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Plant virus proteins involved in natural vector transmission

Stewart M. Gray

Plant viruses transmitted by invertebrate vectors either reversibly bind to vector mouthparts or are internalized by the vector and later secreted. Viral proteins mediate the binding of plant viruses to vector mouthparts and the transport of virus across vector-cell membranes. Both mechanisms probably involve conformational changes of virus proteins during their association with the vector.

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Most plant viruses depend on one of a variety of organisms acting as vectors for transmission between plant hosts, but most plant viruses do not replicate in their vectors. Insects, particularly homopterans with piercing–sucking mouthparts, are by far the most numerous and important vectors, although other arthropods, nematodes and fungi are also important vectors of plant viruses[1]. The biological relationships between viruses and their specific vectors are known for most economically important viruses, and the involvement of virus-encoded proteins in transmission has been demonstrated[2–11]. Although the precise interactions between virus and vector remain elusive, data on transmission-associated viral proteins have revealed common features among diverse virus–vector combinations. This review considers the requirement for virus-encoded proteins in transmission and the mechanisms by which these proteins might mediate virus–vector interactions.

The terminology used to describe plant virus transmission is biased towards aphid vectors, and does not accurately reflect the transmission processes of other vector taxa[12]. In this review, I divide plant viruses into two broad categories with different transmission processes: circulative and noncirculative. Circulative viruses are usually defined as moving from the alimentary canal of an insect vector into its hemocoel (its open circulatory system) and back out through the salivary secretory system. However, in this review, I expand the definition of circulative transmission to include any plant virus that must be actively transported across vector membranes and survive inside the vector to be transmitted. Noncirculative viruses associate with the cuticular lining of the insect mouthparts or foregut and are released as the insect expels digestive secretions into the plant when it begins to feed. These viruses are not actively transported across vector-cell membranes, nor are they carried internally. The external cuticular lining of insects (and nematodes) extends well into the mouthparts and foregut, but is shed when the animal molts.

Circulative transmission

The circulative viruses are divided into two groups: propagative and nonpropagative. Circulative propagative viruses replicate both in their vectors and in their plant hosts, and include the tospoviruses, Phytoreoviridea, plant Rhabdoviridea, tenuiviruses and marafiviruses. These viruses encode genes that are differentially expressed in insect and plant hosts[13,14]. Although their transmission mechanisms are currently being studied[15,16], there is little new information on this group not covered in previous reviews[2,3].

The circulative nonpropagative viruses do not replicate in their vector. The vector primarily facilitates virus movement between plant hosts; however, these viruses have evolved very specific mechanisms that allow them to exploit the physiological systems of the vector. These viruses include the luteoviruses, geminiviruses and pea enation mosaic virus (PEMV). The fungally transmitted furoviruses and bymoviruses are also included, as these are internalized by the fungi[17,18]. The beetle-transmitted tymoviruses, comoviruses, bromoviruses and sobemoviruses could also be included, as these viruses are transported across gut membranes into the hemolymph of the insect[19]; however, this might not be an essential requirement for transmission[20].

Circulative transmission in insect vectors

Luteoviruses and PEMV are the best studied of the circulative nonpropagative viruses, and they share many fundamental features and mechanisms related to their transmission by aphids[7,21]. After uptake into the alimentary canal, virus particles attach to and are transported across the hindgut, and occasionally the midgut, epithelium into the hemocoel via a receptor-mediated endocytotic pathway[7,22,23]. The hindgut can act as a barrier to luteovirus movement into the hemocoel, but it does not appear to inhibit the uptake of most luteovirus isolates[22–24]. Virus particles are carried by the hemolymph from the abdomen to the head, where they can associate with the accessory salivary gland (ASG). Here, virus is actively transported across two distinct barriers to transmission, the ASG basal lamina and the ASG plasmalemma, and then released into the salivary canal. Virus is then injected into a plant as the aphid feeds[25] (Figs 1–3).

