract multiple defense responses that vary in their intensity from host to host (Miyashita et al., 2016). In the wild, plants and viruses are exposed to long-term ongoing selection pressures from multiple biotic and abiotic stresses (McLeish et al., 2018). Mixed virus infections are common in plants and can result in synergistic or antagonistic interactions (Mascia and Gallitelli, 2016) that also influence virus evolution and adaptation to new hosts (McLeish et al., 2018). The strict requirement of many viruses for vector transmission (most often insects) also drives virus evolution and virulence (Hily et al., 2014; Roossinck, 2015; Blanc and Michalakakis, 2016; Hamelin et al., 2017). While viruses may afford to kill or damage their hosts in agricultural settings because of the prevalence of specialized insect vectors adapted to specific crops, extending the lifespan and fitness of the host is a more viable option in natural environments. Finally, it should also be noted that in nature many persistent viruses do not depend on vector transmission (Roossinck, 2014; Roossinck and Bazan, 2017). Rather, they are strictly vertically transmitted through seeds and must ensure successful reproduction of their host. While the prevalence of tolerant and often mutually beneficial interactions in the wild is well-documented, the molecular mechanisms that govern these interactions have not yet been characterized. This will likely become a focus of future research.

### Age-Dependent Tolerance to Virus Infection

Plants exhibit more tolerance to disease as they age. The maintenance of TGS and PTGS can differ in plants that are in vegetative or reproductive stages and some VSRs are not active in older plants at the reproductive stage (Jackel et al., 2015).

For example, mature plants show decreased concentration of the small RNAs that regulate the expression of a tobacco R gene directed at tobacco mosaic virus (the *N* gene) (Deng et al., 2018). Furthermore, plant pre-exposed to other diseases also shows increased tolerance to new infecting viruses, a phenomenon referred to as priming (Jung et al., 2009). In natural environments where multiple pathogens are present and mixed infections are prevalent, plant priming could be a common occurrence.

### Impact of Environmental Conditions on Symptom Severity

Environmental conditions such as temperature, light duration and intensity, water availability and concentration of CO<sub>2</sub> affect viral symptom expression (Hily et al., 2016; Berges et al., 2018). Attenuation of virus-induced symptoms on tobacco plants at extreme temperatures (>36°C or <11°C), called temperature masking, was described almost a century ago (Johnson, 1921; Grainger, 1936). Although, detailed molecular studies in such extreme environments are lacking, the effect of temperature on symptom severity is well-documented in the permissive range (15–30°C). In many cases, temperature-dependent symptom attenuation has been correlated with the regulation of antiviral RNA silencing, as evidenced by the increased accumulation of vsRNAs at higher temperatures (Szittyta et al., 2003). Indeed, plants that are deficient in silencing factors show increased susceptibility to viral infection at higher temperatures (Qu et al., 2005; Zhang et al., 2012; Ghoshal and Sanfaçon, 2014). On the other hand, viruses that are deficient in VSR activity can only successfully infect plants at lower temperatures (Szittyta et al., 2003). However, the effect of temperature on RNA silencing efficiency can vary with the plant species. siRNAs are abundantly detected in grapevine plants grown at a range of temperature from 4 to 26°C, but they are not detected in *A. thaliana* plants grown at 4°C (Romon et al., 2013). Indirect effects of temperature on the induction of RNA silencing have also been proposed. Higher temperatures allow more efficient viral RNA replication (Zhang et al., 2012) and this is often associated with earlier symptom development (Obrępańska-Stęplowska et al., 2015). At lower temperatures, although the initial viral titer is lower, viruses accumulate to higher levels later on and consequently, more severe symptoms can develop at late stages of infection (Szittyta et al., 2003; Chellappan et al., 2005; Qu et al., 2005; Ghoshal and Sanfaçon, 2014; Xu et al., 2016; Paudel et al., 2018). It is possible that the onset of antiviral RNA silencing, which is triggered when the viral RNA concentration reaches a critical level, occurs earlier at higher temperatures as a consequence of the enhanced virus replication. The efficiency of PTI or ETI is also affected by the growth temperature. In several plant–virus interactions, HR or HR-like responses are slower when the temperature is elevated from 21–22 to 27–28°C and are even prevented at temperatures above 30°C (Whitham et al., 1996; Wang Y. et al., 2009; Jovel et al., 2011). Although increased RNA silencing activity would contribute to temper the expression of defense genes at

higher temperatures, it was also shown that the activity and nuclear localization of two R genes (including the *N* gene) are temperature-sensitive directly affecting the defense response (Zhu et al., 2010).

Light intensity also modulates the outcome of plant virus infection. This is not surprising considering that the chloroplast is a major player in plant–virus interactions (Li et al., 2016; Zhao et al., 2016; Bhattacharyya and Chakraborty, 2017). Plants growing under high light conditions show enhanced PTI and ETI responses to various pathogens, including viruses (Chandra-Shekara et al., 2006; Manfre et al., 2011). High light intensity has also been shown to increase localized RNA silencing but reduce the systemic movement of RNA silencing due to shifts in the sink and source status of the leaves (Patil and Fauquet, 2015). Transgenic *N. benthamiana* plants expressing GFP show increased frequency of silencing at higher light intensity and this was correlated with the increased expression of several silencing genes (e.g., *DCL*) (Kotakis et al., 2010, 2011). Consistently, the promoter regions of *DCL* genes contain a light responsive element (Liu et al., 2009).

