Plant and animal rhabdovirus host range: a bug's view

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Rhabdoviruses affect human health, terrestrial and aquatic livestock and crops. Most rhabdoviruses are transmitted by insects to their vertebrate or plant hosts. For insect transmission to occur, rhabdoviruses must negotiate barriers to acquisition, replication, movement, escape and inoculation. A better understanding of the molecular interactions of rhabdoviruses with insects will clarify the complexities of rhabdovirus infection processes and epidemiology. A unique opportunity for studying how insects become hosts and vectors of rhabdoviruses is provided by five maize-infecting rhabdoviruses that are differentially transmitted by one or more related species of two divergent homopteran families.

The family *Rhabdoviridae* contains several economically important pathogens of humans, livestock and crops, and includes lyssaviruses, vesiculoviruses, ephemeroviruses, the fish-infecting novirhabdoviruses and more than 70 plant-infecting viruses (Fig. 1). Insects play an essential role in the horizontal transmission of most rhabdoviruses. Sandflies and blackflies transmit vesiculoviruses [1], mosquitoes transmit *Bovine ephemeral fever virus* (BEFV) [2], and leafhoppers, planthoppers, aphids and lacebugs transmit plant rhabdoviruses [3] (Fig. 1a). Rhabdoviruses replicate in their insect vectors. Thus, the majority of known rhabdovirus species have two natural hosts: either insects and plants, or insects and vertebrates.

Rhabdovirus phylogeny based on the polymerase (L) gene suggests a monophyletic origin (Fig. 1a). Five of the seven *Rhabdoviridae* genera contain viruses that are insect-transmitted and/or have natural insect hosts. Furthermore, some rhabdoviruses are transmitted to the progeny of insect hosts, whereas vertical transmission has not been observed in plants or vertebrates [3–6]. Thus, it seems likely that an insect was the primary host of the rhabdovirus ancestor [3,7,8].

Some rhabdoviruses have a broad host range. For example, vesiculoviruses naturally infect livestock, fish, blackflies and sandflies [9–12]. Experimentally, vesiculoviruses replicate in many other insects including the planthopper vector of *Maize mosaic virus* (MMV), *Peregrinus maidis* [13]. On the basis of rhabdovirus phylogeny and the broad host ranges of rhabdoviruses, we propose that insects are the primary determinants of the rhabdovirus plant and animal host range. Therefore, understanding the interactions of rhabdoviruses with insects is crucial to assessing rhabdovirus disease epidemiology. Because more insect species appear to be rhabdovirus hosts than vectors, the crucial question becomes: what limits an insect host from being a rhabdovirus vector?

The relevance of lyssaviruses and vesiculoviruses to human and livestock health has led to extensive molecular studies of rhabdovirus–vertebrate interactions. Molecular aspects of plant–rhabdovirus interactions have been focused primarily on *Sonchus yellow net virus* (SYNV) [14]. Although much is known about the distribution of plant rhabdoviruses in their insect vectors [3,15], molecular aspects of rhabdovirus transmission by insects are not well studied. Therefore, we will relate current knowledge on the molecular aspects of rhabdovirus infection of vertebrates to rhabdovirus transmission by insects.

What does it take for a rhabdovirus to be transmitted by an insect?

Insects transmit rhabdoviruses horizontally in a persistent propagative manner (i.e. the virus must enter and replicate in the insect before transmission) [3,12,15,16]. Thus, rhabdoviruses must negotiate several barriers in the insect vector to be transmitted to vertebrates or plants. Successful completion of horizontal transmission requires interactions of insect and virus factors, as well as compatibility of the vector with vertebrate or plant hosts (Fig. 2a).

The insect gut appears to be a barrier for transmission because bypassing the gut by injection of virus into the hemolymph increases transmission efficiency and often allows transmission of rhabdoviruses by non-vectors [15–17]. However, virus injection does not always result in transmission. Both infection of and escape from the salivary gland can be barriers for rhabdovirus transmission. For example, *Sowthistle yellow vein virus* (SYVV) is found in various tissues of non-vectors but not in the salivary gland [16]. In another non-vector, the virus accumulated in salivary glands but was still not transmitted.

