REVIEW ARTICLE

Under siege: virus control in plant meristems and progeny

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Short title: Virus control in plant meristems and progeny

One-sentence summary: We review what is known about the biological mechanisms regulating virus exclusion from - or invasion of - plant host meristems and progeny, including possible consequences and implications of these phenomena.

ABSTRACT

In the arms race between plants and viruses, two frontiers have been utilized for decades to combat viral infections in agriculture. First, many pathogenic viruses are excluded from plant meristems, which allows the regeneration of virus-free plant material by tissue culture. Second, vertical transmission of viruses to the host progeny is often inefficient, thereby reducing the danger of viral transmission through seeds. Numerous reports point to the existence of tightly linked meristematic and transgenerational antiviral barriers that remain poorly understood. In this review, we summarize the current understanding of the molecular mechanisms that exclude viruses from plant stem cells and progeny. We also discuss the evidence connecting viral invasion of meristematic cells and the ability of plants to recover from acute infections. Research spanning decades and performed on a variety of virus/host combinations has made clear that, beside morphological barriers, RNA interference (RNAi) plays a crucial role in preventing – or allowing – meristem invasion and vertical transmission. How a virus interacts with plant RNAi pathways in the meristem has profound effects on its symptomatology, persistence, replication rates, and, ultimately, entry into the host progeny.

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INTRODUCTION

Viruses are invisible molecular machines – they cannot move on their own and are completely dependent on living organisms to propagate, but in doing so damage or kill their hosts. Much public and scientific interest has focused on the human smallpox, polio, influenza, measles, and corona viruses, but plant viruses can be similarly devastating foes with staggering consequences. The experiments that led to the discovery of viruses were performed by the pioneer plant pathologists Dmitri Ivanovsky and Martinus Beijerinck at the end of the 19th century, when they demonstrated that tobacco mosaic disease was transmitted to a new host from finely-filtered extracts prepared from tobacco (Nicotiana tabacum) plants affected by tobacco mosaic disease, now known to be caused by tobacco mosaic virus (TMV). The study of plant viruses has laid the foundation for virology, and plant virology has contributed a great deal to our understanding of the molecular mechanisms regulating viral life cycles and transmission to new hosts. Nevertheless, some very fundamental aspects of plant virus-host interactions remain poorly understood, including the rarity and inefficiency of vertical transmission (Table 1), as most pathogenic viruses are absent from the sexually produced progeny of their hosts (Bennett, 1969; Johansen et al., 1994; Sastry, 2013). This is in contrast to horizontal transmission (Table 1), which occurs frequently between separate individuals independently of lineage. The rarity of vertical transmission might relate to the frequent observation that viruses move throughout the entire plant body but are excluded from the host shoot apical meristem (SAM) (Table 1). This tissue contains the stem cells that give rise to all above-ground organs, including flowers, gametophytes, and the gametes within. To be vertically transmitted, a virus may need to overcome this meristematic exclusion to invade and eventually infect the reproductive organs developing from the meristems (Figure 1) (Bennett, 1940; Johansen et al., 1994; Martín-Hernández and Baulcombe, 2008). However, invasion of the progeny can also take place independently of meristem invasion, occurring after fertilization (Roberts et al., 2003). Invasion of the meristem has also been correlated with recovery (Table 1), a phenomenon referring to the emergence of nearly or fully symptom-free tissues from plants with strongly symptomatic infections (Ghoshal and Sanfaçon, 2015). Therefore, the ability to enter the host meristems likely determines viral transmission, persistence, and symptomatology, but the underlying mechanisms that enable or prevent meristem entry are surprisingly poorly understood.
In this review, we focus on extragenomic viruses and viroids causing acute infections (Table 2), summarizing earlier work reporting viral exclusion from - or invasion of - the plant meristem and its derived progeny. We concentrate on aspects that provide hints as to the molecular and genetic mechanisms behind meristem exclusion and the lack of vertical transmission, and how these phenomena might be connected to recovery from infection and persistence of plant viruses.

We discuss the possibility that transgenerational antiviral barriers/defenses may already be established in the meristem before the development of reproductive organs. These barriers constitute potent obstacles to invading viruses, yet some viral species can overcome them. Two possible explanations come to mind: either (i) these antiviral barriers are always active and some viruses have evolved the ability to suppress them, or (ii) these barriers are activated upon infection by most viruses, and only virus species that do not activate them can invade the meristem and progeny. While a brief or limited entry of viruses into the meristem is technically challenging to document, genetic tools in model organisms might help explore this option.

**Plant viruses and antiviral defense**

To achieve successful infections, viruses need to multiply and move within their hosts. They have evolved sophisticated mechanisms that reprogram their hosts to support both these requirements. Their minimalist genomes encode only those components that are essential to utilize the host molecular machinery to complete the infection cycle (Hull, 2014). However, co-evolution has also generated equally refined anti-viral defense mechanisms on the plant side, like highly specific resistance (R) genes (de Ronde et al., 2014) or efficient autophagy (Kushwaha et al., 2019). An important component in the defense arsenal against viral multiplication and spread is RNA interference (RNAi), a pan-eukaryotic antiviral mechanism. While its role in mammalian antiviral defense remains contested (Maillard et al., 2019), it plays a pivotal role in plant antiviral responses (Ding and Voinnet, 2007; Guo et al., 2019). RNAi uses an obligate intermediate of replication for genomic RNA-based viruses – a double-stranded RNA (dsRNA) - to generate virus-specific effector molecules, 21- to 24-nt long small interfering RNAs (siRNAs). The long dsRNA, formed by viral RNA replication or via secondary structures, is processed into virus-derived siRNAs (vsiRNAs) by host-encoded Dicer-like (DCL) RNAse III enzymes. In the model plant Arabidopsis (*Arabidopsis thaliana*), several DCL proteins exhibit partial redundancy, with DCL4 and DCL2 being the
main players in RNAi against RNA viruses (Guo et al., 2019). vsiRNAs are then loaded into Argonaute (AGO) proteins to form sequence-specific RNA-induced silencing complexes (RISC) that cleave viral RNA molecules complementary to the vsiRNA, thereby preventing virus accumulation (Poulsen et al., 2013; Carbonell and Carrington, 2015). With RNA-dependent RNA polymerases (RDRs), plants can also boost the RNAi reaction by generating more dsRNAs (Wassenegger and Krczal, 2006; Csorba et al., 2015), which are then further processed by DCLs. Naturally, viruses did not stop evolving, and in response to the versatility and potency of RNAi in fighting viral infections, they have evolved tools to circumvent or block the RNAi machinery. The best-studied strategy is illustrated by viral suppressors of RNAi (VSR), proteins that neutralize the host antiviral RNAi pathway through diverse mechanisms, including vsiRNA sequestration, AGO impairment and AGO depletion, among many others (Incarbone and Dunoyer, 2013; Csorba et al., 2015).