The level of CO<sub>2</sub> is another factor that influences plant defenses to pathogen infection (Noctor and Mhamdi, 2017). Growth under high CO<sub>2</sub> levels triggers the synthesis of SA and primes plant defense responses (Mhamdi and Noctor, 2016). In the context of virus infection, CO<sub>2</sub> levels have also been shown to influence symptom development (Aguilar et al., 2015; Del Toro et al., 2015; Del Toro et al., 2017). Increased levels of CO<sub>2</sub> generally result in larger leaf size and can attenuate the impact of virus infection in a virus-specific manner. Higher CO<sub>2</sub> exposure alleviated some of the negative effects of potato virus Y infection allowing increased accumulation of biomass, nitrogen content and soluble protein but decreased carbon/nitrogen ratio (Ye et al., 2010). Finally, water availability can also impact virus virulence and/or transmission by insect vectors (van Munster et al., 2017; Berges et al., 2018).

The studies described above were conducted in the controlled conditions of experimental greenhouses or growth chambers. However, it is more difficult to predict the impact of the seasonal and diurnal fluctuations of environmental conditions

(Sanfaçon, 2017; McLeish et al., 2018). Clearly, more studies are warranted to examine plant–virus interactions under field conditions and determine how fluctuating environmental conditions could influence the effectiveness or durability of tolerance.

## SYMPTOM RECOVERY AS AN INDUCIBLE FORM OF TOLERANCE

Symptom recovery is a typical outcome of some plant–virus interactions, in which plants initially displaying systemic symptoms later recover from infection as exemplified by the emergence of young asymptomatic leaves (Ghoshal and Sanfaçon, 2015) (Figure 2). Although the level of viral nucleic acid accumulation is often reduced in recovered leaves (Covey et al., 1997; Szittyta et al., 2003; Chellappan et al., 2005; Santovito et al., 2014; Korner et al., 2018), this is not a strict requirement. For example, in the interaction between tomato ringspot virus and *N. benthamiana*, early onset of recovery is not accompanied with a significant reduction of viral RNA levels, although the concentration of viral proteins is reduced (Jovel et al., 2007; Ghoshal and Sanfaçon, 2014). Viruses present in recovered tissues maintain their infectivity and protect the plant against secondary infection in a sequence-specific manner (Ratcliff et al., 1997, 1999; Jovel et al., 2007; Santovito et al., 2014; Paudel et al., 2018). This has been attributed to the induction of antiviral RNA silencing during the symptomatic phase of infection (Santovito et al., 2014). Depending on the specific virus, PTGS (viral RNA slicing and/or translation repression), TGS (DNA methylation) or a combination of PTGS and TGS is associated with symptom recovery (Ghoshal and Sanfaçon, 2015; Korner et al., 2018). In all cases, the accumulation of viral proteins is reduced to a level below the threshold required for symptom induction. Because young tissues are symptom-free, the host is able to produce seeds. Interestingly, many viruses associated with recovery phenotypes are seed-transmitted. They apparently escape host surveillance mechanisms to invade meristem tissues, at least transiently (reviewed in Ghoshal and Sanfaçon, 2015). Thus, symptom recovery can be viewed as an inducible form of tolerance. This makes it an ideal model



**FIGURE 2 |** Symptom recovery in *Nicotiana benthamiana* plants infected with tomato ringspot virus. Symptoms are shown during the symptomatic phase of infection as they appear on inoculated leaves (**left**) and systemically infected leaves (**center**). (**right**) Shows a plant after symptom recovery with asymptomatic young leaves emerging above older symptomatic leaves. Reproduced with permission from Jovel et al. (2007).

system for the study of molecular mechanisms associated with tolerance.

## INSIGHTS IN THE COMPLEXITY OF TOLERANT PLANT-VIRUS INTERACTIONS DERIVED FROM GENETIC AND TRANSCRIPTOMIC STUDIES

### Field Tolerance to Virus Infection in Agricultural Crops: Mapping and (Limited) Characterization of Associated Genes

Although tolerance to virus infection is a well-known phenotype in the context of agriculture, the genetic basis for field tolerance is still poorly understood. Genetic crosses and mapping studies have identified a number of quantitative traits loci (QTL) or genes that are associated with tolerance. For example, several genes and QTLs have been linked to tolerance to barley yellow dwarf virus in barley, oat, and wheat (McKenzie et al., 1985; Singh et al., 1993; Jin et al., 1998; Riedel et al., 2011; Del Blanco et al., 2014; Foresman et al., 2016). While in some cases the tolerance was mapped to a single gene, in many cases a combination of major and minor loci were shown to contribute to tolerance and segregation analysis only indicated partial dominance of the major loci. In maize, one to four QTLs were found to be associated with tolerance to maize chlorotic mottle virus in different maize populations (Jones et al., 2017). The QTLs differed with the population, revealing a variety of natural sources for tolerance. In okra, tolerance to yellow vein mosaic virus was mapped to a single dominant gene in two different tolerant cultivars, although other factors were also involved (Senjam et al., 2018). As above, the dominant gene proved to be different in the two cultivars. Tolerance to tomato yellow leaf curl virus is also associated with single dominant genes in wild tomato species and was successfully introgressed into cultivated tomato (Zamir et al., 1994; Vidavsky and Czosnek, 1998). In peach, tolerance to plum pox virus (a potyvirus) was mapped to three loci (Cirilli et al., 2017). One of these loci included a candidate gene with similarities to the *A. thaliana* *RTM-2* gene, which is implicated in the restriction of the systemic movement of other potyviruses (Cirilli et al., 2017). However, functional validation will be required to confirm whether the *RTM-2*-like gene is indeed responsible for the tolerance. In summary, the variety of dominant, semi-dominant, or recessive tolerance genes found in agricultural crops and the common requirement for multiple loci suggests that molecular mechanisms associated with field tolerance are numerous and complex.