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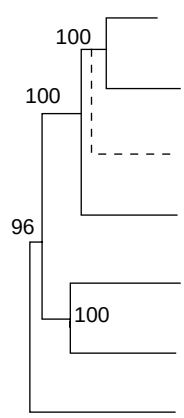
(a)



Genus	Species	Economic hosts	Insect vectors or hosts
Vesiculovirus	VSINV, VSNJV	Cattle, swine, fish	Blackflies, sandflies
Ephemerovirus	BEFV	Cattle	Mosquitoes
Sigma virus	SIGMAV	*none*	*Drosophila**
Lyssavirus	RABV, MOKV	Humans, mammals	none[@]
Cytorhabdovirus	SYNV, MFSV	Higher plants	Planthoppers (PH), aphids (A)
Nucleorhabdovirus	NCMV	Higher plants	Leafhoppers, PH, A
Novirhabdovirus	VHSV, HIRRV	Fish	*none*

(b)

Animal viruses	Abbrev.
Bovine ephemeral fever virus	BEFV
Hirame rhabdovirus	HIRRV
Mokola virus	MOKV
Sigma virus	SIGMAV
Rabies virus	RABV
Vesicular stomatitis Indiana virus	VSINV
Vesicular stomatitis New Jersey virus	VSNJV
Viral hemorrhagic septicemia virus	VHSV
Plant viruses	
maize fine streak virus[#]	MFSV
Maize mosaic virus	MMV
Northern cereal mosaic virus	NCMV
Sonchus yellow net virus	SYNV
Sowthistle yellow vein virus	SYVV

(c)

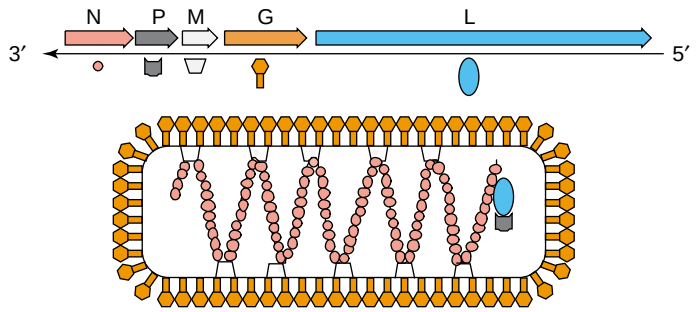


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Fig. 1. Characteristics of the rhabdovirus family. (a) Phylogenetic relationships among rhabdovirus genera. The tree is based on the RNA sequence from a region of the L protein [18]. Bootstrap values (1000 replications) are indicated next to the nodes. Because sequence information for the corresponding portion of *Sigma virus* (SIGMAV) is not available, its position is based on preliminary analysis of N protein sequences (M.G. Redinbaugh, unpublished). The economically important human, livestock and crop hosts are generally thought of as the principal viral host but most rhabdovirus genera also infect insect hosts as indicated. *SIGMAV is found in natural populations of *Drosophila melanogaster* and spreads vertically through the gametes of female and/or male flies but has no known vertebrate or plant host [6]. (a) [@]A culture-adapted variant of mokola virus (MOKV) replicates in inoculated *Aedes aegypti* mosquitoes [7]. (b) List of the rhabdovirus species discussed and their ICTV (International Committee on the Taxonomy of Viruses) abbreviations. ([#]The species name, maize fine streak virus, has not yet been approved by ICTV.) (c) Representations of the minimal rhabdovirus genome (above) and virion (below). The core of the virus particle contains the single-stranded negative-sense genomic RNA of 11 to 15 kb that is neither capped nor polyadenylated [6]. The minimal rhabdovirus genome, exemplified by vesiculoviruses, contains five structural protein genes (the open reading frames and their encoded proteins are indicated above and below the genome, respectively): the nucleocapsid protein (N), the polymerase complex consisting of the P and L proteins, the matrix (M) protein, and the glycoprotein (G). The most abundant virion proteins are the N and M, which coat the genomic RNA. L and P are present at low levels, and transcribe viral mRNAs on virus entry into a host cell. The G protein is anchored in the lipid layer of the virion with the glycosylated portion of the protein on the exterior of the virus particle. Although rhabdoviruses exhibit variations in genome organization, current information suggests the 'extra' genes do not determine host range. Vesiculoviruses, with only the basic five genes, have a broad host range including higher and lower vertebrates and insects.

At the molecular level, organ barriers could result from failure to enter, replicate in, move between, or exit from cells, or from virus activation of host defense responses.