The ASG basal lamina is a fibrous network consisting primarily of collagen, which provides support and may also act as a filter[26]. Luteovirus isolates differentially bind the ASG basal lamina and selectively

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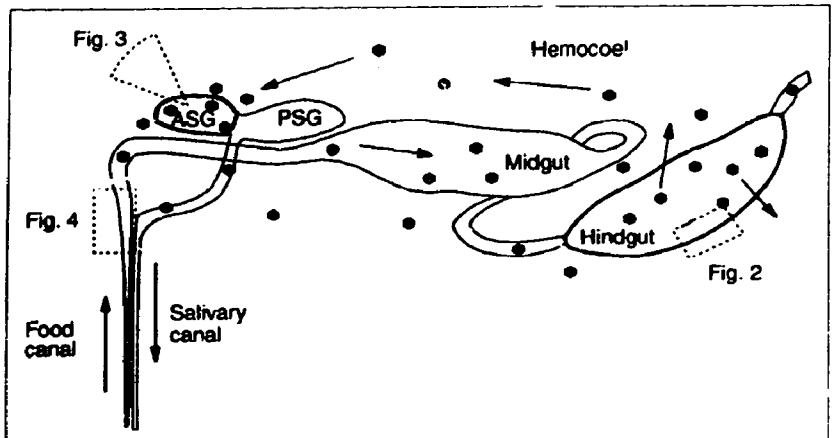

Fig. 1. Internal structures of an aphid involved in the transmission of circulative (route depicted by arrows) and noncirculative viruses. Ingested virus moves through the alimentary canal and is actively transported into the hemocoel across the hindgut epithelial cells (see Fig. 2 for details). Viruses must associate with the accessory salivary gland (ASG), be actively transported across two cellular barriers (see Fig. 3 for details) and be released into the salivary canal. There is no evidence that the principal salivary gland (PSG) is involved. Noncirculative viruses would be retained in the food canal and the foregut (see Fig. 4 for details). The internal organization of other insect vectors with piercing–sucking mouthparts is similar, but not identical.

move across the basal lamina matrix. Luteoviruses do not interact with the basal lamina of other tissues, including the principal salivary gland[22,25,27]. The transport of luteoviruses across the ASG plasmalemma, which is also selective for specific isolates, appears to occur by receptor-mediated endocytosis[21]. The hindgut, ASG basal lamina and ASG plasmalemma have various effects on the transmission efficiency of different combinations of aphid species and virus isolate[22,25,27], suggesting that the molecular mechanisms involved in virus movement across these three barriers are likely to involve different viral proteins or protein domains.

The capsid of luteoviruses and PEMV contains two proteins, a predominant coat protein and a secondary protein that is present in small amounts and is translated via readthrough of the coat protein stop codon[7,8,28–30]. Heterologous encapsidation is common between barley yellow dwarf luteoviruses when multiple isolates infect the same plant[31–33]. If complete or partial exchange of capsid proteins occurs, the vector-specific transmission phenotype of one or both isolates is altered[32,33]. The readthrough protein, although not required for particle assembly or plant infection[7,8,34], is required for aphid transmission[7,8,35]. Although luteovirus particles lacking the readthrough protein are acquired by aphids and can cross the hindgut barrier to accumulate in the hemocoel, no transmission to plants occurs[8,35]. These observations suggest that the readthrough protein is required for viruses to move across transmission barriers in the ASG, and that the coat protein is probably therefore responsible for virus movement across the hindgut.