### Host Resource Reallocation in Some but Not All Tolerant Plant-Virus Interactions

Plants can respond to pathogen infection by reallocating resources from vegetative growth to reproduction (i.e., production of seeds). In the *A. thaliana*-cucumber mosaic

virus interaction, plants with longer vegetative growth cycles (i.e., longer life spans) are more tolerant to infection (Pagan et al., 2008; Hily et al., 2014; Shukla et al., 2018). Tolerance is also associated with increased seed yield and a shortened reproduction period, reducing the time span between the production of reproductive structures and seed production (Pagan et al., 2008). However, *A. thaliana* that were tolerant to cucumber mosaic virus did not show similar resource reallocation in response to more virulent viruses, suggesting that this response is virus specific (Shukla et al., 2018). In addition, tolerant plants with extended vegetative growth resulting from resource allocation were less competitive in the context of dense plant populations (Pagan et al., 2009). Additional studies using a variety of tolerant plant-virus interactions grown under various environmental conditions should shed more light on the biological relevance of resource allocation. Little is known regarding underlying molecular mechanism associated with resource reallocation. However, it is likely that they would require multiple genetic determinants affecting various regulatory mechanisms that control plant growth and development.

### Reprogramming of the Plant Transcriptome in Tolerant Interactions Affecting Defense Pathways, Primary Metabolism, and Hormone Signaling

Virus infection induces global changes in the plant transcriptome and proteome in both susceptible and resistant interactions (Palukaitis et al., 2008; Llave, 2016). To date, only a limited number of transcriptomic studies have focussed on tolerant interactions (reviewed in Bengyella et al., 2015). Transcriptome changes have been characterized at different stages of virus infection in a tolerant interaction (Stare et al., 2015). Time-course studies have also allowed monitoring symptomatic and asymptomatic phases of infection associated with symptom recovery or with delayed symptom induction (Allie et al., 2014; Madronero et al., 2018). Finally, transcriptomes or proteomes have been compared in susceptible, resistant or tolerant cultivars infected with the same virus strain (Allie et al., 2014; Wang et al., 2016b) or in plants infected with virulent or mild virus strains (Kogovsek et al., 2016; Geng et al., 2017). Not surprisingly, these studies have highlighted both similarities and differences in the transcriptome changes induced by viruses in susceptible, tolerant, and resistant interactions. In many cases, similar plant pathways are affected in the different types of interactions but to different extents or with different dynamics. Pathways commonly impacted by virus infection include defense responses (e.g., R-like genes and PR proteins), primary metabolism, photosynthesis, and hormone signaling.

In the interaction between potato virus Y and the tolerant potato cultivar Désirée, photosynthesis genes were shown to be transiently induced at early stages of infection but then rapidly repressed at the onset of virus multiplication (Stare et al., 2015). It was suggested that the early induction of photosynthesis (and other primary metabolism associated genes) helps promote the induction of defense responses. Transgenic

Désirée, transformed with the *NahG* gene that down-regulates SA signaling, showed more severe symptoms upon virus infection and a diminished induction of photosynthesis genes at early stages of infection (Stare et al., 2015). Analysis of small RNA signaling in the potato virus Y-potato cv. Désirée interaction revealed induction of miRNAs known to down-regulate R-like genes and the presence of vsiRNAs that target plant stress signaling response genes. Plant small RNAs that down-regulate the gibberellin synthesis were also induced and this affected the levels of miR482f, a key regulator of R-like gene expression (Kriznik et al., 2017). This complex regulation of small RNA pathways was shown to be dependent on SA signaling.

Other studies have also shown increased induction of SA signaling, defense response proteins or R-like genes in tolerant cultivars or in asymptomatic phases of infection compared to corresponding symptomatic interactions (Sahu et al., 2012; Allie et al., 2014; Louis and Rey, 2015; Wang et al., 2016b; Madronero et al., 2018). Many of these studies also noted altered primary metabolism. In some cases, increased expression of antiviral RNA silencing genes was also observed in tolerant interactions (Sahu et al., 2012; Allie et al., 2014). The impact of JA and Et signaling pathways is less clear. Delayed symptom induction in the interaction between papaya and the papaya meleira virus complex is associated with concomitant induction of both SA-defense responses and the antagonistic JA pathway (Madronero et al., 2018). Similarly, although susceptible cassava cultivars show reduced JA and Et signaling after infection with South African cassava mosaic virus, a tolerant cultivar does not (Allie et al., 2014). Taken together these studies highlight the complex regulatory networks between various plant hormone signaling pathways and defense responses.

