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Transmission activation in non-circulative virus transmission: a general concept?

Martin Drucker and Christiane Then

Many viruses are transmitted by arthropod vectors. An important mode of transmission is the noncirculative or mechanical transmission where viruses attach to the vector mouthparts for transport to a new host. It has long been assumed that noncirculative transmission is an unsophisticated mode of viral spread, and in the simplest case mere contamination of the vector mouthparts. However, emerging evidence strongly suggests that noncirculative transmission, like other transmission strategies, results from specific interactions between pathogens, hosts, and vectors. Recently, new insights into this concept have been obtained, by demonstrating that a plant virus responds instantly to the presence of its aphid vector on the host by forming transmission morphs. This novel concept, named Transmission Activation (TA), where viruses respond directly or via the host to the outside world, opens new research horizons.

Address
INRA, UMR 385 BGPI (CIRAD-INRA-SupAgroM), TA A54K, Campus International de Baillarguet, 34398 Montpellier Cedex 5, France

Corresponding author: Drucker, Martin (drucker@supagro.inra.fr)

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Introduction

Transmission is a key step in the infection cycles of pathogens because it determines their spread in the environment. Thus it is not surprising that pathogens have developed sophisticated strategies to guarantee the success of this event. This includes not only (1) choosing an appropriate shuttle mechanism, in many cases involving vectors (biological organisms carrying pathogens to a new host), to bridge the distance between two hosts, but also (2) the pathogens' deliberate manipulation of both the vectors and the hosts in order to optimize pathogen acquisition, transport, and inoculation into a new host. The latter has been described in particular for eukaryotic parasites [1], but there is no reason to exclude prokaryotic pathogens such as bacteria and viruses from this concept.