Besides replication, movement within the host organism is another requirement for successful infection. In addition to short-distance cell-to-cell movement, viruses exploit long-distance routes for the transport of their genomes between organs via the vasculature, achieving systemic infection (Hipper et al., 2013). Most plant cells are connected with their neighbors by plasmodesmata, which are highly dynamic channels that form an almost continuous organism-wide network known as the symplasm (Sager and Lee, 2014). Viruses can cross these channels, often with the help of dedicated movement proteins (MPs) encoded by the viral genomes (Heinlein, 2015). Defensive mechanisms deployed by plants to restrict systemic infection also include RNAi since, in addition to their cell-autonomous effects, vsiRNAs can move systemically within the plant and ahead of the virus, providing naïve tissues the virus-specific sequences they need to prime RNAi defenses (Sarkies and Miska, 2014; Guo et al., 2019). Once again, however, different viral suppressors interfere with this defense mechanism, e.g. by sequestering vsiRNAs. The common evolutionary history shared by viruses and their host plants has created a vast diversity of attack and defense mechanisms, which all contribute to determining the degree of observed infectivity and susceptibility. However, preventing harmful viruses from entering stem cells in the SAM and infecting the progeny appears to be a common and successful strategy adopted by all plants to survive and propagate.

**Virus exclusion from the meristem**
The absence of viral infection in apical meristems was deduced for several viral species already in the 1930s (Bennett, 1940). By contrast, viral particles in meristematic tissues were first documented for nepoviruses and tobraviruses by electron microscopy much later (Kitajima and Costa, 1968; Walkey and Webb, 1968). These cases appear to represent a minority, although numbers for virus-host combinations that result in plant meristem invasion are not available. Exclusion from meristems has been reported for many pathogenic viruses and viroids and can be considered a common feature, suggesting the existence of an antiviral barrier against movement into and/or replication within this tissue. For viroids, there is some evidence that exclusion from the meristem is already established in embryos (Matsushita and Tsuda, 2014). The in vitro regeneration of virus-free plants from meristematic tissues originating from virus-infected individuals is widely applied for many commercial varieties (Mori, 1971; Panattoni et al., 2013). Despite this long-term practical utilization of meristematic antiviral barriers, studies to elucidate the molecular details of virus-meristem interactions have been performed mainly with species of the *Nicotiana* genus and are therefore difficult to generalize. Factors shown or suggested to play a role in excluding viruses from meristems are the availability of connections between cells or with the vasculature, RNAi-related mechanisms, and RNAi-independent defense pathways.

The symplastic network between the SAM and surrounding tissues has been investigated in several species (Sager and Lee, 2014; Kitagawa and Jackson, 2017) and is highly dynamic in relation to the plant developmental stage (Gisel et al., 1999). Cell-to-cell movement of proteins and small RNAs through meristematic plasmodesmata (Kitagawa and Jackson, 2017) attest to the presence of connections that might potentially be exploited by viruses, yet experimental evidence during virus infections is missing. Interestingly, two genes encoding members of the PLASMODESMATA-LOCATED PROTEIN (PDLP) family are specifically expressed in the Arabidopsis SAM, each with a defined, and only partially overlapping expression pattern (Bayer et al., 2008). PDLP proteins localize to plasmodesmata and are exploited by viruses to move from cell to cell (Amari et al., 2010), further implying that plasmodesmata would support viral movement into and within the SAM. There are no data as to whether viral infections might change PDLP gene expression and PDLP localization, or the number and aperture of plasmodesmata. However, ectopic accumulation of the first protein of the triple gene block (TGB1) from white clover mosaic virus (WCIMV) (Table 3), a MP that can increase plasmodesmatal width (Lough et al., 1998), allowed WCIMV and the related potexvirus potato virus X (PVX) to enter the meristem (Foster et al., 2002). Notably, TGB1 from PVX functions as a MP as well as a viral suppressor of silencing (Bayne et al.,
Intercellular connections are very likely to play a role in viral exclusion from the meristem, balanced between their restriction by the plant through callose deposition and the interaction of viral proteins with plasmodesmata. Virus entry might be hindered by the default size limitations of intercellular connections in the SAM (Cohen et al., 2000), or by the induced closure of these connections specifically upon viral infection. The latter situation may constitute a target for viral strategies that inhibit plasmodesmatal closure and/or force their opening to achieve meristem invasion. However, supporting experimental data are lacking and the phenomenon needs to be investigated in the context of specific virus infections.

Several studies have reported RNAi to be responsible for meristem exclusion: RDR6, a key player in RNAi, has been shown to be important, as knocking down NbRDR6 transcript levels in Nicotiana benthamiana allows meristem invasion by viruses and viroids including PVX, TMV, and potato spindle tuber viroid (PSTVd) (Qu et al., 2005; Schwach et al., 2005; Di Serio et al., 2010). Heterologous overexpression of MtRDR1 from barrelclover (Medicago truncatula) in N. benthamiana restricted TMV movement in growth tips compared to control plants, but the meristems themselves were not specifically observed in this study (Lee et al., 2016). Of note, recently published data showed that Arabidopsis RDR4 and RDR5 transcripts are enriched in meristematic stem cells (Gutzat et al., 2020). The role of the Dicer-like RNAi components has not been much investigated: knocking down NbDCL2 or NbDCL4 was not sufficient to allow meristem invasion in N. benthamiana by a recombinant cymbidium ringspot virus (CymRSV) with compromised VSR capability (Medzihradszky et al., 2019), but as the knock-down in this experiment was based on RNAi, the degree of downregulation in meristems remains to be determined.

