Published in final edited form as:

Nat Med. 2010 January ; 16(1): 25–27. doi:10.1038/nm0110-25.

Cloaked virus slips between cells

Kathryn S Jones and

Basic Science Program, Science Applications International Corporation-Frederick, Inc., National Cancer Institute-Frederick, Frederick, Maryland, USA.

Patrick L Green

Center for Retrovirus Research, Departments of Veterinary Biosciences and Molecular Virology, Immunology, and Medical Genetics, The Ohio State University, Columbus, Ohio, USA.

Kathryn S Jones: joneska@mail.nih.gov

Abstract

A common retrovirus encases itself in an extracellular matrix, enabling its transfer between T4 cells. The discovery of this new mode of infectivity has the potential to lead to new ways to combat the virus, human T cell leukemia virus type 1 (HTLV-1), which is associated with cancers and inflammatory disorders (pages 83–89).

The interactions between a virus and its host are a continual game of cat and mouse. The hosts have developed a variety of mechanisms to block viral infection and persistence, including physical barriers to entry, intracellular proteins that interfere with viral infection and the innate and adaptive immune responses. Viruses have evolved a number of strategies to counteract and evade host cellular defenses. They encode proteins that inhibit antiviral proteins and have developed various mechanisms to escape surveillance by the immune system.

In the current issue of *Nature Medicine*, Pais-Correia *et al.*¹ uncover a previously unknown mechanism for viral transmission and persistence. They study a virus associated with cancer and inflammatory disorders, HTLV-1, and find that after budding from the membrane of infected CD4⁺ T cells, viral particles remain associated with the cell, transiently stored in protective extracellular microenvironments. During interactions between T cells, these structures are transferred from infected to uninfected cells, ultimately resulting in the infection of the target cell. The study provides evidence for a role of the extracellular matrix in viral transmission.

HTLV-1 infects approximately 20 million individuals worldwide² and is spread from person to person primarily by infected cells in breast milk, blood and semen³. In approximately five percent of infected individuals, HTLV-1 is associated with disease: adult T cell leukemia, a CD4⁺ T cell malignancy, or one of several inflammatory disorders including HTLV-1-associated myelopathy–tropical spastic paraparesis (HAM-TSP)³.

Soon after the discovery of the virus⁴, it was observed that, unlike HIV and most other retroviruses, HTLV-1 nearly always requires cell-to-cell interactions for transmission and infection; it is poorly infectious as a cell-free viral particle. Infection rates after blood transfusions indicated that HTLV-1 transmission requires passage of infected cells⁵, and, in cell culture, cell-free viral particles cannot routinely infect primary CD4⁺ T lymphocytes, the natural targets of HTLV-1. Although it is known that HTLV infection requires cell-to-cell contact, the precise interactions between cells required for the infection of the target have not been well characterized.

Pais-Correia *et al.*¹ began their studies by performing confocal and electron microscopy analyses of HTLV-1-infected CD4⁺ T cells. They examined cells isolated from HTLV-1-infected individuals, as well as transformed cell lines chronically infected with HTLV-1, and observed assemblies of mature viral particles on the surface of infected cells¹ (Fig. 1). Characterization of these viral assemblies showed that they were enriched in specific components of the extracellular matrix and cellular linker proteins. Direct comparison of infected and uninfected CD4⁺ T cells showed that expression of HTLV-1 increased the expression of these specific proteins on the cell surface and resulted in their redistribution to the extracellular viral assemblies.

Further studies revealed that the extracellular viral assemblies have a key role in ushering HTLV-1 to neighboring T cells. The researchers exposed CD4⁺ T cells from HTLV-1-infected individuals to CD4⁺ T cells from uninfected individuals and observed that the virus quickly moved to multiple places on the surface of the target cells, including points distal to the point of cell-to-cell contact¹. Extracellular matrix components colocalized with viral proteins, indicating that the HTLV-1 was being transferred in the context of the viral assemblies. The authors then showed that the structures they observed by microscopy were important for infection; removing these structures from HTLV-1-infected cells, although not affecting the ability of the infected cells to make contacts with uninfected T cells, dramatically reduced their ability to infect target cells.

Previous work, originally by Ikagura *et al.*⁴, indicated that HTLV-1 can spread between T cells by forming a supramolecular structure, termed a virological synapse. They observed HTLV-1 core proteins and RNA genome in infected cells at the point of contact with uninfected cells, along with local reorganization of cellular components, followed by the appearance of virus inside the target cell⁴. These observations, along with later work, supported the notion that HTLV-1-infected cells polarize after contact between the T cells and that the virus buds into closed synaptic clefts before binding and infecting target cells⁶.

In contrast, Pais-Correia *et al.*¹ observed the rapid transfer of fully formed HTLV-1 particles stored (and protected) on the surface of infected cells to target cells in a manner that does not appear to involve synaptic clefts or cytoskeletal rearrangements. It is not yet clear whether the two groups were observing similar phenomena under different conditions or two distinct methods of transmission.

Many retroviruses, including HTLV-1 and HIV, infect cells of the immune system, and the immune response involves multiple interactions between cells. Although the use of cell-to-cell interactions during transmission was originally believed to distinguish HTLV from other retroviruses, later studies indicated that transmission of several other retroviruses is two to three orders of magnitude more efficient when cells physically interact. Virological synapses play a part in HIV transmission from dendritic cells (DCs) and macrophages to CD4⁺ T cells^{7,8} as well as between T cells⁹.