Barriers to virus acquisition by insects

The first step of the virus transmission cycle is acquisition of the pathogen from the vertebrate or plant host by the insect's piercing and sucking mouthparts, and subsequent infection of the insect midgut by virus particles. Although an insect's ability to transmit a specific rhabdovirus is constrained by its host range, insects that feed on the same host plants do not necessarily transmit the same rhabdoviruses. For example, the leafhopper *Graminella nigrifons* transmits maize fine streak virus (MFSV) but not MMV, and the planthopper *P. maidis* transmits MMV but not MFSV [18]. Other plant rhabdoviruses are transmitted specifically by one or related insects [15,16,18,19]. Insect feeding behavior and tissue-specific virus localization in plants might both have a role in vector specificity.

After ingestion, rhabdoviruses invade the epithelial cell layers of the insect gut probably by pH-dependent receptor-mediated endocytosis [20]. MMV infects the epithelial and regenerative cells of the midgut of *P. maidis* [21]. The

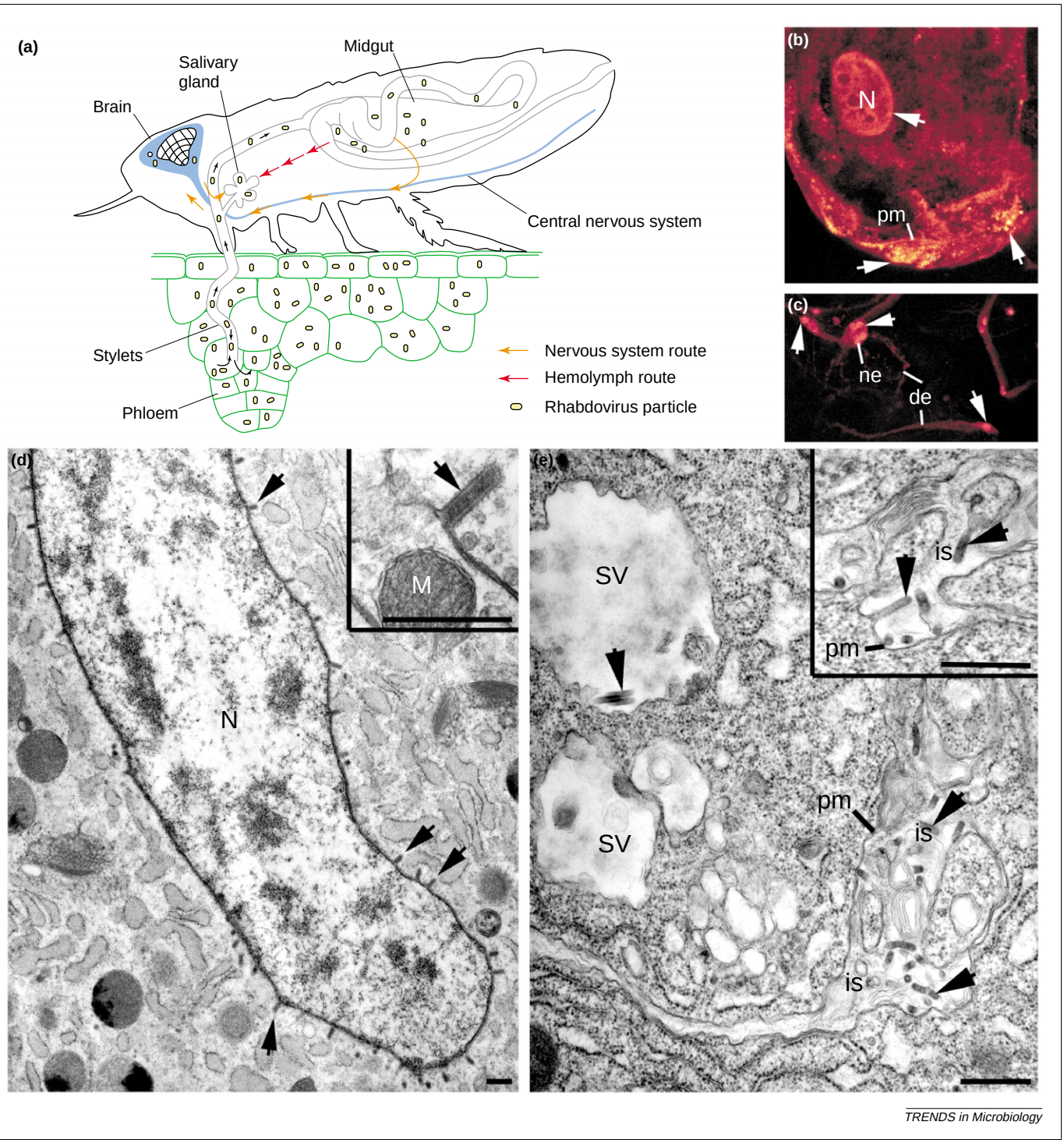

Fig. 2. Graphic and microscopic illustrations of insect transmission of plant rhabdoviruses. (a) Persistent propagative transmission of a plant rhabdovirus by a leafhopper. Viruses are acquired from plant cells through the food canal inside the stylet and move from the midgut lumen through the epithelial-cell layer into the hemolymph, and/or nerve cells and brain. They spread throughout the insect and infect the salivary gland tissues, and are introduced into new plant hosts through the salivary canal during insect feeding. (b) Immunolocalization confocal microscopy of *Maize mosaic virus* (MMV) in salivary gland cells of *P. maidis*. Labeling (arrows) was detected in the nuclei (N) and near the plasmamembranes (pm) of cells. (c) Immunolocalization confocal microscopy of maize fine streak virus (MFSV) in neurons (ne) and dentrites/axons (de) of *G. nigrifrons* showing dense accumulations (arrows) of viruses similar to Negri body inclusions observed in *Rabies virus* (RABV)-infected neurons of human and animals. (d) Electron micrograph of MMV particles (arrows) budding through nuclear (N) membranes of a cell from the accessory salivary gland of the planthopper vector *P. maidis*. The inset shows a MMV particle (arrowhead) budding through cytoplasmic membranes near a mitochondrion (M) of the neurophile in a nerve ganglion from *P. maidis*. (e) Electron micrograph of MMV particles (arrows) budding through the plasma membrane (pm) and accumulating in intercellular space (is) and in secretory vacuoles (sv) of a cell from the principal salivary gland of *P. maidis*. Salivary vacuoles and intercellular spaces (is) lead to the canaliculi, the salivary ducts and the salivary canal of the stylet. The inset shows virus particles (arrows) budding from the plasma membrane into the intercellular space. Bars = 500 nm.

trimeric rhabdovirus glycoprotein (G protein), the only rhabdoviral protein protruding from the virion's lipid envelope, is essential for interaction with host cell receptors [22] (Fig. 1c). It is a type I integral membrane protein comprised of ecto-, transmembrane and cytoplasmic domains. Although putative receptors have been identified in insects for some plant viruses, rhabdovirus receptors have not been identified in insects [23,24]. On the other hand, there is evidence for the presence of rhabdovirus receptors in cultured vertebrate cells, determined by saturation of binding, dose–response curves and antibody-neutralizing studies [25,26]. Vertebrate rhabdoviruses interact with acetylcholine receptors [27], neural cell adhesion molecules [28] and the low-affinity nerve-growth receptor $p75^{NTR}$ [29]. The primary receptor for fish rhabdoviruses is a cell-surface complex that contains fibronectin [30].

Rhabdovirus vector specificity could be determined by recognition events between gut cell receptors and rhabdovirus G proteins. The numbers and types of receptors could vary among insects. Although there is little sequence homology among G proteins, structural features of these proteins, including cysteine residues, antigenic sites and secondary structure elements (α-helices, β-strands and loops), are conserved among plant and vertebrate rhabdoviruses and are likely to be important for receptor recognition [31–33]. Virions in which the *Rabies virus* (RABV) G protein was replaced with the human immunodeficiency virus type I (HIV-1) envelope protein entered cells by the pH-independent pathway and with the cell specificity characteristic of HIV-1 [34]. This suggests that the G protein is important for both uptake and specificity. In addition to interaction with cellular receptors, insect-transmitted rhabdoviruses must be able to withstand degradation by potent proteases in the insect's saliva and midgut lumen, and to cross physical barriers, such as the multilayer peritrophic-like membranes separating the microvilli from the midgut lumen in planthoppers [21].