A recent landmark study in Arabidopsis provided evidence that the removal of the meristem-defining transcription factor WUSCHEL (WUS) causes several RNA viruses to invade the meristem (Wu et al., 2020). WUS expression is induced in meristems upon infection by cucumber mosaic virus (CMV) and was shown in heterologous systems to regulate the rates of protein translation and ribosome maturation through methyltransferase enzymes. The chemically induced removal of WUS affected the expression of over one thousand genes, suggesting that this transcription factor may determine meristematic virus exclusion in more than one way. Mutants in various RNAi-related genes in this study did not allow early entry of CMV into the meristem, as determined by RNA in situ hybridization, but a more systematic and less time-intensive approach is missing.
Prominent among the scarce experimental data is the evidence for a crucial role of RDR proteins in virus and viroid meristem exclusion. The current understanding is that RNAi requires a viral RNA substrate to acquire sequence-specific function, so how can RNAi carry out its antiviral activity in a virus-free meristem? One possibility is that vsiRNAs move from infected tissues into the meristem and prime RNAi against the virus ahead of the systemic infection spread. Several experiments on the movement of RNAi-mediated silencing have provided conflicting results regarding the meristem. PVX-GF, a virus that does not enter the meristem (Schwach et al., 2005), induced ubiquitous virus-induced gene silencing (VIGS) of an ectopically expressed GFP in N. benthamiana plants, except in the apical growth point (Ruiz et al., 1998). RNAi-based silencing of transgenes was also shown to occur throughout the plant but not in meristems in other cases (Béclin et al., 1998; Voinnet et al., 1998), suggesting that small RNAs are unable to enter and/or trigger silencing in this tissue. However, in two other studies, meristem-excluded viruses were able to trigger VIGS within meristems (Jones et al., 1998; Peele et al., 2001).

Once a virus enters a meristem, it can trigger potent and persistent RNAi there. For example, turnip yellow mosaic virus (TYMV) is vertically transmitted in Arabidopsis (de Assis Filho and Sherwood, 2000) and may therefore be able to enter meristems, as recombinant TYMV induced VIGS of a gene expressed in Arabidopsis flower primordia (Pflieger et al., 2008). In the landmark study cited earlier, entry of WCIMV into the meristem caused silencing of a transgene containing WCIMV-encoded TGB1, which remained in a silent state in all subsequently generated tissues (Foster et al., 2002). Moreover, these tissues were able to block super-infection by PVX-TGB1 in a sequence-specific manner, in a way that will be further described later (Meristem invasion and plant recovery). Together, these observations led to the conclusion that WCIMV cannot efficiently suppress RNAi in the meristem, neither in the case of the TGB1 transgene nor the cognate viral RNA.

A body of compelling data implicates suppression of RNAi as a viral strategy for meristem invasion, mostly via specific VSRs. The 16K VSR of tobacco rattle virus (TRV) allowed meristem invasion in N. benthamiana (Martín-Hernández and Baulcombe, 2008), and TRV co-infection allowed TMV entry into root meristems (Valentine et al., 2002). CMV was shown to enter meristems due to its 2b VSR protein, although the outermost meristematic dome remained virus-free (Sunpapao et al., 2009). It has also been suggested that meristem invasion may be achieved through a “weak” VSR that inefficiently suppresses RNAi in a GFP silencing assay, such as 16K from TRV (Martín-Hernández and Baulcombe, 2008). Citrus leaf blotch virus (CLBV), which can enter meristems, also encodes a weak VSR.
(Renovell et al., 2012; Agüero et al., 2013), and a point mutation in HC-Pro VSR of turnip mosaic virus (TuMV) leads to meristem invasion (Kung et al., 2014; Hu et al., 2015). Support for the idea of incomplete RNAi suppression as a “key” to entering the meristem also comes from the observation that persistent viruses such as endornaviruses are not known to encode a VSR, yet are believed to be present in meristems of infected plants (Fukuhara, 2019). However, CMV can invade the meristem despite having the potent VSR 2b (Guo and Ding, 2002), suggesting that weak RNAi suppression is likely not the only factor involved, or that the current experimental assessment of VSR strength is inadequate. It should be considered that the degree and pattern of meristem invasion vary for different combinations of hosts and viruses (Figure 2), indicating a complex network of defenses and barriers within this tissue. Documentation of the patterns can also be technically challenging, and transient or limited presence of viral RNA in the meristem preceding (and possibly later causing) exclusion might escape detection.

For viruses and viroids to infect gametophytes and gametes, they must enter flower primordia early in development, which can be achieved by invading the meristems first (Bennett, 1940, 1969; Johansen et al., 1994; Maule and Wang, 1996). This has been demonstrated for asparagus virus 2 (AV-2) and chrysanthemum chlorotic mottle viroid (CChMVd) (Kawamura et al., 2014; Ebata et al., 2019). Viruses belonging to the genera nepovirus and tobravirus have been shown directly or indirectly to enter meristems in several hosts (Lister and Murant, 1967; Walkey and Webb, 1968; Roberts et al., 1970; Walkey and Webb, 1970; Valentine et al., 2004; Martín-Hernández and Baulcombe, 2008; Dong et al., 2009; Santovito et al., 2014) and many viruses belonging to these families are transmitted to the host progeny (Lister and Murant, 1967). A possible mechanistic link between meristem invasion and vertical transmission is the high similarity between the VSR proteins 16K of TRV and 12K of pea early-browning virus (PEBV), the latter allowing vertical transmission of PEBV (Wang et al., 1997), suggesting that these two proteins may perform similar molecular functions. While PEBV is vertically transmissible in pea, TRV can enter meristems of N. benthamiana and Arabidopsis but is not vertically transmitted (Valentine et al., 2002; Valentine et al., 2004; Martín-Hernández and Baulcombe, 2008). Meristem invasion and absence of vertical transmission were also observed for tobacco ringspot virus (TRSV) in tobacco plants (Price, 1932; Roberts et al., 1970). Therefore, entry into the SAM can be a gateway for vertical transmission, but not necessarily. Since most studies have evaluated different host/virus combinations, it is difficult to determine common principles behind the ability to invade meristems and be vertically transmitted.
Virus exclusion from the progeny

Vertical transmission of pathogenic viruses can be dangerous because (i) inoculum can easily travel worldwide with seed stocks, (ii) inoculum can be distributed over fields where the seeds are sown, and (iii) inoculum can survive in seeds from one growing season to the next (Sastry, 2013). However, more than a century ago, Allard (1916) studied tobacco mosaic disease caused by TMV and concluded that “a very efficient barrier guards against embryonic infection or the subsequent successful continuation of the disease from parent to seedling”. Considering the efficient spread of many plant pathogenic viruses within a host and horizontally to new hosts, the scarcity of their vertical transmission is indeed surprising, which was readily noticed by pioneer virologists (Bennett, 1940). More recent surveys have reported that around 18% of plant viruses are vertically transmitted on at least one host species (Mink, 1993). The reported studies were mostly conducted with crop species and covered the full spectrum of possible transmission rates, from 0.01% to 100% (Sastry, 2013).