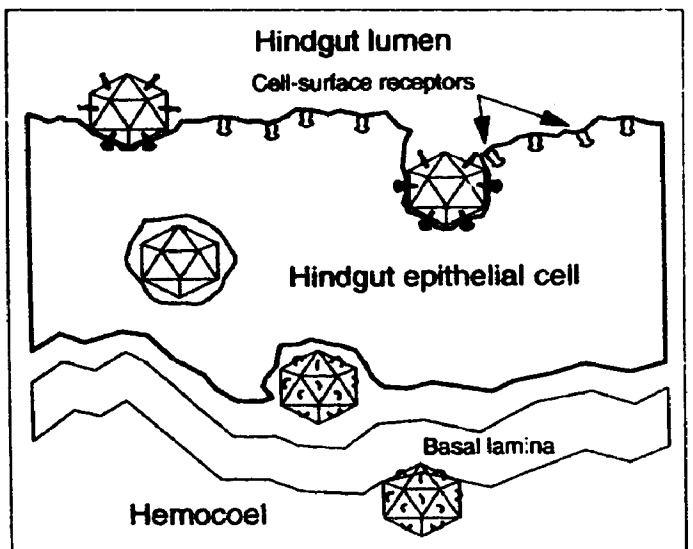

Fig. 2. Mechanism of the proposed receptor-mediated endocytotic transport of circulative nonpropagative viruses across the hindgut epithelial cells. Accessible or protruding capsid-protein domains bind to receptors on the apical plasmalemma of the hindgut epithelial cells. The process of virus uptake or the environment within the cytoplasmic transport vesicles might strip off the receptor-binding domain. The vesicle membrane fuses with the epithelial cell basal plasmalemma, and virus is released into the hemocoel. The environment of the hemocoel possibly alters the conformation of the capsid proteins and exposes domains required for interactions at the accessory salivary glands (see Fig. 3).

The circulative transmission of geminiviruses through their whitefly or leafhopper vectors has not been studied in detail, but is thought to be similar to that of luteoviruses in aphids. Unlike the luteoviruses, only the coat protein is required for transmission, and the coat protein appears to regulate the specificity of transmission by both whiteflies and leafhoppers[36,37]. The whitefly-transmitted geminiviruses have a highly conserved amino acid sequence in their coat proteins, and are all transmitted efficiently by one whitefly species, *Bemisia tabaci*. Conversely, the leafhopper-transmitted geminiviruses each have distinct coat proteins, and are transmitted by different principal vector species[38].

Circulative transmission in fungal vectors

Furoviruses and bymoviruses are carried internally by their fungal vectors; the mechanisms involved are not well understood, but there are some similarities with insect-transmitted, circulative nonpropagative viruses. One of the furovirus coat proteins is translated by readthrough[39,40]; this protein is required for efficient transmission[5]. Bymoviruses express a nonstructural protein (P2), which has sequence similarities with the furovirus readthrough protein[41]. Repeated passage of virus through host plants by mechanical rather than fungal inoculation often generates transmission-deficient mutants[5,41,42]. The loss of fungal transmission is always correlated with deletions in the genes encoding the furovirus readthrough protein and bymovirus P2 protein.

Interestingly, within the mechanically inoculated plants, the nontransmissible isolates predominate, but vector-transmissible isolates can be recovered[42,43]. These observations could suggest that viruses can jettison unnecessary portions of their genome when they are not required. For example, the root-infecting fungal vectors are not found in aerial portions of the plant, yet virus is translocated throughout the plant. Transmission-associated proteins would only be required in plant tissues where the fungi and virus can associate. In this context it is interesting that viruses with mammalian and insect hosts often cause a persistent infection in only one type of host. In several cases, the viral RNAs isolated from the persistent infections have undergone substantial deletions or rearrangements. Could infection of the aerial portion of a plant be analogous to a persistent or latent infection, while that of the root tissue represents an acute infection? The differential expression of genes between hosts is common in viruses that infect different types of host, and may also occur within different tissues of a single host.