Barriers to virus replication in insects

Upon invasion of cells, the rhabdovirus nucleocapsid (composed of genomic RNA and the N, P and L proteins) is released for transcription of viral mRNAs and replication [35]. Subsequently, newly synthesized nucleocapsids form. Viruses recruit several host proteins during the infection and replication processes. In humans, intracellular transport of RABV requires dynein light-chain protein binding [36]. At least six *Drosophila* genes control *Sigma virus* (SIGMAV) replication. Of these, *ref(2)P* is most extensively investigated, and is active throughout development, particularly in the adult nervous system and female germline [37,38]. The *ref(2)P* product is a highly polymorphic 599-amino-acid cellular protein [39]. Some alleles of *ref(2)P* limit intracellular replication of SIGMAV [40]. The *ref(2)P* protein shares conformation-dependent epitopes with the SIGMAV N protein, and is found in complexes with the viral P protein that are required for RNA polymerase activity [41]. Interestingly, upon exposure to CO_2, SIGMAV replicates rapidly in nervous tissues and kills the insect. Plant rhabdovirus-infected insects might also be sensitive to CO_2, with a variable LD_{50} for CO_2 for each rhabdovirus vector combination [16]. This suggests that, similarly to *Drosophila*, insect vectors control rhabdovirus replication levels. Whether insect vectors have *ref(2)P* homologs remains to be investigated.

It is possible that rhabdoviruses can successfully invade gut cells of more insects than hosts but virus spread might be restricted to the site of infection by a process involving programmed cell death (apoptosis). To successfully infect a host cell, the virus must avoid induction of apoptosis, although a timely apoptosis event (i.e. late in infection) might aid rhabdovirus escape from cells [42]. The viral G protein apparently induces apoptosis in mice cells, as a RABV variant with higher pathogenicity and more efficient spread also shows downregulation of G protein accumulation [43]. In addition, apoptosis is prevented by efficient transport of the viral N protein into neuronal processes and by interaction of the viral M protein with ribonucleoprotein complexes [42,44].

Barriers to virus escape from vectors

Rhabdoviruses escape cells by budding from cellular plasma membranes, with the newly assembled nucleocapsid passing through host cellular membranes to acquire G proteins and a lipid bilayer [45]. Plant rhabdoviruses are classified as nucleorhabdoviruses or cytorhabdoviruses, depending on whether virions bud predominantly from host nuclear or cytoplasmic membranes, respectively. The nucleorhabdovirus, MMV, buds primarily from inner nuclear membranes of maize cells in most planthopper vector (*P. maidis*) tissues (Figs 2d and 3a). The virus accumulates in either the perinuclear space or intracytoplasmic, dilated cisternae connecting to the outer nuclear membrane and endoplasmic reticulum (ER; Fig. 2d). However, in salivary gland secretory cells of the planthopper, MMV particles commonly bud from the plasma membranes (Figs 2b,e) and accumulate in the intercellular spaces (Fig. 2e). These spaces ultimately connect to the salivary ducts, where the virus can move to a new plant host through the saliva [46]. Similarly, in vertebrates, RABV buds from the ER, except in the salivary glands, where it buds primarily from plasma membranes into the salivary secretion space [47]. The delivery of infectious virus to the saliva in this way is considered essential for virus transmission and survival [21].

The viral G and M proteins appear to target virions to intracellular membranes for budding. G protein endodomains of RABV and vesiculoviruses are required for efficient export from the ER, basolateral membrane delivery and membrane fusion [48–50]. The M protein drives virus assembly and budding, and contains a conserved membrane-binding domain [51,52]. In vesiculoviruses, 10% of the M proteins associate with the inner layers of plasma membranes where assembly and budding take place, suggesting that it plays a major role at the site of virus budding. We hypothesize that this protein influences the release of virus from the cytoplasmic membranes of the salivary gland of the insect vector.

Barriers to virus movement in insects

After escape from gut cells, rhabdovirus infection usually spreads to other organs and tissues in the vector. In