In addition, transmission rates vary within genera, and even species, for both host and virus (Bennett, 1969; Johansen et al., 1994; Maule and Wang, 1996). Several detailed analyses reported dramatic changes in transmission rates between host cultivars/varieties (Carroll et al., 1979; Wang and Maule, 1992; Cobos et al., 2019). Conversely, different virus and viroid isolates show remarkable differences in their transmission rates on the same host (Bowers and Goodman, 1991; Edwards, 1995; Johansen et al., 1996; Tsushima and Sano, 2018).

Two cases of apparent vertically transmitted infection of seedlings by contact with infected seed coats after germination have been recorded only for TMV and southern bean mosaic virus (SBMV), but this phenomenon is believed to be rare (Johansen et al., 1994). Genuine vertical (or seed) transmission occurs when a virus infects an embryo during seed formation that will germinate into an infected seedling (Figure 3). Infection of the embryo can happen through infection of the gametes prior to fertilization or post-fertilization through viral movement from the maternal tissue into the embryo (Bennett, 1969; Johansen et al., 1994; Wang and Maule, 1997). These non-mutually exclusive modes of embryo infection have been suggested to correspond to two “windows of opportunity” for virus penetration, which are determined by the presence of open plasmodesmatal connections (Maule and Wang, 1996; Wang and Maule, 1997). The first window, leading to infection through gametophytes, is open during early flower development. As symplastic connections between the gametophytes and the parent plant appear to be interrupted early in gametophyte
development (upon meiosis in the case of pollen) (Johansen et al., 1994; Sager and Lee, 2014), a virus must enter the gametophytes before this point in order to reach the gametes. This notion was confirmed for barley stripe mosaic virus (BSMV), which enters early developing barley female and male gametophytes before loss of symplastic connections, resulting in vertical transmission (Carroll and Mayhew, 1976a, b). A second window is open after fertilization, when viruses can move into the embryo through the suspensor, as reported for pea seed-born mosaic virus (PSbMV) on pea plants (Wang and Maule, 1992, 1994; Roberts et al., 2003). However, insight into plasmodesmatal openings during gamete and embryo development in different species remains scarce, and potential changes in symplastic connections induced by virus infection remain to be investigated. Evidence for such changes is provided by the deposition of callose at plasmodesmata, which regulates their aperture during infection with different viruses (Roberts and Oparka, 2003), but such changes also need to be examined in reproductive tissues.

Vertical transmission through pollen has been reported for a number of viruses and viroids (Bennett, 1969; Johansen et al., 1994; Matsushita et al., 2018). Given the high mobility of pollen, this mode of transmission is potentially a successful dissemination strategy for viruses, although infection can negatively affect pollen performance (Yang and Hamilton, 1974; Amari et al., 2007). However, some pollen possesses effective antiviral barriers. In hop (Humulus lupulus), hop latent viroid (HLVd) is abundant in immature pollen but dramatically decreases during maturation and becomes undetectable in germinating pollen (Matousek et al., 2008). Interestingly, decreasing HLVd levels are correlated with an increase in RNAse activity, but not in the accumulation of vsiRNAs. A previous study showed that RNAse activity, particularly targeting dsRNA, was 150 times higher in developing tobacco pollen than in leaves (Matousek et al., 1994). PSTVd-infected petunia pollen tubes germinating in vitro contain abundant viroid RNA, while pollen tubes germinating in vivo on the female style were progressively cleared of PSTVd (Matsushita and Yanagisawa, 2018), indicating a further defensive barrier elicited by the female organs. While infected pollen can cause systemic horizontal infection of the plant it fertilizes (Hull, 2014; Matsushita et al., 2018), this does not guarantee efficient vertical transmission. In addition to the barriers mentioned above, certain strains of alfalfa mosaic virus (AMV), soybean mosaic virus (SMV), and SBMV are inactivated during seed maturation through unknown mechanisms (Uyemoto and Grogan, 1977; Bowers and Goodman, 1979; Bailiss and Offei, 2007).

Many attempts to identify the variables that determine whether a virus can be vertically transmitted have led to the consensus that there are many biotic and environmental factors at
Several reports have suggested that lower temperatures favor vertical transmission, while higher temperatures increase virus titers (Frosheiser, 1974; Tu, 1992). Infection at or after the onset of flowering does not result in vertical transmission, suggesting that a virus needs to be systemically established in the host and have access to the floral organs at very early developmental stages (Johansen et al., 1994; Maule and Wang, 1996). This observation is in agreement with recent studies correlating virulence and high speed of movement with seed transmission in Arabidopsis (Cobos et al., 2019; Montes et al., 2021). Genetic approaches towards host determinants have yielded very limited results, with vertical transmission being associated with one genomic locus for BSMV in barley (Carroll et al., 1979) and several loci for PSbMV in pea (Wang and Maule, 1994) that remain to be identified. However, a study of SMV seed transmission determinants in soybean (Glycine max) identified two genomic regions associated with vertical transmission that contain homologs of Arabidopsis DCL3 and RDR6 (Domier et al., 2011).

The most compelling data on the viral determinants of vertical transmission came from experiments with recombinant viruses - chimeras between transmitted and non-transmitted strains or variants with deletions of viral open reading frames (ORFs). These approaches have identified HC-Pro of PSbMV (Johansen et al., 1996), 12K of PEBV (Wang et al., 1997), and γb of BSMV (Edwards, 1995) as key factors in determining seed transmission. γb of BSMV has been shown to be a VSR (Bragg and Jackson, 2004), while HC-Pro of PSbMV and 12K of PEBV are closely related to well-established VSR proteins (Kasschau and Carrington, 2001; Ghazala et al., 2008). Although HC-Pro and γb play multiple roles in viral infection (Carrington et al., 1989; Zhang et al., 2017a; Yang et al., 2018), the involvement in vertical transmission of at least three VSRs from different virus genera suggests that RNAi plays an important role in this process. Whether vertical virus transmission in non-plant model organisms is mechanistically related is not clear, but it should be mentioned that in Caenorhabditis elegans, ablation of the host gene Dicer related helicase 1 (Drh-1), which encodes an RNAi initiator, increases the rate of vertical transmission for vesicular stomatitis virus (VSV) (Gammon et al., 2017).