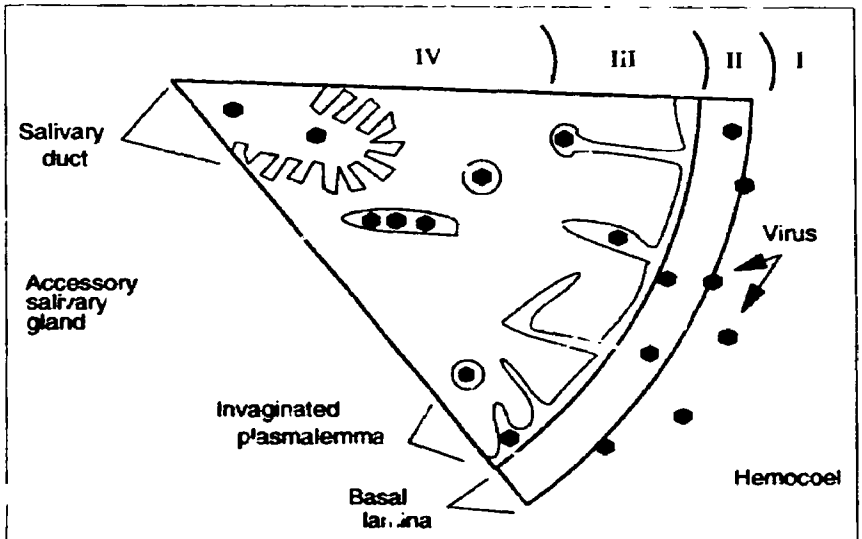

Fig. 3. The aphid accessory salivary gland is composed of four cells joined by a common salivary duct that empties into the salivary canal. The cells are surrounded by a basal lamina and the basal plasmalemma is highly invaginated. Electron-microscopic investigations of luteovirus–aphid interactions indicate that virus transport from the hemocoel into the salivary duct can be blocked by at least three mechanisms: **(I)** failure of viruses to attach to the basal lamina, **(II)** failure of viruses to move into or across the basal lamina, and **(III)** failure of viruses to initiate endocytosis by the basal plasmalemma. If a virus particle is taken up by the plasmalemma and contained within cytoplasmic vesicles **(IV)**, it appears to be released into the salivary duct.

Noncirculative viruses

The majority of plant viruses are not internalized by their vectors. Successful transmission depends on the ability of the virus to associate with cuticular linings of the mouthparts or foregut of the vector and subsequently to be released. Current models of nonpersistent transmission result primarily from work on the aphid-borne potyviruses, caulimoviruses and cucumoviruses, but the nematode-transmitted nepoviruses and tobraviruses have many common features with the aphid-borne viruses.

Noncirculative virus transmission by aphids

Two viral proteins, the coat protein and the nonstructural helper component (HC), are required for aphid transmission of potyviruses. Their molecular characteristics are reviewed in Ref. 3 (see also Refs 9,10,44). A conserved amino acid sequence (Asp-Ala-Gly) in the amino terminus of the coat protein is essential for aphid transmission. Proteolytic treatment of virions, which removes the amino terminus of the coat-protein subunits, prevents the particles from being transmitted by aphids, although they remain infectious when mechanically inoculated into plants[45].

The HC is presumably acquired along with virus particles as the aphid feeds on plant sap, but the role of this protein in transmission is unknown. One hypothesis is that it mediates the binding of virus to sites within the aphid food canal, either directly, by linking the virus to the aphid (Fig. 4A), or indirectly, by modifying viral attachment compounds in the aphid to allow virus binding (Fig. 4B). Virus-like particles have been observed embedded in a matrix material associated with the stylets and foregut of aphids fed on a mixture of virus and HC. No bound particles were observed when aphids were fed on virus alone[46]. In virus mutants containing deletions or substitutions making either the coat protein or the HC incompetent for aphid transmission, the association of virus-like particles with the cuticle did not occur (T.P. Pirone, pers. commun.). Transmission competent HC is required for virus association and retention in the aphid mouthparts and must be present before the virus or simultaneously with it[3]; this suggests that HC is involved in mediating binding between the aphid cuticle and the virus.

An alternative hypothesis is that HC acts indirectly to modify the coat protein and allows a direct interaction between the virus particle and the aphid (Fig. 4C). When a recombinant protein containing the amino-terminal region of a potyvirus coat protein was fed to aphids before feeding them virus and HC, transmission was abolished[47]. Salomon and Bernardi interpret these data to suggest that the recombinant protein saturated virus-binding sites in the aphid and prevented subsequent virus binding. They hypothesize that the amino-terminal region of the coat protein, rather than the HC, attaches to sites on the aphid. They further suggest that the amino-terminal region of the coat-protein monomers assembled into virus particles is not normally available for interaction with the aphids, but that HC mediates a conformational change in the amino terminus of the coat protein that allows binding of the virus to the aphid (Fig. 4C).