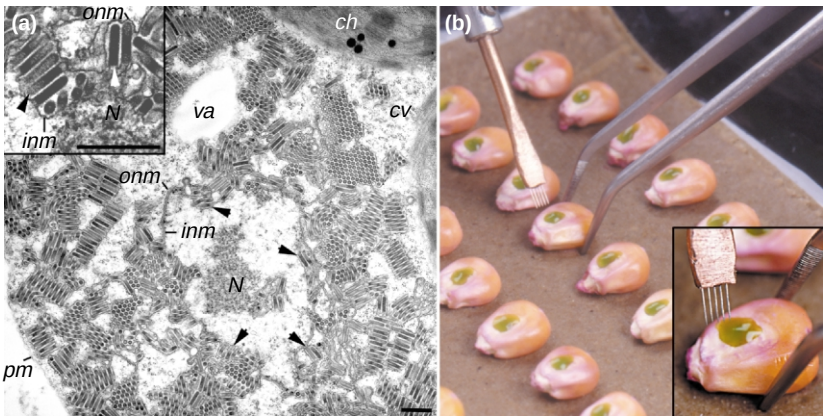

Fig. 3. Rhabdovirus infection of plants. (a) Aggregates of *Maize mosaic virus* (MMV) particles (v) budding through inner nuclear membranes (inm) (at arrow heads) and accumulating in the cytoplasm (cy) of a parenchyma cell from an infected maize leaf. Inset shows detail of virus particle budding into the perinuclear space. Bars = 500 nm. (b) Vascular puncture inoculation of germinating maize kernels uses a jeweler's engraving tool to push vibrating minute pins through a droplet of virus inoculum toward the major vascular bundle in the scutellum of germinating maize (*Zea mays* L.) kernels [60]. Abbreviations: ch, chloroplast; N, nucleus; onm, outer nuclear membrane; pm, plasma membrane; va, vacuole.

addition to the gut, MMV is found in the brain, nerve ganglia, epidermis, fat and connective tissues, retina, muscles, trachea, reproductive tissues, and the principal and accessory salivary glands of *P. maidis* [21]. It is not clear how viruses spread throughout the insect vector but current literature and data suggest that rhabdoviruses could infect other organs through the insect nervous system and/or hemolymph (Fig. 2a).

SIGMAV, RABV and vesiculoviruses spread mainly through the nervous tissues of their vertebrate hosts, and the bloodstream does not appear to contribute significantly to infection of tissues [53,54]. RABV enters animal muscle cells from infected saliva, and subsequently spreads through the nervous tissue and spinal cord to the brain. Once in the brain, the virus multiplies and spreads rapidly to other tissues and organs, particularly the salivary glands [55]. Vesiculoviruses spread in a similar manner in which primary infection of the brain occurs through the olfactory nerve [53]. Immunolocalization-confocal microscopy studies of dissected midguts from MFSV-infected leafhoppers showed high virus accumulation in structures that look like the Negri body inclusions observed in RABV-infected mammalian neurons [56] (Fig. 2c). This observation suggests that plant rhabdoviruses might move through the nervous system of their insect vectors. RABV infection of nervous tissue leads to dramatic changes in animal behavior, including increased aggression and salivation [54]. This behavior increases the probability of virus transmission. Similarly, rhabdoviruses could change feeding behavior and/or increase salivation of their insect hosts, thereby enhancing inoculation efficiency. Indeed, several viruses, bacteria and eukaryotic parasites of plants and animals change behavior of their insect vectors [57–59].

Rhabdoviruses could also move through the host's bloodstream. Rhabdovirus-infected fish go through several cycles of viremia in which viruses are released into the bloodstream from infection sites, including endothelial cells of blood capillaries, hematopoietic tissues and nephron cells, leading to necrosis and hemorrhage [10]. The hematophagous blackflies, sandflies, mosquitoes and midges introduce viruses by damaging host tissues with their mouthparts, releasing virus particles into the bloodstream of vertebrate hosts. Interestingly, whereas vesiculoviruses cannot be detected in the blood of the host, non-infected blackflies can acquire these viruses within 48 hours while co-feeding with infected blackflies [9]. Furthermore, rhabdoviruses can be introduced into the insect host by intrathoracic injection, which is believed to introduce viruses into the insect hemolymph. In addition, vesiculoviruses replicate in the planthopper *P. maidis* after intrathoracic injection [13]. However, injection results in tissue damage, which could allow infection of other tissues, including nerve cells. Although rhabdovirus receptors identified thus far are primarily from animal nervous tissue, several of the receptors are members of protein families conserved among animals including insects. It is therefore possible that insect-transmitted rhabdoviruses recognize similar receptors in their insect and vertebrate hosts. This hypothesis is supported by the phylogenetically broad host range of vesiculoviruses.