**Meristem invasion and plant recovery**

While meristem invasion can be a prerequisite for virus transmission to the host progeny, there is mounting evidence that it can lead to plant recovery from acute infection in certain
virus-host combinations (Figure 4A). The phenomenon of recovery - development of asymptomatic new organs during growth of a plant affected by an initially acute and symptomatic viral infection - has also been known for almost a century. In three groundbreaking studies, pioneer virologists Samuel A. Wingard and W.C. Price described several fundamental properties of recovery from TRSV nepovirus infection in tobacco plants: (i) recovered tissues still contained virus particles and remained asymptomatic upon reinoculation with the cognate virus (Wingard, 1928); (ii) viral particles from recovered tissue caused acute symptoms when used to inoculate other plants, thereby excluding a mutation in the virus itself (Wingard, 1928); (iii) recovery was virus-specific, as infection of recovered tissues with other virus species still produced symptoms (Price, 1936); and (iv) the recovered state was not inherited by the host progeny (Price, 1932). A recovered state often coincides with lower viral titers, but with exceptions (Ghoshal and Sanfaçon, 2015), suggesting that many factors determine symptomatology. While recovery as a phenomenon has been extensively studied (Ghoshal and Sanfaçon, 2015), we will focus here on its appearance in the context of meristem invasion, a connection again proposed decades ago (Price, 1940).

Pioneering experimental evidence came from the observation of TRSV in meristems of recovered tobacco shoots (Roberts et al., 1970), followed by studies with many different virus-host combinations. As described above, WCIMV enters meristems, and it also triggers recovery (Foster et al., 2002). Furthermore, inoculation of recovered tissues with PVX engineered to contain a partial sequence of WCIMV does not result in infection, in contrast to wild-type PVX. Similar sequence-specific cross-protection was observed in tissues recovered from nepovirus and tobravirus infection, although meristem invasion was not assessed for the former (Ratcliff et al., 1997; Ratcliff et al., 1999). TRV entry into the meristem due to its 16K VSR promoted recovery (Martín-Hernández and Baulcombe, 2008) (Figure 4C), while a mutant virus not encoding this protein – and unable to enter the meristem - continued to cause acute symptoms. Similarly, PEBV, a related tobravirus, caused acute symptoms upon deletion of its 12K VSR (Wang et al., 1997). As cited above, 12K allows PEBV vertical transmission through gametophytes, implying it may also allow meristem invasion. CMV protein 2b, responsible for meristem invasion by the virus, is also necessary to initiate recovery (Ding et al., 1995).

Further indirect observations also connect recovery and virus presence in the meristem. Strong suppression of RNAi, suggested above to likely play a role in blocking meristem invasion, also prevents recovery: ectopic accumulation of potent VSRs inhibits recovery during nepovirus infections (Siddiqui et al., 2008; Santovito et al., 2014). Infection by
CymRSV lacking its strong P19 VSR leads to recovery after an initial acute infection, while the wild-type virus kills the host (Szittya et al., 2002). In another convincing example, the N-terminal domain of the CMV coat protein dampens the strong VSR activity of 2b (Zhang et al., 2017b), resulting in early, transient invasion of meristems and subsequent recovery from acute symptoms. In agreement with the data on meristem invasion cited above, this recovery was abolished in rdr6 mutants in Arabidopsis. RNAi factors such as RDR6 and DCL proteins have been linked to recovery in Arabidopsis (Kørner et al., 2018), and further data on the involvement of RNAi have been reviewed (Ghoshal and Sanfaçon, 2015). Of note, viral meristem invasion is not the only basis of recovery, as plants infected with geminiviruses, which are restricted to the phloem (and thus excluded from the meristem) can also recover from symptoms during infection (Sudarshana et al., 1998; Hagen et al., 2008; Raja et al., 2008).

Finally, regarding the relation between meristem invasion and recovery, the following contradiction needs to be resolved. How can RDR6 mediate meristem exclusion yet also trigger recovery upon virus entry into the meristem? One possible explanation calls for RDR6 to establish two consecutive defensive barriers, recovery being triggered only upon failure of meristem exclusion. Another intriguing hypothesis (Schwach et al., 2005) suggests that viruses excluded from the meristem may actually enter this tissue very transiently and trigger a recovery-like phenomenon, such that meristem exclusion is a localized form of recovery that does not extend beyond.

**The meristem as source of antiviral memory?**

As described above, the plant shoot apical meristem distinguishes itself from other tissues by exerting control over entry and/or replication of pathogenic viruses, based at least partially on sequence-specific, RNAi-dependent mechanisms, and may thus provide a state of heightened resistance to all subsequently formed tissues. The reviewed data suggest that this is not simply due to cellular preclusion of the virus, but to the potential of meristematic cells to arm cells of newly formed organs with a sequence-specific antiviral memory, allowing recovery from symptoms. Given the sequence-specificity and involvement of RNAi, replicating virus and/or other virus-derived nucleic acid sequences presumably contribute to this putative antiviral memory. Such principles are not limited to plants: compelling work with Drosophila (*Drosophila melanogaster*) and mosquitoes (*Aedes aegypti*) has shown that chimeras of transposon and virus DNA sequences are produced upon infection by RNA viruses (Goic et
al., 2013; Goic et al., 2016; Poirier et al., 2018). These extra-genomic vDNA molecules are generated via reverse transcription, are a source of vsiRNA, and are responsible for establishing a state of dampened, persistent infection. vDNA biogenesis depends on the helicase function of Drosophila Dicer 2 (Poirier et al., 2018). The template for the generation of the DNA chimeras are defective viral genomes (DVGs), a class of aberrant RNA molecules that are by-products of viral replication. During recovery from infection with tombusvirus species in plants, defective interfering (DI) RNAs, also aberrant molecules of viral origin, are an abundant source of vsiRNAs (Havelda et al., 1998). In revelatory experiments with CymRSV (Szittya et al., 2002), recovery mediated by CymRSV DI RNAs did not protect against super-infection with a PVX chimera containing the sequence of these DI RNAs, whereas PVX inoculum containing sequences of CymRSV other than the DI RNAs provided efficient cross-protection. Since CymRSV was still present in the recovered tissues, cross-protection against PVX likely resulted from RDR activity using the CymRSV RNA as template. Several additional examples of sequence-specific cross-protection in recovered tissues that still contain modest amounts of the primary recovery-inducing viruses support such scenarios (Ratcliff et al., 1997; Ratcliff et al., 1999; Foster et al., 2002; Szittya et al., 2002). Several cases can be directly correlated with meristem invasion, and it is interesting to note that after recovery from nepivirus infections, meristems contain more viral nucleic acids than the surrounding tissues (Figure 4B) (Dong et al., 2009; Santovito et al., 2014). Whether these nucleic acids, detected by in situ hybridization, were full-length and replication-competent viral RNA or some other form of maintained viral sequence remains to be determined. While Santovito and colleagues discussed that recovery was not determined by SAM invasion in their experiments, but rather by virus particles accumulating beyond a certain threshold, we suggest that SAM invasion is an equally valid (and not mutually exclusive) interpretation of their results. Whatever the molecular nature of the memory that enables recovery, its protection is not transmitted by grafting in tobacco (Lindbo et al., 1993), suggesting that it may not be systemically mobile within the plant. Sequence-specific resistance may also be conferred by viral sequences integrated in plant genomes (Chiba et al., 2011). This mechanism would be reminiscent of the recovery induced by viral sequences in transgenes (Lindbo et al., 1993) but is unlikely, as the recovery state is not inherited, at least in Nicotiana plants (Price, 1932; Foster et al., 2002). In reports of viral infection priming transgenerational resistance against pathogen attack (Boyko et al., 2007; Kathiria et al., 2010; Kalischuk et al., 2015), the sequence-specificity of the resistance was
not assessed, suggesting these may have been examples of inherited activation of broader defensive pathways.