Although the analysis of global transcriptome changes provides useful insights in the intricacy of plant-virus interactions, it is not always clear whether these changes are the cause or consequence of tolerance. Also, since transcriptomic studies do not examine post-transcriptional changes in gene expression, it is not known whether changes in the transcriptome are also reflected in the plant proteome. In fact, a recent study highlighted major discrepancies between transcriptomic and proteomic data that may be of biological significance (Stare et al., 2017). In addition, environmental factors are also predicted to impact the outcome of transcriptome studies. Indeed, transcriptomics analysis of plants exposed under combination of three different stresses exhibit significant differences in their gene expression compared to plants exposed under single stress (Prasch and Sonnewald, 2013). These issues are exemplified in a recent analysis of the expression of AGO2 in plants grown at two temperatures and infected with two tomato ringspot virus isolates of varying virulence (Paudel et al., 2018). Although AGO2 mRNAs were transiently induced to similar levels under all conditions, the accumulation of the AGO2 protein was influenced by the isolate and the growth temperature. Plants that later recovered from infection showed increased accumulation of AGO2 protein at early stages of infection. However, mutation of AGO2 did not prevent the symptom

recovery suggesting that other factors influence the outcome of infection.

## MOLECULAR MECHANISMS ASSOCIATED WITH ACHIEVING A BALANCE BETWEEN ANTIVIRAL RNA SILENCING AND VIRUS COUNTER-DEFENSE RESPONSES

As described above, symptom recovery, an inducible form of tolerance, is associated with the induction of antiviral RNA silencing. Thus, it could be assumed that viruses that are associated with symptom recovery phenotypes do not suppress silencing efficiently. In fact, mutation of potent VSRs from virulent viruses can lead to symptom recovery (reviewed in Ghoshal and Sanfaçon, 2015). On the other hand, ectopic expression of potent VSRs (e.g., the potyvirus HC-Pro) can prevent symptom recovery in nepovirus-infected plants (Siddiqui et al., 2008; Santovito et al., 2014). However, viruses that encode strong VSRs can also be associated with symptom recovery, as long as the activity of these VSRs is reduced in recovered leaves as recently shown in *A. thaliana* plants infected with oilseed rape mosaic virus (Korner et al., 2018). Thus, suppression of antiviral RNA silencing occurs during the initial stages to allow systemic viral infection, and symptom recovery depends on achieving a balance between antiviral RNA silencing and VSR activity during the recovery stage.

Some viruses deploy self-attenuation mechanisms to achieve this balance. Indeed, some viral proteins function to attenuate the accumulation and/or activity of VSRs. Symptom recovery is the normal outcome of the interaction between an isolate of cucumber mosaic virus and *A. thaliana*. However, symptoms were exacerbated by mutation of an Arg-rich region of the CP (Zhang et al., 2017). The wild-type CP was shown to attenuate the silencing suppression activity of the VSR (the 2b protein). This is probably achieved by inhibiting the translation of 2b, via the RNA-binding activity of the CP (Zhang et al., 2017). It was also proposed that binding of the CP to the viral RNA may protect it from degradation and allow enhanced production of vsiRNAs (Zhang et al., 2017), although this will need to be confirmed experimentally.

Another example of viral self-attenuation is provided by the plum pox virus-*N. benthamiana* pathosystem. Plum pox virus proteins are initially expressed as a single large polyprotein (Revers and Garcia, 2015). The P1 protease is the N-terminal protein domain in the polyprotein. Cleavage by P1 contributes to the release of the VSR (HC-Pro, the second protein domain) from the polyprotein. Because the HC-Pro silencing suppression activity is impaired by fusion to P1, the efficiency of the P1 proteolytic cleavage directly affects the activity of HC-Pro (Pasin et al., 2014). Deletion of the N-terminal region of P1 accelerated the release of HC-Pro from the polyprotein, enhanced its VSR activity, stimulated initial accumulation of the virus and enhanced the induction of the HR necrotic response, contributing to the enhanced symptomatology

(Pasin et al., 2014). It was suggested that the N-terminal region of P1 interacts with a host factor to down-regulate the P1 proteolytic activity. The N-terminal region of the P1 protein is highly variable and later work confirmed that it is involved in host adaptation (Shan et al., 2015, 2017). It was hypothesized that the N-terminal region of the P1 protein, although dispensable, is maintained to prevent virus over-accumulation (Pasin et al., 2014).

Strikingly, a viral protein was also shown to enhance the plant antiviral RNA silencing. Viral RNAs move cell-to-cell by modifying the natural channels between plant cells (the plasmodesmata), creating a virus front that invades naïve cells (reviewed in Harries and Ding, 2011; Heinlein, 2015). The vsiRNAs follow a similar route, moving through the plasmodesmata. Intriguingly, the tobacco mosaic virus MP was shown to facilitate the movement of vsiRNAs, thus functioning in a manner opposite to that of many characterized VSRs that hinder vsiRNAs movement (Vogler et al., 2008). Thus, while tobacco mosaic virus encodes a potent VSR to suppress anti-viral silencing, this activity is apparently counter-balanced by that of the MP. Since the MP is only expressed transiently early in infection, this self-attenuation effect would likely also only be effective in the critical initial stages of infection, i.e., at the front of infection (Vogler et al., 2008; Amari et al., 2012). On the other hand, enhancing vsiRNAs movement may also render naïve cells more susceptible to the incoming virus by down-regulating specific plant genes that are targeted by these vsiRNAs (Amari et al., 2012).

