VIRAL PATHOGENESIS

HIV hitchhikes on migratory T cells

HIV causes a generalized infection of the immune system, but the mechanistic basis of systemic viral spread had been unclear. Now, Murooka *et al.* reveal that when the virus infects CD4⁺ T cells, it exploits the migratory potential of these cells by hitching a ride to remote sites of the body. Moreover, the authors provide the first *in vivo* evidence to support the idea that direct transmission of HIV virions between cells could occur through structures known as virological synapses.

In vitro studies have indicated that the formation of virological synapses between HIV-infected and uninfected T cells is an effective mechanism of viral transfer. However, whether these contacts are sufficiently stable to promote HIV transmission between cells *in vivo* had not been investigated. Thus, the authors set out to determine the motility of, and interactions between, T cells in the lymph nodes of HIV-infected humanized mice.

First, they used multiphoton intravital microscopy to track the dynamics of CD4⁺ T cells infected with GFP-tagged HIV. After 2 days, infected CD4⁺ T cells were uniformly distributed throughout the lymph node cortex, indicating that these cells are motile; however, they migrated at a slower rate than uninfected CD4⁺ T cells. Furthermore, a subpopulation of infected cells displayed an unusual elongated morphology, reaching up to ten times the length of uninfected cells, and often having branched extensions as a result of tethering to uninfected cells and the formation of syncytia. Infection with an HIV-derived lentiviral vector that lacked HIV proteins failed to induce these morphological changes, suggesting that one or more HIV proteins are responsible for both the alteration in T cell shape and the observed deceleration of infected cells.

Previous studies had implicated the surface-exposed HIV Env glycoprotein in synapse formation between T cells, as it is expressed on the cell surface during virus release and stimulates the formation of intercellular adhesive contacts between cells expressing CD4 *in vitro*. Indeed, when an HIV variant with a non-functional form of Env was used to infect CD4⁺ T cells, the elongated phenotype disappeared, suggesting that Env is responsible for the tethering interactions between cells. However, these cells still showed decreased motility, indicating that a factor other than Env is responsible for the reduced migratory speed of infected cells.

Finally, to assess the importance of T cell trafficking for the spread of HIV, mice were treated with the sphingosine 1-phosphate receptor antagonist FTY720 (fingolimod), which inhibits T cell migration from lymph nodes. This compound prevented the establishment of high-level viraemia when administered to mice at the time of initial infection, but not when given to mice with a pre-established infection, revealing a central role for T cell migration in systemic HIV dissemination.

These data suggest that efficient HIV infection requires a trade-off between two potentially opposing T cell behaviours: motility (involving short-term contacts between cells) to promote viral dissemination, and longer lasting cell-to-cell contacts to accomplish intercellular viral transfer. The authors conclude that the observed reduced motility of HIV-infected CD4⁺ T cells might represent a compromise between these two opposing demands, ultimately facilitating the systemic spread and direct cell-to-cell transmission of the virus.

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ORIGINAL RESEARCH PAPER Murooka, T. T. *et al.* HIV-infected T cells are migratory vehicles for viral dissemination. *Nature* 1 Aug 2012 (doi:10.1038/nature11398)

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