In summary, we argue that limited virus entry into meristems may trigger the establishment of an RNAi-dependent virus-specific memory that is imparted to all emerging tissues. These tissues would have their RNAi machinery primed with cognate virus sequences, which would, at least in some cases, lead to (i) persistent, but asymptomatic infection by the primary virus and/or (ii) resistance to super-infection by secondary viruses carrying cognate sequences.

**Recovery, persistence and vertical transmission**

The fact that meristem invasion by a virus can potentially trigger recovery, a state of heightened antiviral defense, and/or vertical transmission, resulting from the relaxation or suppression of antiviral defenses, may seem contradictory. However, persistent, asymptomatic infection has often been linked to high rates of vertical transmission (Johansen et al., 1994; Roossinck, 2010). In a comprehensive milestone study, Lister and Murant (1967) evaluated seed transmission rates of several nepoviruses and tobraviruses on a range of host species. They found that these viruses, which often elicit recovery in their hosts, are also frequently transmitted through seeds. As mentioned above, the 12K VSR of tobravirus PEBV elicits both recovery and vertical transmission in pea (Wang et al., 1997). Similarly, a vertically transmitted BSMV strain produces milder symptoms on barley than a strain that is not transmitted by seed, with a major role for the γb VSR in this phenomenon (Edwards, 1995).

Serial rounds of successive vertical transmission of CMV in Arabidopsis led to a dramatic increase in seed transmission rates, coupled with overall reduction of viral titers and symptoms (Pagán et al., 2014). Crucially, these effects were not observed during an equal number of successive horizontal transmission events. Four strains of PSbMV on pea plants were barely detectable in vegetative tissues after only three successive rounds of vertical transmission, but remained abundant in flower and seed tissues, in line with the mode of transmission (Ligat and Randles, 1993). How fast these traits evolved is well in agreement with a highly selective and tight evolutionary bottleneck of vertical transmission, which was also reported in a study of population dynamics with PSbMV (Fabre et al., 2014).

Since viruses are obligate parasites, their means of transmission and the viral lifestyle in the host must be tightly connected and are expected to evolve together. Lister and Murant (1967)
suggested that vertical transmission of nepoviruses and tobraviruses supports long-range spreading through seeds and/or pollen, to compensate for the very short movement range of nematodes, their vectors for horizontal transmission. The ability of these viruses to enter the meristem, trigger recovery, and achieve vertical transmission may have evolved at the expense of high rates of replication and accumulation, similarly to the evolution of a mechanism in CMV to limit VSR activity and trigger recovery (Zhang et al., 2017b).

Conversely, viruses mainly relying on horizontal transmission through flying arthropod vectors may benefit more from high accumulation of virions in vegetative tissues but are not significantly limited by the lack of vertical transmission. Avoiding meristem entry, which would trigger recovery, may be under positive selection for these viruses. While the advantages of a recovered state for host plants are obvious, vertical transmission of lightly symptomatic or asymptomatic viruses may arguably also have positive effects. Several examples of viruses conferring advantages to their hosts are documented (Roossinck, 2015).

In the context discussed here, it can be envisaged that maintaining a replicating virus in a tightly controlled fashion throughout generations may preserve a sequence-specific memory for plants, providing cross-protection against closely-related but more aggressive viruses. Such protection would be particularly advantageous in case the recovered state is not inherited, as described in Nicotiana species (Price, 1932; Foster et al., 2002). There is one striking example illustrating how RNAi from the host plant controls replication of a persistent virus: Oryza sativa endorna virus (OsEV) is an asymptomatic, persistent endornavirus that is widely distributed in many rice (Oryza sativa) varieties and achieves almost 100% vertical transmission (Moriyama et al., 1996; Fukuhara, 2019). Although no VSR protein is known for this virus, OsEV dsRNA accumulates steadily to approximately 100 copies per somatic cell, while this number is 10-fold higher in pollen (Moriyama et al., 1995; Moriyama et al., 1999). OsEV-derived vsiRNAs can readily be found in several tissues (Urayama et al., 2010).