The transmission of the caulimoviruses also requires a nonstructural HC (Ref. 48), and recent studies support

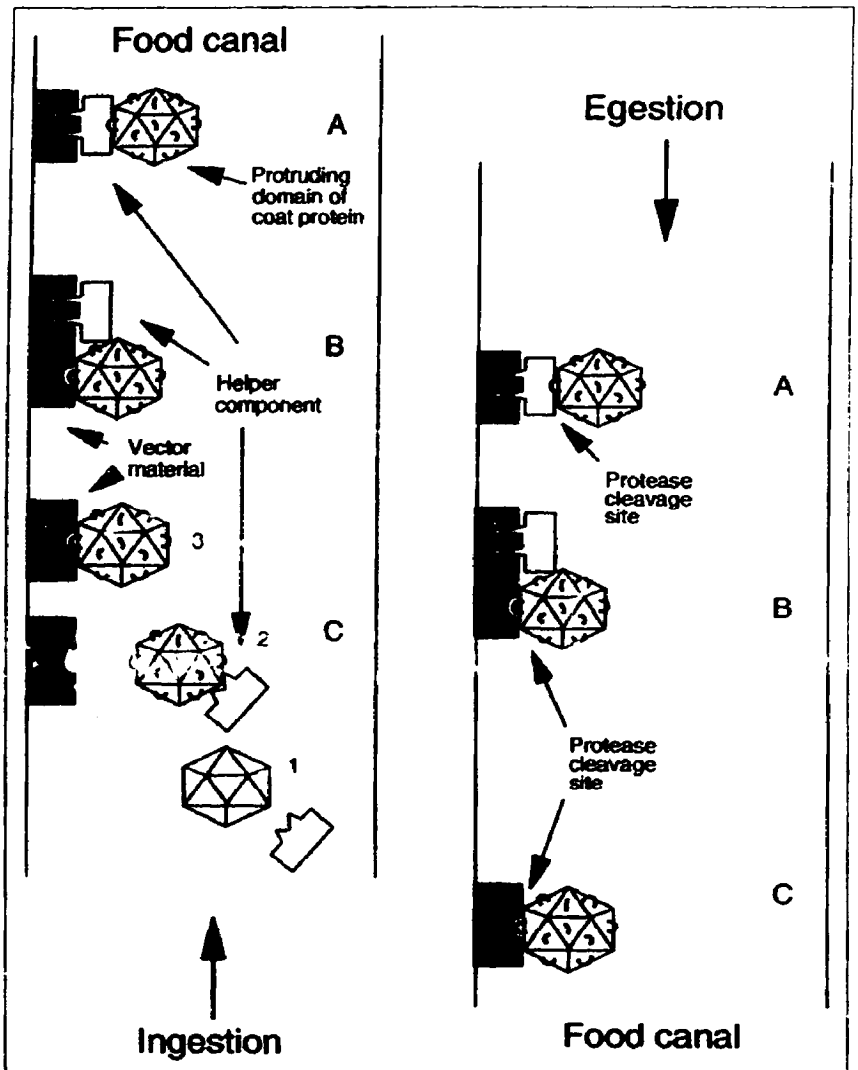

Fig. 4. Three models of the interaction between a noncirculative virus, the virally encoded helper component and the vector material lining the cuticle in the food canal. Most experimental evidence supports either model **A** or model **B**. In model **A**, the helper component directly facilitates virus binding by first attaching to sites in the food canal; virus then binds to the helper component. In model **B**, the helper component indirectly facilitates the binding of virus directly to the cuticle. Helper component first binds to a specific site causing a conformational change that allows virus to bind. In model **C**, helper component interacts directly with the virus causing a conformational change in the virus. This exposes sites on the virus that can then interact directly with binding factors on the cuticular lining of the food canal. The release of the virus, regardless of the binding process, occurs during the intermittent phases of feeding when the vector expels digestive secretions into the plant. The model proposes that proteases in the digestive secretions cleave exposed sites on the virus capsid proteins that are involved in binding the virus to the helper component or to the vector.

