HIV

Double trouble

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Using an *ex vivo* organ-culture system that successfully allows the separation of the vaginal epithelial-cell layer from the underlying stroma, Hladik *et al.* report in *Immunity* that the initial events in HIV-1 infection involve simultaneous entry by the virus of $CD4^+$ T cells and Langerhans cells (LCs) in human vaginal epithelium.

More women than men are infected with HIV-1, and the main route of transmission is the female genital tract following sexual contact. Blocking the local transmission of the virus to prevent the spread of HIV-1, therefore, requires an understanding of the initial events in the establishment of vaginal HIV-1 entry and infection. Previous studies have identified $CD4^+$ T cells and LCs as probable first targets of HIV-1 in the lower reproductive tract after the virus has breached the vaginal epithelium. But how the initial infection occurs in the outer human vaginal epithelium and how the virus then gains entry into the intra-epithelial cells to establish infection remained unclear, partly owing to the lack of appropriate experimental models.

Hladik *et al.* addressed this problem by developing an *ex vivo* model in which the first barrier encountered by the virus, the squamous vaginal epithelium, was separated from the underlying stroma; this allowed direct observation of how HIV-1 targets cells exclusively within the outer vaginal epithelium, and of the cells that subsequently migrate from this layer into the culture medium. Focusing on the intra-epithelial $CD4^+$-T-cell and LC populations, the authors performed *in situ* studies with isolated sheets of stroma-free epithelial cells, which were exposed to fluorescently tagged HIV-1 virions that used CC-chemokine receptor 5 (CCR5) to gain entry.

They showed that CCR5-tropic HIV-1 efficiently entered both $CD4^+$ T cells and $CD1a^+$ LCs that reside in the vaginal epithelium. Confocal microscopy studies showed that viral entry into the $CD4^+$ T cells occurred almost exclusively by CD4- and CCR5-mediated direct fusion, and that the ensuing productive infection did not require stable conjugation with LCs. By contrast, HIV-1 entry into $CD1a^+$ LCs occurred mainly by endocytosis, through several receptors, and intact virions persisted in the cytoplasm for several days. Productive infection was not seen in LCs emigrating from the vaginal epithelium. Interestingly, viral particles were observed at the cell–cell junctions in emigrating T-cell–LC conjugates, supporting the suggestion that an 'virological synapse', in which the passage of virions between two cell types is facilitated, might also occur.

So, the earliest events in HIV-1 infection involve the simultaneous entry by the virus of $CD4^+$ T cells and LCs in the outer vaginal epithelium. This is in contrast to previous reports indicating that HIV-1 is transmitted to T cells in the mucosal stroma and local lymphatics by adjacent dendritic cells that are infected first. Although this can still occur, the initial infection is established in the outer epithelium where viral entry occurs simultaneously and independently in $CD4^+$ T cells and LCs. These results could have important implications for the design of effective therapies to prevent the transmission and spread of HIV-1.

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ORIGINAL RESEARCH PAPER Hladik, F. *et al.* Initial events in establishing vaginal entry and infection by human immunodeficiency virus type-1. *Immunity* **26**, 257–270 (2007)
FURTHER READING Boggiano, C. & Littman, D. R. HIV's vagina travelogue. *Immunity* **26**, 145–147 (2007)

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