More recently, transmission of retroviruses between cells has also been observed to occur along filopodial membrane bridges¹⁰ and via thinner membrane extensions called nanotubes¹¹. Nanotubes also seem to mediate the transmission of HTLV-1 (N. Van Prooyen and G. Franchini, US National Cancer Institute, personal communication). More studies will be needed to clarify how the transfer of viral assemblies is related to the previously described methods of cell-to-cell transmission.

The discovery of Pais-Correia *et al.*¹ further supports the notion that, *in vivo*, retroviruses exploit interactions between immune cells to facilitate their spread. At first glance, viral spread by extracellular assemblies seems to be most similar to HIV transmission from DCs and macrophages, where viruses assembled on the cell surface are stored in large

invaginations and then mobilized to sites of cell-to-cell contact for subsequent transmission. DCs are known to also facilitate HTLV-1 transmission; infected DCs can rapidly pass HTLV-1 to CD4⁺ T cells, resulting in efficient infection¹². Electron microscopy analysis of HTLV-1-infected DCs have revealed the presence of multiple virions associated with the cell surface of DCs (K.S. Jones, G. Franchini and F.W. Ruscetti, unpublished data), suggesting that extracellular viral assemblies are involved in DC-to-T-cell transmission, as well as between T cells.

Why have HTLV-1 and other viruses evolved to use cell-to-cell transmission? One reason might be efficiency: the mechanism eliminates the step of viral diffusion before attachment and entry. This would be particularly crucial for HTLV-1, which is produced at low levels by infected T cells and is very inefficient at productively infecting CD4⁺ T cells as a cell-free viral particle. Cell-to-cell transmission could also help in viral persistence, by allowing the virus to avoid neutralization by antibodies; perhaps the extracellular matrix cocoons the viral particles, protecting them from physical shearing as well as from neutralization by antibodies. This effect would be analogous to bacterial biofilms, where a bacterially produced polysaccharide matrix can confer resistance to antibiotics.

For HTLV-1, whose envelope proteins are highly conserved and poorly glycosylated, these protective structures would seem to be particularly important. Such protective structures may also explain the persistence of high numbers of HTLV-1-infected cells in individuals with HAM-TSP, who have high levels of neutralizing antibodies.

A number of viruses other than retroviruses have also been shown to be transmitted cell to cell, to be poorly infectious as cell-free particles or to have substantial viral loads in the presence of neutralizing antibodies. It seems possible that some of these viruses may also form extracellular viral assemblies on infected cells.

The discovery of these viral assemblies suggests possible future therapeutic avenues for treatment of the HAM-TSP, a disease that progresses more rapidly in the presence of high amounts of HTLV-1. Agents that disrupt the assemblies may lower virus levels, either directly by decreasing viral transmission or indirectly by making the virus more susceptible to immune clearance. Such compounds might target the interactions between the extracellular matrix, linker proteins and carbohydrate moieties that ensure the cohesiveness of the biofilm. Such drugs could turn out to be the elusive ‘better mousetrap’ in the fight against HTLV-1 infection.

References

1. Pais-Correia MS, et al. *Nat. Med.* 2010; 16:83–89. [PubMed: 20023636]
2. Mahieux R, Gessain A. *Rev. Clin. Exp. Hematol.* 2003; 7:336–361. [PubMed: 15129647]
3. Lairmore, M.; Franchini, G. Human T cell leukemia virus types 1 and 2. In: Martin, M., editor. *Fields Virology*. Vol. Ch. 56. Philadelphia: Lippincott, Williams and Wilkins; 2007. p. 2071-2106.
4. Poiesz BJ, et al. *Proc. Natl. Acad. Sci. USA.* 1980; 77:7415–7419. [PubMed: 6261256]
5. Donegan E, et al. *Transfusion.* 1994; 34:478–483. [PubMed: 8023388]
6. Igakura T, et al. *Science.* 2003; 299:1713–1716. [PubMed: 12589003]
7. Carr JM, Hocking H, Li P, Burrell CJ. *Virology.* 1999; 265:319–329. [PubMed: 10600603]
8. McDonald D, et al. *Science.* 2003; 300:1295–1297. [PubMed: 12730499]
9. Piguet V, Sattentau Q. *J. Clin. Invest.* 2004; 114:605–610. [PubMed: 15343375]
10. Sherer NM, et al. *Nat. Cell Biol.* 2007; 9:310–315. [PubMed: 17293854]
11. Sowinski S, et al. *Nat. Cell Biol.* 2008; 10:211–219. [PubMed: 18193035]
12. Jones KS, Petrow-Sadowski C, Huang YK, Bertolette DC, Ruscetti FW. *Nat. Med.* 2008; 14:429–436. [PubMed: 18376405]

Figure 1.

Cell-to-cell transmission of HTLV-1 by extracellular viral assemblies. **(a)** An uninfected CD4⁺ T cell (right), like most cells, is covered by an extracellular matrix consisting of proteoglycans, structural proteins and other specialized proteins. CD4⁺ T cells infected by HTLV-1 (left), express higher amounts of several specific extracellular matrix components and cellular linker proteins, which relocate to sites where HTLV-1 virions are budding to form an extracellular viral assembly. **(b,c)** When the HTLV-1-infected cell interacts with an uninfected CD4⁺ T cell, these viral assemblies are rapidly transferred to the surface of the uninfected cell **(b)**, which ultimately results in infection of the target cell **(c)**.