the role of HC in mediating binding between the aphid cuticle and the virus. Biologically active HC, isolated from infected plants or a baculovirus expression system, binds coat protein *in vitro*[48,49]. Two of the carboxy-terminal 31 amino acids of the HC are required for HC to bind coat protein, and loss of binding abolishes aphid transmission. HC expressed in *Escherichia coli* as an amino-terminal glutathione-S-transferase–HC (GST–HC) fusion protein can bind coat protein *in vitro*, but cannot mediate transmission. If supplied along with functional HC and virus, the GST–HC fusion protein inhibits transmission[49]. Schmidt *et al.* suggest that the GST–HC protein outcompetes the native HC and saturates virus-binding sites. As the amino-terminal portion of the HC in the fusion is attached to GST, it cannot interact with binding sites in the aphid, and so transmission is prevented.

In contrast to the potyviruses and caulimoviruses, nonstructural helper components are not required for the aphid transmission of cucumoviruses; their transmission is regulated mainly by the coat protein[50]. Site-specific mutagenesis of cucumber mosaic virus (CuMV) has identified two regions of the coat protein that are involved in efficient transmission, and has pinpointed the amino acids needed[51]. The same regions of the coat protein, but not the same amino acids, have been implicated in a second poorly transmissible CuMV strain. The transmission efficiency of CuMV has been attributed to properties of the coat protein, but not to identifiable linear amino acid sequences. These observations suggest that one or a few amino acid changes in the coat protein could alter the vector-transmission phenotype by preventing direct interaction between the virus and the vector. Alternatively, the amino acid changes could influence the three-dimensional structure of the coat protein or capsid, and indirectly affect the ability of the virus to interact with its vector.

Noncirculative virus transmission by nematodes

The noncirculative nematode-transmitted nepoviruses and tobraviruses also associate with the cuticular lining of the vector food canal. Acquired virus particles bind to specific regions of the stylet sheath, pharynx or esophagus, and a carbohydrate-containing material of unknown origin is associated with bound virus particles. The involvement of nonstructural virus proteins has not been established for the nepoviruses, but recent evidence suggests that a nonstructural protein might be required for transmission of tobraviruses in addition to the coat protein[52]. Virus release is thought to be mediated by a pH change resulting from salivary secretions flowing through the food canal when the nematode begins to feed on a plant[2,53]. Like the amino-terminal domain of the potyvirus capsid protein, the carboxy-terminal domain of the tobravirus coat protein can be cleaved from the virus particle by some proteases without adversely affecting the virus[54]. It is not known whether or not the

modified particles can be transmitted by nematodes. Interestingly, the aggregation state of coat-protein monomers does respond to changes in pH, and the carboxyl terminus of the tobacco rattle tobravirus coat protein contains a segment that does not appear to be part of the structural framework of the virus particle[54]. Could this be a conformationally active region of the coat protein that is exposed only in the nematode foregut and that acts as a cleavage site for virus release?

In noncirculative transmission, the virus must associate with the cuticular lining of the food canal of the vector. Binding requires viral protein sequences and perhaps specific vector substances. The binding must be reversible, and release can involve specific proteolytic cleavage events or can be passive. The ends of the coat-protein subunits of the virion are likely points of interaction with sites in the vector or with the viral helper component. Although there is no definitive proof, many of these observations suggest that conformational changes in the capsid-protein subunits facilitate transmission. The conformational change might be mediated by a helper component, the environment within the food canal or binding of the virus to the vector, all resulting in the exposure of cleavage sites on the coat proteins. Exposure of these sites to digestive secretions during feeding would create a mechanism by which bound virus could be released from the vector and injected into a plant host (Fig. 4).