Barriers to virus inoculation of vertebrates and plants

Although insects inoculate vertebrates and plants in nature, rhabdoviruses could be mechanically inoculated in the laboratory. Vesiculoviruses and RABV can be introduced into animal hosts by syringe inoculation; in plants, mechanical inoculation of abraded leaves (also known as leaf-rub-inoculation or LRI) and/or vascular puncture inoculation (VPI) (Fig. 3b) produce systemic rhabdovirus infection. For LRI, a virus-containing solution is rubbed on the leaf surface, making wounds in the epidermal cells. LRI mimics wounds made by aphids as they use their stylets to probe epidermal cells before feeding, depositing virus in these cells as they probe [6]. Indeed, LRI works well for most of the aphid-transmitted rhabdoviruses. However, MMV and MFSV are transmitted by planthoppers and leafhoppers, respectively, and cannot

be introduced into maize leaves by LRI [6,18]. This suggests that epidermal cells might not support initial replication of MMV and MFSV and subsequently these viruses must be introduced into other plant-cell types for infection to occur [6]. Planthoppers and leafhoppers might deposit the virus mainly in mesophyll or phloem cells [3,6]. Interestingly, MMV and MFSV can be transmitted by VPI, which uses a jeweler's engraving tool to drive minute pins through virus inoculum and into the scutellum of germinating maize kernels [60] (Fig. 3b).

The efficiency of rhabdovirus inoculation by insect vectors also depends on the level of resistance to rhabdovirus infection in vertebrate and plant hosts. Insects, vertebrates and plants all have an innate immune response that aids in protection against microbes [61], and there is evidence that this system is important in both the animal and plant response to rhabdovirus infection. In vertebrates, the rhabdovirus G protein induces an early non-specific interferon-mediated immune response. The interferon-induced protein Mx of Japanese flounder prevents replication of the novirhabdovirus, *Hirame rhabdovirus* (HIRRV), *in vivo* and *in vitro*, and is 40% identical to mammalian interferon regulatory factors 1 and 2 [62,63]. Other genes associated with the innate immune response that are induced by rhabdoviruses include the *vig-1* and *vig-2* genes of rainbow trout [64], and the mouse homolog of *vig-1*, *mvig* [65]. The function of these genes remains to be investigated but they could be part of transduction pathways that leads to inflammatory responses. An innate defense response that limits pathogen spread is also induced by virus infection in plants [61]. This response, which can include a rapid programmed-cell-death commonly referred to as the hypersensitive response is rapidly upregulated in plants carrying pathogen-specific resistance genes. For example, the N gene of tobacco confers resistance to Tobacco mosaic virus [66]. Resistance to maize-infecting rhabdoviruses has been identified for both MMV and MFSV [18,67]. Plants also respond to insect feeding by induction of defense response genes [68].

Although rhabdoviruses can be transmitted mechanically, the insect is likely to be more than a flying injection needle, because insect saliva could have a significant role in the establishment of rhabdovirus infection in vertebrate and plant hosts. Additionally, insects transmit rhabdoviruses much more efficiently than mechanical inoculation, requiring significantly lower concentrations of virus than syringe inoculation, LRI or VPI. Saliva from plant-feeding insects could contain factors that reduce the effect of the plant wound and defense responses [68]. The insect's modulation of the host's innate immune response might facilitate virus replication at the site of inoculation. Indeed, tick salivary gland extracts inhibit the antiviral activity of interferon, and increase replication of vesiculoviruses [69]. The potentiating effect of insect saliva on pathogen transmission was observed with protozoans, arboviruses, bacteria and nematodes [70].

Conclusions and perspectives

There is no doubt that research on the molecular interactions between rhabdoviruses and insects is likely to make valuable contributions to clarifying the complexities of the rhabdovirus infection process. Insect vectors play a crucial role in determining the host range of vertebrate and plant rhabdoviruses, and multiple barriers to rhabdovirus transmission are present in insects. The availability of closely related insect species that differentially transmit maize-infecting rhabdoviruses provides an excellent tool for studying aspects of the rhabdovirus infection process [18]. In addition, the available *Drosophila* genome sequence and defined genetic interactions between *Drosophila* and SIGMAV will facilitate studies of rhabdovirus–vector interactions at the molecular level.

There are four major questions for future research. What are the roles of gut and salivary gland receptors and the insect innate-immune response in vector specificity of rhabdovirus transmission? Does rhabdovirus infection change the behavior of the vector to increase probability of transmission? Is movement of plant-infecting rhabdoviruses through the insect nervous system required for transmission? How does insect saliva affect rhabdovirus survival and ability to establish an infection in the plant host? Answers to these questions will significantly enhance our understanding of how new rhabdovirus disease outbreaks occur in humans, livestock and crops.

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