Defective-interfering RNAs (diRNAs) are associated with several viruses and have been shown to attenuate symptoms induced by the parent virus. The diRNAs contain non-contiguous segments from the parent viral RNA and are produced by template-switching of the viral RNA-dependent RNA polymerase (RdRp) during viral RNA replication (Simon et al., 2004; Pathak and Nagy, 2009). They contain all the *cis*-acting elements necessary for their continued replication by the viral RdRp and can accumulate *de novo* to very high levels. They interfere with the replication of the parent viral RNAs and prevent over-accumulation of viral products. The mechanisms of diRNA interference are not completely understood. While the *cis*-acting elements present on diRNAs may out-compete the viral RNAs for the viral RdRp and for host factors, other mechanisms likely also play a role, including the enhancement of antiviral RNA silencing (Simon et al., 2004; Pathak and Nagy, 2009). In tombusvirus infected-plants, diRNAs are recognized by DCL enzymes, leading to the enhanced synthesis of siRNAs that share sequences with the parent viral RNAs (Havelda et al., 2005). As described above, the tombusvirus p19 VSR functions by binding to vsiRNAs and sequestering them away from RISC complexes (Scholthof, 2006). However, the binding capacity of p19 was shown to be saturated in the presence of diRNAs leading to increased antiviral RNA silencing against the parental virus (Havelda et al., 2005). Interestingly, a second silencing suppression activity of p19 is not affected by the presence of diRNAs, suggesting that the VSR and the diRNAs act in an antagonistic manner to regulate the levels of virus accumulation in infected plants (Varallyay et al., 2014). Indeed, p19 induces the synthesis of miR168, which down-regulates the expression of AGO1, one of the main

effectors of antiviral RNA silencing. The induction of miR168 by p19 was found to be similar in the presence or absence of diRNAs (Varallyay et al., 2014).

Additional evidence for antagonistic interactions between VSRs and diRNAs is documented for the interaction between a crinivirus and *N. benthamiana* (Lukhovitskaya et al., 2013). The 8K viral protein is a weak VSR that enhances virus accumulation. Interestingly, the coding region for the 8K protein was implicated in the template-switching mechanism that produces the diRNAs. It was suggested that diRNAs are essential regulatory molecules that minimize the impact of crinivirus infection on their hosts (Lukhovitskaya et al., 2013). While the role of diRNAs in symptom attenuation is well-established in model hosts under laboratory conditions, their impact on infections in the field or in natural environments is not well-studied and clearly deserves further investigation.

## MOLECULAR MECHANISMS AIMED AT LIMITING THE ACCUMULATION OR ACTIVITY OF VIRAL PROTEINS

Plants may be able to accommodate substantial levels of viral nucleic acid accumulation without significant damage, as long as they manage the concentration or activities of viral proteins that orchestrate interactions with plant factors and act as virulence factors (Culver and Padmanabhan, 2007). As will be described below, this can be achieved by repressing the translation of viral RNAs, by destabilizing viral proteins or by modulating their activity.

### Repression of Viral Genome Translation

Translation repression has emerged as a common mechanism of RNA silencing-mediated gene regulation in plants (Brodersen et al., 2008; Iwakawa and Tomari, 2013) and has also been suggested to operate against plant viruses in association with tolerance or with symptom recovery phenotypes. In *N. benthamiana* plants infected with tomato ringspot virus, the initial stages of symptom recovery are associated with a drastic reduction in viral protein levels but not with a concomitant reduction in viral RNA concentration (Jovel et al., 2007; Ghoshal and Sanfaçon, 2014). Translation of viral RNA2 was shown to be repressed at the onset of symptom recovery and silencing of AGO1 prevented both the translation repression and the symptom recovery (Ghoshal and Sanfaçon, 2014). Similarly, recovery of *A. thaliana* from oilseed rape mosaic virus was shown to be dependent on AGO1 and was associated with translation repression preventing over-accumulation of the VSR (Korner et al., 2018). Finally, the reduction of viral titers in late stages of the asymptomatic infection of *A. thaliana* plants with tobacco rattle virus was concomitant with a decrease in ribosome-associated viral RNAs and an increase in the number of processing bodies (Ma et al., 2015), which are RNA granules often associated with translation repression mechanism (Makinen et al., 2017). Although these studies suggest a role for antiviral RNA silencing translation repression mechanisms in tolerant interactions, a direct role for AGO-containing RISC

complexes in the translation repression of viral RNAs has not been experimentally confirmed.

A distinct translation repression mechanism is directed by a transmembrane receptor, NIK1 (NSP-interacting kinase), which is related to leucine-rich repeat receptor-like kinases implicated in the innate immune PTI response (Machado et al., 2015). NIK1 was first identified as an interactor of begomovirus NSP1 protein. NIK1 also interacts with and phosphorylates ribosomal protein RPL10A, redirecting this protein to the nucleus (Carvalho et al., 2008). Once in the nucleus, RPL10A interacts with L10-INTERACTING MYB DOMAIN CONTAINING PROTEIN (LIMYB), a transcription factor that regulates the expression of ribosomal genes (Zorzatto et al., 2015). The RLP10A-LIMYB interaction causes massive down-regulation of ribosomal genes and global translation repression, which also impairs virus translation. Importantly, the translation repression is specifically induced upon virus infection and depends on the autophosphorylation of NIK1 at tyrosine 474. Knock-out of the *NIK1*, *RPL10A*, or *LIMYB* genes exacerbates symptoms and enhances virus accumulation, confirming the importance of the translation repression mechanism in limiting virus-induced damage to the plant (Carvalho et al., 2008; Zorzatto et al., 2015). As a counter-defense, the viral NSP protein suppresses the activity of NIK1 preventing its autophosphorylation (Fontes et al., 2004). Interestingly, ectopic expression of a phosphomimic mutant of AtNIK1 with a mutation of tyrosine 474 to aspartic acid, bypassed the counter-defense and provided broad-spectrum tolerance to begomoviruses in tomato, with minimal impact on plant growth in non-infected plants (Brustolini et al., 2015).