Intriguingly, knock-down of rice DCL2 caused OsEV to decrease in copy number and/or disappear (Urayama et al., 2010), suggesting that DCL2 is indispensable for OsEV maintenance. This counter-intuitive observation can be explained if rice DCL2 generates a putative form of “tolerant” RNAi that does not cause complete OsEV elimination but allows limited accumulation of the virus. In the absence of DCL2, OsEV might replicate and accumulate uncontrollably and trigger other “intolerant” mechanisms that efficiently eliminate it.
Concluding remarks

Apical meristems likely possess effective antiviral barriers that prevent many pathogenic viruses from entering and/or establishing infection. The real and potential perils of virus seed transmission in staple crop species and the commercial relevance of maintaining virus-free plant material should challenge investigators to better understand the meristematic and transgenerational antiviral barriers deployed by plants. The mechanisms underlying these phenomena appear to be qualitatively and/or quantitatively distinct from defense in the rest of the plant. Available data suggest that RNAi on the plant side and RNAi suppressors on the viral side are integral players of these barriers, albeit in different ways than in other plant tissues. Furthermore, RNAi-independent meristematic antiviral mechanisms, like regulation by the transcription factor WUSCHEL or aperture regulation of intercellular connections, add additional complexity. Meristem invasion by a virus may result in vertical transmission and/or the emergence of new tissues that have recovered from acute infection, with the outcome being dependent on several qualitative and quantitative parameters specific to each host/virus combination. The relationship between meristem exclusion, vertical transmission, and recovery (Figure 5) is therefore very complex. Given the ongoing arms race between hosts and pathogens and the high mutation rate of viruses, the underlying attack/defense elements are likely rapidly co-evolving traits. The ways a virus interacts with the components of the RNAi pathway that are active in the meristem are likely to have profound consequences for viral parameters such as persistence, spread, symptomatology, and modes of transmission. Fundamental processes such as meristem invasion, vertical transmission and recovery must be investigated through comprehensive studies addressing multiple related questions with specific virus-host combinations, using the wide range of molecular tools available today. These should include genetic and genomic data, more sensitive detection methods, environmentally controlled experiments, structural aspects of the components, refined reporter systems, and evolutionary perspectives. Complementary and cooperative approaches are expected to provide mechanistically fascinating insight as well as a much better basis for crop plant protection against devastating pests.

LIST OF PLANT SPECIES AND THEIR COMMON NAMES

We assemble the plant species mentioned in this review here, since they often only appear as part of the virus name: Arabidopsis (Arabidopsis thaliana), white clover (Trifolium repens), potato (Solanum tuberosum), Nicotiana benthamiana, barrelclover (Medicago truncatula),...
Cymbidium, cucumber (*Cucumis sativus*), turnip (*Brassica rapa*), tobacco (*Nicotiana tabacum*), Citrus, asparagus (*Asparagus officinalis*), chrysanthemum (*Chrysanthemum × morifolium*), pea (*Pisum sativum*), bean (*Phaseolus vulgaris*), barley (*Hordeum vulgare*), hop (*Humulus lupulus*), petunia (*Petunia × atkinsiana*), alfalfa (*Medicago sativa*), soybean (*Glycine max*), rice (*Oryza sativa*).

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**AUTHOR CONTRIBUTIONS**

G.B. and M.I. researched the topic and assembled relevant literature. M.I. drafted the manuscript and tables. G.B. prepared the figures. O.M.S. edited and improved the manuscript.

**FIGURE LEGENDS**

**Figure 1. Levels of control over vertical transmission of viruses/viroids.**

Many pathogenic viruses invade the entire plant body but most cannot enter shoot apical meristems, gametophytes, gametes, and/or embryos/seeds. Experimental data and agricultural practice suggest the existence of meristematic and transgenerational antiviral protection systems that prevent vertical transmission to progeny. How these defense mechanisms work, and the conditions under which some viruses can bypass the barriers, remains poorly understood.

**Figure 2. Schematic representation of experimentally observed virus/viroid distribution in relation to the shoot apical meristem (SAM).**

Virus-infected tissues are colored in violet. The virus is excluded from (A) the meristem dome (Sunpapao et al., 2009), (B) the entire SAM (e.g.: WCIMV (Foster et al., 2002); PSTVd (Di Serio et al., 2010)), or (C) the entire apex except the vasculature (e.g.: BDMV...
The virus invades the SAM, including the outer layers of the meristem dome and leaf/flower primordia (e.g.: CChMVd (Ebata et al., 2019); AV-2 (Kawamura et al., 2014)).

**Figure 3. Schematic representation of experimentally observed virus/viroid infection routes during plant sexual reproduction.**

Virus-infected tissues are colored in violet. (A) The virus invades all reproductive organs and is transmitted to the next generation, resulting in vertical transmission. (B) The virus invades the reproductive organs only partially, with various temporal and spatial distribution patterns, except gametes and/or embryos. This is not vertical transmission sensu stricto but mimics vertical transmission to the seedling by post-germination mechanical inoculation of virions from the seed coat. (C) A virus-infected pollen grain fertilizes a healthy plant and transmits infection to the mother plant (horizontal transmission) and/or the progeny (vertical transmission). Vertical transmission mechanisms proposed here were extrapolated from the following papers: (A) (Amari et al., 2007; Amari et al., 2009; Matsushita and Tsuda, 2014); (B) (Matsushita et al., 2011); (C) (Matsushita and Yanagisawa, 2018; Matsushita et al., 2018).

**Figure 4. Schematic representation of recovery in connection to meristem invasion.**

Virus-infected tissues are colored in violet. (A) In certain virus-host combinations, newly emerging organs from a systemically infected plant with strong disease symptoms show light or no symptoms, indicating recovery. Recovered tissues (colored in violet stripes) are resistant to super-infection by viruses containing RNA sequences homologous to the originally infecting virus. Recovery and cross-protection can be related to meristem entry of the initial virus. (B) During early stages of infection, nepoviruses predominantly invade the vasculature of the main stem, the leaf primordia, and the meristem dome (left). Later during recovery (right), the virus appears restricted to the meristem dome (Dong et al., 2009; Santovito et al., 2014). (C) During early stages of infection e.g. with TRV, the virus invades the SAM (left), but is later excluded from this tissue (right) (Martín-Hernández and Baulcombe, 2008).