Future directions

Recently, rapid progress has been made in dissecting the relatively simple genomes of plant viruses and identifying the proteins that are involved in their transmission by vectors. Changes in the linear sequence of transmission-associated proteins can alter the transmission phenotype of a virus, but the three-dimensional structure of protein subunits or virus capsid is also likely to be involved in virus–vector interactions. Conformational changes in a virus protein could alter in response to environmental changes, and this could prevent virus transmission. However, most plant-infecting viruses do not replicate in their vectors and do not appear to undergo major morphological changes within the vector. The environment within the alimentary system or hemolymph of a vector is probably significantly different from that within a plant cell or *in vitro*. Possibly, viruses undergo more-subtle conformational changes within the vector that are not readily detectable. It is well known that changes in pH or ionic strength can alter the conformation of plant viruses[54,55]. Hence, the biochemical environment within a vector might alter the virion structure such that different protein domains are accessible for interaction with a vector. I discuss this hypothesis for noncirculative viruses, but it is also likely to apply to circulative viruses.

The readthrough protein of luteoviruses is required for efficient transmission of virus through the aphid ASG. The readthrough protein is thought to protrude from the particle surface, or at least to be part of the surface topography[28,29,34]. However, antibodies that specifically label the proteins *in vitro* do not label whole virus[5,30], suggesting that the protein is not accessible. Perhaps conditions within the aphid hemocoel alter the conformation of the luteovirus particle to expose different regions of the readthrough protein on the surface of the virion and to allow interactions with the aphid ASG.

Questions for future research

- What are the components of the vectors that interact with viruses?
- How do viruses avoid detection and destruction by insect immune systems?
- Are viruses modified within the vector?
- How have viruses evolved to take advantage of new vectors or to become transmitted more efficiently by current vectors?

Such speculation has yet to be verified experimentally under conditions that mimic the environment within the vector. Plant viruses have probably evolved to use existing structures and pathways within vectors. It is unlikely that such viruses alter normal processes in the vectors because there appears to be neither benefit nor harm derived from transporting viruses between plants. Although great strides have been made in understanding the virus components of transmission, the mechanisms by which a plant virus recognizes or is recognized by its vector largely remain a mystery.

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The murine coronavirus as a model of trafficking and assembly of viral proteins in neural tissue

Kishna Kalicharran and Samuel Dales

The replication of JHM, a murine coronavirus, provides a useful model of the assembly and dissemination of viral components in neuronal cells. Involvement of microtubules in virus trafficking is an important feature which may explain dissemination of the infection from primary cell targets at olfactory, hippocampal and cerebellar sites within the central nervous system, resulting in severe neuropathies.

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Infections of the central nervous system (CNS) by neurotropic viruses result in highly variable diseases and pathologies, depending on the agent involved. The outcome of the infectious process may be the consequence of both the replication strategy of the virus and the host's ability to control the infection and the neural cells that are targeted. Information about the dissemination or trafficking of virions and virus components within the neuronal, glial and other cells of the CNS is, therefore, essential for understanding the disease process.

Coronavirus diseases of the Central Nervous System

Much attention has recently been focused on the pathogenesis of virus-induced neurological diseases in rodent and primate model systems. Among the agents studied is the neurotropic murine J. Howard Mueller coronavirus (JHM), which is capable of inducing CNS disease in susceptible rodents and monkeys[1,2]. This virus–host model has been the focus of our attention. A spectrum of pathological processes is observed after intracranial inoculation of JHM virus (JHMV) into preweanling rats, ranging from acute, fulminant encephalitis to delayed onset and chronic demyelination[2,3]. Previous studies have shown the nature of the disease process that predominates in rat pups inoculated intracranially to be a function of several host and viral determinants including the strain of the animal used, postnatal age at the time of inoculation, length of time elapsing between inoculation and development of clinical signs, immunologic status of the host[4,5] and variance in the molecular phenotype of the virion's major spike glycoprotein[6–8].

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