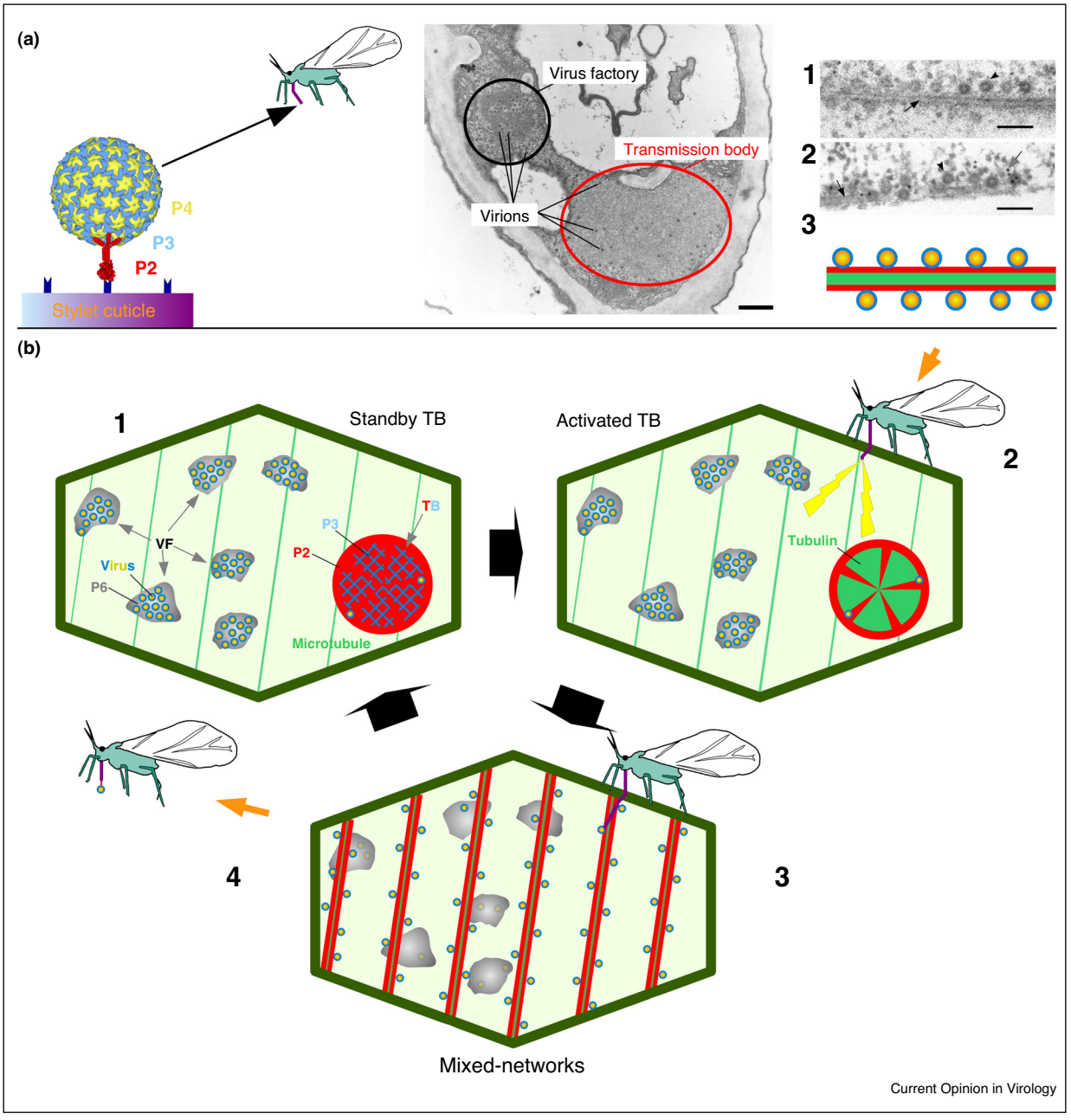
Virus transmission

Viruses are often vectored by arthropods feeding on blood (for vertebrate and human viruses) or phloem sap (for plant viruses), especially those with a piercing sucking feeding behavior such as mosquitoes, ticks, tsetse flies, among others (vertebrate viruses) or aphids, whiteflies, thrips, among others (plant viruses). Arthropods transmit many viruses of medical, veterinary, and agricultural impact, for example yellow fever, Dengue infection, tick-borne encephalitis, Chikungunya, bluetongue disease, maize streak, wheat streak, tomato spotted wilt, potato leaf roll disease, among others. These viruses are also called arthropod-borne viruses or arboviruses (reviewed in [2–4], Blanc and Gutierrez, this issue). There are different modes of virus–vector interaction: in circulative transmission vectors acquire virus during feeding on an infected host, the virus traverses the intestine and cycles through the haemolymph to reach the salivary glands. From there the virus is inoculated together with saliva into a new host during feeding (Ghanim et al., this issue). In many cases the viruses replicate in one or several tissues and vector organs (Whitfield et al., this issue). In noncirculative transmission, viruses bind only to the mouthparts of the vectors (the needle-like stylets for most arthropods, Figure 1a); internalization or replication in the vector does not occur. Many plant and vertebrate viruses are noncirculatively transmitted, for example hundreds of plant viruses of the families *Potyviridae* and *Cucumoviridae* and numerous vertebrate viruses of the *Poxviridae* and *Caliciviridae*. Noncirculative arthropod transmission of vertebrate viruses is also referred to as mechanical transmission because many of these viruses are also transmitted by direct physical contact between two hosts or between the vector and the host. For plant viruses, physical contact as a means of mechanical transmission rarely occurs outside laboratory conditions.

Vector manipulation

It is obvious that circulative transmission depends on intimate virus–vector relationships that allow for crossing the intestinal barrier and invasion of the salivary glands. This is less clear for noncirculative transmission, where binding of virus particles (virions) to vector mouthparts (analogous to transmission by direct physical contact) is often considered as mechanical contamination. However, also in noncirculative transmission there is a certain degree of vector specificity, suggesting that this transmission mode is not a random event. Furthermore, the existence of viral proteins specialized in vector-binding

Figure 1



CaMV transmission activation. **(a)** Distribution of CaMV virions and P2 in infected cells. Left: The CaMV transmissible complex includes the virus particle, composed of capsid protein P4 (yellow), virus-associated protein P3 (blue) and P2 (red; the helper component that binds to a receptor in the stylet tips [magenta]) Middle: Electron microscopy of an infected cell prior to transmission activation (TA) showing that most virus particles accumulate in virus factories (encircled in black), whereas a transmission body (encircled in red) contains only few virions. However, TBs contain all of the cell's P2. Scale bar: 600 nm. Right: Electron microscopy of mixed networks (MN) momentarily following TA, showing typical spherical CaMV virus particles (arrowheads) that decorate microtubules (black arrows) in cortical regions of a CO_2-treated cell. (1) Transmission electron microscopy, (2) Immunogold labeling for P2 (the gray arrow points to an exemplary nanogold particle) shows that the virus-decorated microtubules display transmissible complexes. (3) Schema of a MN, containing a tubulin backbone (green) and associated virions (blue-yellow circles) and P2 (red). Scale bars: 100 nm. **(b)** Model of CaMV acquisition. (1) An infected cell in the unstressed 'standby' state with many virus factories (VF) and a single transmission body (TB). The microtubules are drawn in green. (2) An aphid arrives on an infected plant and inserts its stylets (magenta) into a cell to test a plant (note that aphid and plant cell are not drawn to scale). The aphid stylets exert 'aphid stress' (yellow flashes) that is probably a combination of mechanical stress (by stylet puncture) and chemical stress (by aphid stylet or saliva components and/or plant components). The initial aphid recognition event is transduced in a fast TB response starting with the influx of tubulin (green) into the TB. (3) Then the TB dissociates within seconds and P2 as well as some virions originating from VF associate with microtubules to form mixed networks. Transmissible complexes are now homogeneously dispersed throughout the cell periphery on the microtubule scaffold and easily acquired by the vector. (4) After the aphid