**Figure 5. Control by host- and virus-encoded factors over virus meristem invasion, vertical transmission, and recovery from acute infection.**
Virus-infected tissues and viral proteins/factors are colored in violet, host plant-encoded proteins are shown in green. Virus invasion of the SAM (bottom) can occur upon depletion of host proteins RDR6 and/or WUS, or due to virus-encoded proteins such as 16K (TRV), 2b (CMV) and TGB1 (WCIMV). Weak/inefficient suppression of RNAi by viruses has also been suggested to allow viral SAM invasion. Virus invasion of the host progeny (top, left) resulting in vertical transmission has been linked to VSR proteins 12K (PEBV), HC-Pro (PSbMV), and γb (BSMV). Meristem invasion can also lead to recovery of newly emerging tissues from acute infection (top, right). Recovery has been linked to host antiviral RNAi factors including RDR6, and to VSR proteins 12K (PEBV), 2b (CMV), and 16K (TRV). Weak or inefficient suppression of RNAi by a virus can trigger both meristem invasion and recovery. A “recovered” state may in some instances correlate with high rates of vertical transmission.
| Term                        | Definition                                                                                                                                 |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Vertical transmission       | The transmission of a virus from an infected parent to its progeny, also known in plants as seed transmission. It can occur through (i) viral invasion of the gametes prior to fertilization and/or the embryo after fertilization, or (ii) viral infection of the seedling after germination by infected maternal seed tissues. As the latter is believed to be uncommon and must coincide with mechanical damage, here we focus on genuine vertical transmission, its biological causes and implications. |
| Horizontal transmission     | The transmission of a virus from an infected host to any other host independent of lineage. In plants, horizontal transmission is most often mediated by arthropods, nematodes, protozoa, and/or mechanical damage. |
| Shoot apical meristem (SAM) | Tissue present at the aerial growth tip of every plant. It contains pluripotent stem cells that eventually generate all above-ground organs, including flowers and the gametes within. The SAM has long been known to be resistant to invasion by most pathogenic viruses. |
| Recovery                    | Disappearance or mitigation of symptoms in newly emerging plant tissues from an otherwise systemic and symptomatic viral infection. Recovered tissues still contain viral nucleic acids but are resistant to re-infection by the cognate virus in a sequence-specific manner. |
| Cryptic/Persistent          | Adjectives describing plant viruses that accumulate to low titers, cause little or no symptoms, yet can often infect plant lineages over generations. |
Table 2. Virus categories.
For the purpose of this article, we divided viruses into three categories with regard to vertical transmission. Assignment to these categories can depend on the virus-host combination but distinguishes basic differences in viral “lifestyles”.

| Category                  | Defining characteristics                                                                                                                                 |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intragenomic              | Viral sequences that are vertically transmitted by default, as they are integrated into the host genome. They are copied and inherited along with the host genome regardless of whether they are in a quiescent, inactive, or a replicative, infectious state. They include endogenous viral elements (EVEs), which are widespread in eukaryotic genomes but less common in plants (Chabannes and Iskra-Caruana, 2013; Feschotte and Gilbert, 2012), and retrotransposons, selfish nucleic acids that are very abundant in plants and bear many similarities to viruses. |
| Extragenomic and cryptic  | Viruses that are little known or understood but are vertically transmitted at high frequency (Fukuhara, 2019; Roossinck, 2010). They copy their genome through their own polymerases, accumulate in limited amounts, and cause little or no symptoms. Their components are believed to move along with cell division, including in the meristems of infected plants. |
| Extragenomic and pathogenic| The vast majority of viral species that have been experimentally investigated, due to their pathogenicity in cultivated plants (Hull, 2014). These viruses carry all information necessary to copy their genome efficiently, assemble virions, and move systemically from cell to cell or to new hosts. Many of these viruses cause acute, strongly symptomatic infections. They are the focus of this review, as most are vertically transmitted at a low frequency. |
Table 3. Virus and viroid species mentioned in this review.

| Acronym | Full name                          | Genus, Family           | Relevant viral protein and its function |
|---------|------------------------------------|-------------------------|----------------------------------------|
| AMV     | Alfalfa mosaic virus                | Alfamovirus, Bromoviridae |                                        |
| AV-2    | Asparagus virus 2                   | Ilarvirus, Bromoviridae  |                                        |
| BSMV    | Barley stripe mosaic virus          | Hordeivirus, Virgaviirdae | γb VSR mediates vertical transmission  |
| CLBV    | Citrus leaf blotch virus            | Citirivirus, Betaflexiviridae | 2b VSR mediates meristem invasion and recovery |
| CMV     | Cucumber mosaic virus                | Cucumovirus, Bromoviridae |                                        |
| CymRSV  | Cymbidium ringspot virus            | Tombusvirus, Tombusviridae |                                        |
| OsEV    | Oryza sativa endornavirus           | Alphaendornavirus, Endornaviridae |                                        |
| PEBV    | Pea early-browning virus            | Tobravirus, Virgaviirdae  | 12K VSR mediates vertical transmission |
| PSbMV   | Pea seed-borne mosaic virus         | Potyvirus, Potyviridae   | HC-Pro VSR mediates vertical transmission |
| PVX     | Potato virus X                      | Potexvirus, Alphaflexiviridae |                                        |
| SBMV    | Southern bean mosaic virus          | Sobemovirus, Solemoviridae |                                        |
| SMV     | Soybean mosaic virus                | Potyvirus, Potyviridae   |                                        |
| TMV     | Tobacco mosaic virus                | Tobamovirus, Virgaviirdae |                                        |
| TRSV    | Tobacco ringspot virus              | Nepovirus, Secoviridae   |                                        |
| TRV     | Tobacco rattle virus                | Tobravirus, Virgaviirdae  | 16K VSR mediates meristem invasion     |
| TuMV    | Turnip mosaic virus                 | Potyvirus, Potyviridae   |                                        |
| TYMV    | Turnip yellow mosaic virus          | Tymovirus, Tymoviridae   |                                        |
| VSV     | Vesicular stomatitis virus          | Vesiculovirus, Rhabdoviridae |                                        |
| WCIMV   | White clover mosaic virus           | Potexvirus, Alphaflexiviridae | TGB1 MP (+VSR?) mediates meristem invasion |
| CbVd    | Coleus blumei viroid                | Coleviroid, Pospiviridae  |                                        |
| CChMvd  | Chrysanthemum chlorotic mottle viroid | Pelamoviroid, Avsunviroidae |                                        |
| HLVd    | Hop latent viroid                   | Cocadiroid, Pospiviridae  |                                        |
| PSTVd   | Potato spindle tuber viroid         | Pospoviriod, Pospiviridae  |                                        |
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31
Progeny (embryos, seeds)

Gametophytes and gametes

Shoot apical meristem

Systemically infected plant

Virus
Meristem dome exclusion

Vascular invasion

Meristem invasion
A

Healthy plant → Acute systemic infection → Meristem invasion? → Recovery

B

Recovery as observed for nepoviruses

Early → Late

C

Recovery as observed for TRV

Early → Late
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