In addition to the plant responses described above, viruses minimize the accumulation of viral virulence factors (e.g., VSRs, RdRps) using sub-optimal translation initiation codons or inefficient frameshift or read-through translation mechanisms (reviewed in Miras et al., 2017). These are highly conserved features of viral genomes, highlighting their importance for viral self-attenuation mechanisms.

## Using Cellular Protein Degradation Pathways to Prevent Over-Accumulation of Viral Proteins and to Regulate Plant Defense Responses

Cellular protein degradation mechanisms, in particular the ubiquitin/26S proteasome system (UPS) and the autophagy pathway are key regulators of plant–virus interactions (Alcaide-Loridan and Jupin, 2012; Verchot, 2016b; Clavel et al., 2017; Ustun et al., 2017). By controlling the accumulation of viral and/or plant proteins, they modulate plant defense responses, regulate viral counter-defense responses, control the viral infection cycle and mitigate symptoms. It could be argued that both partners in the interaction benefit from manipulating protein degradation pathways. Indeed, that viral proteins maintain conserved signature sequences for recognition by plant degradation pathways could be viewed as evidence for virus self-attenuation.

Protein substrates targeted by the UPS are ubiquitinated at lysine residues by cellular E3 ubiquitin-ligases, a large family of

plant proteins (1400 genes in *A. thaliana*). Depending on the nature of the ubiquitination (mono- or poly-ubiquitination), proteins are selectively targeted to the 26S proteasome for degradation. Cellular E3 ubiquitin ligases are common interactors of plant virus proteins, including, MPs and RdRps, many of which are destabilized by the UPS (Alcaide-Loridan and Jupin, 2012; Verchot, 2016b). Turnip yellow mosaic virus RdRp contains a highly-conserved PEST sequence, which is recognized as a degradation trigger (Camborde et al., 2010). Interestingly, the viral protease acts as a deubiquitinase to protect the RdRp from UPS degradation (Chenon et al., 2012). These results suggest that a delicate cross-talk between viral enzymes and the plant UPS regulates the accumulation of the viral RdRp.

Direct evidence for a role for the UPS in facilitating tolerance is exemplified in the interaction between *N. benthamiana* and tomato yellow leaf curl China virus (TYLCCV) (Shen et al., 2016). The TYLCCV-associated betasatellite DNA encodes  $\beta$ C1, a symptom determinant and a VSR.  $\beta$ C1 interacts with NtRFP1, a plant RING E3 ligase and is targeted to degradation by the 26S proteasome.  $\beta$ C1 induces severe stunting and leaf curling symptoms when over-expressed in transgenic lines (Yang et al., 2008). However, in natural infection it only accumulates to low levels, and symptoms are milder. Symptoms are further attenuated in plants overexpressing NtRFP1, while plants knocked-down for NtRFP1 develop more severe symptoms (Shen et al., 2016). Importantly, viral DNA accumulation is not affected by manipulation of NtRFP1 expression. Thus, this study demonstrates how the destabilization of a viral pathogenicity factor by the UPS can mitigate symptom expression while allowing systemic virus infection. A separate study demonstrated an interaction between cotton leaf curl Multan virus (CLCuMuV)  $\beta$ C1 protein and a distinct E3 ligase complex (the SCF complex) (Jia et al., 2016). However, the CLCuMuV  $\beta$ C1 protein was shown to inhibit the SCF E3 ligase, allowing enhanced virus accumulation and more severe symptoms. These apparently conflicting results are not necessarily mutually exclusive. Rather, they highlight the complexity of the interactions between plant viruses and various branches of the UPS pathway.

Autophagy is another highly conserved protein degradation pathway implicated in many aspects of plant–pathogens interactions including the regulation of programmed cell death (Ustun et al., 2017). Proteins targeted by the autophagy pathway are directed to double-membrane vesicles, autophagosomes, before they are finally released in the vacuoles for degradation. There are extensive cross-talks between autophagy and the UPS degradation pathways. For example the AUTOPHAGY-RELATED GENE 6 (ATG6) protein is ubiquitinated by SINAT E3 ligases and degraded by the 26S proteasome (Qi et al., 2017). Therefore, it is perhaps not surprising that the CLCuMuV  $\beta$ C1 protein is not only interacting with UPS components, but it is also targeted for degradation by the autophagy pathway following its interaction with ATG8 (Haxim et al., 2017). Preventing the interaction between  $\beta$ C1 and ATG8 exacerbated symptoms and enhanced virus accumulation. Similarly, silencing of ATG5 and ATG7 increased the plant susceptibility to three geminiviruses. These results highlight a role for autophagy in mitigating the impact of geminivirus

infection. Similarly, other VSRs are also degraded through the autophagy pathway, notably the potyvirus HC-Pro protein and the cucumovirus 2b protein (Nakahara et al., 2012). This requires an interaction between the VSRs and rgsCaM, a calmodulin-like protein and an endogenous suppressor of silencing, which is itself destined to autophagic degradation. Interestingly, rgsCaM is also a component of the SA-mediated systemic acquired resistance (Jeon et al., 2017).

Another interesting example of regulated autophagic protein degradation comes from the interaction between cauliflower mosaic virus and *A. thaliana* (Hafren et al., 2017). The viral CP interacts with NEIGHBOR OF BRCA1 (NBR1), an autophagy receptor and is targeted to autophagic degradation. This limits virus accumulation early in infection. Later on, virus particles accumulate in inclusion bodies, where they are protected from autophagy (Hafren et al., 2017). The CaMV P6 protein, which represses SA-mediated autophagy, may also help relieve the CP degradation (Zvereva et al., 2016). Similarly, NBR1 is required for the autophagic degradation of the turnip mosaic virus HC-Pro but this is counteracted by two other viral proteins (Hafren et al., 2018). Thus, viral proteins have evolved to be susceptible to degradation by the autophagy pathway and protected from this degradation at different stages of infection. In addition, induction of the autophagy prevented early cell death in these two pathosystems. Indeed, *A. thaliana* mutants deficient in the autophagy pathway display more severe symptoms than wild-type plants after infection with either turnip mosaic virus or cauliflower mosaic virus in a manner that is independent of the level of viral accumulation (Hafren et al., 2017, 2018). Inhibition of SA-mediated autophagy by the CaMV P6 protein also contributes to symptom severity. P6 activates the TOR (target of rapamycin) kinase, a down-regulator of autophagy and exacerbates symptoms, which are normally mitigated by the autophagy pathway (Zvereva et al., 2016). Transgenic lines that express the P6 protein from severe CaMV isolates display chlorotic and dwarfing symptoms, while those expressing the P6 protein from a mild isolate do not (Yu et al., 2003). Interestingly, the P6 protein from this mild isolate is unable to activate TOR or disrupt SA-mediated autophagy (Zvereva et al., 2016).

Finally, the UPS and autophagy pathways are usurped by viruses to target plant defense proteins. A case in point is the ability of several VSRs to target plant RNA silencing factors (notably AGO proteins) to degradation (Csorba et al., 2015). Thus, plant protein degradation pathways modulate both the plant antiviral defenses and the virus counter-defenses.

## Regulating the Activity of Viral Proteins With Post-translational Modifications

Another approach to mitigate the impact of toxic viral proteins is to control their activity. This can be achieved by post-translational modification. For example, phosphorylation of the  $\beta$ C1 protein from the betasatellite DNA of TYLCCV by the SNF1-related protein kinase 1 (SnRK1) reduces its silencing suppression activity and diminishes symptom severity (Zhong et al., 2017). Similarly, phosphorylation of the cabbage leaf curl virus VSR (the AL2 protein) delays the symptom formation in

*A. thaliana* (Shen et al., 2014). In the case of the turnip yellow mosaic virus RdRp, phosphorylation of the conserved PEST sequence is a prerequisite for its subsequent destabilization by the plant proteasome degradation pathway (Jakubiec et al., 2006). On the other hand, phosphorylation has also been shown to be required for the function of viral CPs, MPs, or RdRps (Stork et al., 2005; Champagne et al., 2007; Kleinow et al., 2009). While the role of protein modification in the regulation of plant–virus interactions is still poorly understood, especially in the context of tolerance, its importance cannot be underestimated.

## MOLECULAR MECHANISMS DEPLOYED TO RELIEVE VIRUS-INDUCED STRESS OF THE PLANT ENDOPLASMIC RETICULUM

As mentioned above, virus infection commonly causes ER stress, which needs to be relieved to prevent cell death (Zhang and Wang, 2012; Verchot, 2016a). In plants, ER stress is sensed by transmembrane proteins [e.g., the inositol requiring enzyme (IRE1) and the Bax inhibitor 1 (BI-1) proteins] that induce the unfolded protein response (UPR) to restore proper protein folding in the ER and prevent aggregation. Activation of IRE1 causes splicing of the bZIP60 transcription factor transcript and production of a truncated form of the transcription factor, which translocate to the nucleus to induce the expression of UPR-related genes, including calcium-dependent protein chaperones (e.g., Bip, calmodulin, calreticulin). The ER-associated degradation (ERAD) pathway is also activated as part of the UPR. ERAD functions by translocating unfolded or misfolded proteins back into the cytoplasm where they are degraded by the cytosolic UPS or autophagic pathways. Evidence for the importance of the UPR in mitigating the consequences of virus-induced ER stress is accumulating. Expression of viral integral membrane proteins has been reported to induce the UPR (Ye et al., 2011, 2013; Zhang L. et al., 2015; Gaguancela et al., 2016). For example, the expression of IRE1 and BI-1 is induced by the potyvirus TGB3 or potyvirus 6K2 integral membrane proteins (Gaguancela et al., 2016). Down-regulation of BI-1 or bZIP60 in *N. benthamiana* allowed increased systemic accumulation of potato virus X and potato virus Y and exacerbated systemic necrosis symptoms indicating that the UPR is induced to release ER stress, control virus accumulation, and prevent cell death (Gaguancela et al., 2016). Consistently, overexpression of the ER Bip chaperone suppresses TGB3-induced cell death in *N. benthamiana* infected with potato virus X (Ye et al., 2011, 2013). Intriguingly, down-regulation of IRE1/bZIP60 has also been shown to hinder accumulation of turnip mosaic virus, in *A. thaliana* and to ameliorate non-necrotic virus-induced symptoms, suggesting that in this interaction the UPR actually promotes virus infection, possibly also by mitigating the consequences of ER stress (Zhang L. et al., 2015). Other plant–virus interactions will need to be examined before we can obtain a more complete understanding of the role of the UPR in facilitating tolerant plant–virus interactions.

Finally, how the ERAD and downstream protein degradation pathways contribute to mitigating virus-induced ER stress is also not well-characterized.

## TOLERANCE CONFERRED BY MUTATION OF AN INEFFECTIVE R-LIKE GENE TO PREVENT SYSTEMIC LETHAL NECROSIS

The *A. thaliana* *TTR1* semi-dominant locus was shown to determine symptom expression following infection with tobacco ringspot virus (Lee et al., 1996). Screening of 97 *A. thaliana* lines revealed that although the virus accumulated to similar levels, the intensity of symptoms varied greatly. Systemic necrosis killed the most susceptible lines while tolerant plants were either asymptomatic or only displayed mild symptoms. The *TTR1* gene present in susceptible lines was later shown to correspond to a R-like gene (Nam et al., 2011). An HR-like response was activated in plants with the *TTR1* gene, but the replication and movement of the virus were not restricted and systemic acquired resistance was not established. It was suggested that the systemic lethal necrosis phenotype was caused by a runaway HR response. Interestingly, transfer of the *TTR1* gene to *N. benthamiana* also caused lethal systemic necrosis. The tolerant phenotype in *A. thaliana* accessions was found to be associated with mutations of the *TTR1* gene which prevented the establishment of the systemic HR response (Nam et al., 2011).

## ENGINEERING TOLERANCE TO VIRUS DISEASE FOR FIELD APPLICATION: CURRENT PROGRESS AND FUTURE OPPORTUNITIES

As highlighted above, tolerance is a complex genetic trait that involves multiple molecular mechanisms operating simultaneously, many of which are yet to be discovered. The benefits of tolerance compared to resistance have also been described in terms of reduced selection pressure for the emergence of virulent isolates, increased breadth and stability of the phenotype and potential benefits to the host (as exemplified in natural environments). Although natural sources of tolerance are available for some economically important crops, they are generally poorly characterized and have been of limited use. The next question becomes: is it feasible to engineer tolerance for practical field applications?

Only a few examples of engineered tolerance to virus diseases can be found in the literature. Most relate to the identification and manipulation of plant genes involved in signal transduction pathways associated with basal innate immune defense responses. Some are broad-spectrum and also provide tolerance to abiotic stress, in part because some of the signaling pathways are overlapping. We have already

discussed how the ectopic expression of a phosphomimic mutant of AtNIK1, an immune receptor kinase, conferred broad-spectrum tolerance to begomovirus infection in tomato (Brustolini et al., 2015). Other kinases implicated in defense signal transduction pathways have also been manipulated to mitigate viral symptoms. Overexpression of SIMAPK3, a MAP kinase, showed enhanced expression of defense genes associated with SA- and JA-signaling, lower accumulation of reactive oxygen species, increased accumulation of antioxidant enzymes, and stronger tolerance to tomato yellow leaf curl virus infection as expressed by a 2-week delay in symptom induction which was sufficient to allow plant flowering (Li et al., 2017). Similarly, overexpression of OsCIPK30, a kinase involved in calcium signaling, in rice provided enhanced tolerance to rice stripe virus, that was associated with delayed and milder symptoms and enhanced expression of PR genes (Liu et al., 2017).

Overexpression of a transcription factor, the soybean GmERF3 gene, in tobacco also conferred increased tolerance to tobacco mosaic virus (Zhang et al., 2009). This transcription factor is induced in response to various stresses and up-regulates the expression of many defense genes, including PR proteins. Thus, overexpression of this gene activated the plant basal immunity, achieving a result similar to the plant transcriptome reprogramming observed in several natural tolerant interactions. The tolerance level was modest resulting in delay in the establishment of symptoms rather than long-term symptom attenuation. Increased tolerance to salt, drought, and fungal diseases was also achieved after overexpression of this gene (Zhang et al., 2009).

As discussed above, manipulation of plant genes implicated in protein degradation pathways or the UPR response may also provide novel avenues to engineer tolerance. Examples include the overexpression of the NtRFP1 RING E3 ligase to promote tolerance in *N. benthamiana* plants infected with a begomovirus (Shen et al., 2016), or of the ER Bip chaperone to suppress cell death associated with potyvirus infection of *N. benthamiana* (Ye et al., 2013). Down-regulation of genes associated with the UPR response has been shown to reduce symptom expression in other plant–virus interactions (Zhang L. et al., 2015).

The study of highly symptomatic interactions can help identify novel sources of tolerance. For example, a transcriptomic study of a systemic symptomatic infection associated with runaway HR necrosis conferred by a soybean R gene in response to a virulent isolate of soybean mosaic virus identified eIF5A as a highly induced gene (Chen et al., 2017). eIF5A is a translation factor previously implicated in symptom development in the interaction between *A. thaliana* and the bacterium *Pseudomonas syringae*. Interestingly, silencing of this gene diminished the systemic necrosis and reduced virus accumulation (Chen et al., 2017).

Although tolerance can be enhanced by manipulating plant signaling pathways in herbaceous hosts under controlled environmental conditions, the feasibility of field applications needs to be examined. Indeed, modifying vital plant signaling pathways is likely to have pleiotropic effects that could vary

depending on each plant–virus interaction and could also impact tolerance to other biotic or abiotic stresses. In addition, even if experiments conducted with herbaceous hosts under limited time periods show minimal impact on the plant growth and development, plants with longer lifespans (for example trees) could be affected differently. Further research aimed at elucidating the molecular mechanisms associated with tolerance, in particular in wild plant–virus interactions, may identify novel targets for engineering tolerance or assist in the development of improved agriculture practices.

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## AUTHOR CONTRIBUTIONS

DP and HS jointly wrote the manuscript, and read and approved the final manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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