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Biology of HIV Mucosal Transmission

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Abstract

Purpose of review—HIV-1 mucosal transmission plays a critical role in HIV-1 infection and AIDS pathogenesis. This review summarizes the latest advances in biological studies of HIV-1 mucosal transmission, highlighting the implications of these studies in the development of microbicides to prevent HIV-1 transmission.

Recent findings—New studies of initial HIV-1 infection using improved culture models updated the current view of mucosal transmission. Mechanistic studies enhanced our understanding of cell-cell transmission of HIV-1 mediated by the major target cells, including dendritic cells, $CD4^+$ T cells, and macrophages. Increasing evidence indicated the significance of host factors and immune responses in HIV-1 mucosal infection and transmission.

Summary—Recent progress in HIV-1 mucosal infection and transmission enriches our knowledge of virus-host interactions and viral pathogenesis. Functional studies of HIV-1 interactions with host cells can provide new insights into the design of more effective approaches to combat HIV-1 infection and AIDS.

Keywords

HIV; mucosal; transmission; infection; biology

Introduction

HIV-1 mucosal infection through sexual transmission plays a critical role in viral pathogenesis [1*–3*]. Defining the mechanisms of HIV-1 mucosal transmission can potentially help our combat against HIV-1/AIDS. Current antiretroviral therapies cannot eradicate HIV-1, and no effective vaccine is achievable soon; therefore, topical microbicides hold promise for HIV-1 prevention [2]. Recent studies of HIV-1 interactions with target cells provide new insights into understanding HIV-1 mucosal transmission. Host factors and immune responses are multifaceted contributors to HIV-1 infection and transmission (Figure 1). This review highlights the latest research advances in HIV-1 mucosal transmission, focusing on the mechanisms of cell-cell transmission of HIV-1.

Initial events of HIV-1 mucosal infection and transmission

$CD4^+$ T cells, macrophages, and dendritic cells (DCs) including Langerhans cells (LCs) are considered as early targets of HIV-1 infection and transmission in the vaginal mucosa [1*–3*]. However, the initial events in establishing vaginal HIV-1 infection are poorly characterized owing to the lack of a suitable model. Hladik *et al*. developed a culture model of epithelial sheets separated from human vaginal stroma to study HIV-1 entry and infection

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[4**]. HIV-1 enters intraepithelial $CD4^+$ T cells by viral receptor-mediated fusion, leading to productive infection. By contrast, HIV-1 enters vaginal LCs via endocytosis mediated by multiple receptors. Intact HIV-1 particles were retained within LCs for 3 days without detectable viral replication. The LC-T-cell conjugates with concentrated HIV-1 were observed at 60 hr, but not at 2 hr after infection [4**]. These results suggest that initial HIV-1 infection of T cells is independent of LCs, while LC-mediated HIV-1 transmission to T cells may occur at the later stage of infection. Although HIV-1 replication may not be readily detected in LCs at the initial infection, it is possible that DCs hold infectious HIV-1 and augment viral replication upon interaction with $CD4^+$ T cells [1*,5–11].

LCs have been speculated to support HIV-1 *trans*-infection through Langerin, a LC-specific C-type lectin. Unexpectedly, a recent study suggests that Langerin can be a natural barrier to HIV-1 infection [12*]. Langerin mediates HIV-1 internalization and intracellular degradation in skin-derived LCs, thereby inhibiting HIV-1 replication and transmission [12*]. However, it remains possible that a proportion of endocytosed HIV-1 escapes from the degradation, and initiates *trans*-infection of $CD4^+$ T cells upon cell-cell contact. A recent report indicates that epithelial LCs in human skin explants account for >95% of HIV-1 dissemination [13*]. HIV-1 infection was detected only in LCs, but not dermal DCs and macrophages in the skin emigrants, suggesting that productive HIV-1 infection of LCs plays a critical role in occupational HIV-1 transmission [13*]. Moreover, $CD34^+$ progenitor cell-derived LCs mediate HIV-1 *trans*-infection to $CD4^+$ T cells [10,14].

Epithelial cells in the vaginal mucosa are also involved in HIV-1 mucosal transmission, although controversial results have been reported regarding whether HIV-1 can productively infect epithelial cells (review in [3*]). HIV-1 can penetrate the epithelial layer by transcytosis, although the efficiency of transcytosis appears to be very low (less than 0.02% of the initial HIV-1 inoculum) as indicated in a study using cultured primary genital epithelial cells [15]. HIV-1 may also be endocytosed by epithelial cells to initiate viral spread to target leukocytes [3*]. Additional studies are required to confirm this potential mechanism of HIV-1 mucosal transmission.

Mechanisms of DC-mediated HIV-1 *trans*-infection

Numerous studies have indicated an important role for DCs in HIV-1 mucosal transmission and viral pathogenesis (reviewed in [*1,16]). DCs transfer captured HIV-1 to cocultured $CD4^+$ T cells by *trans*- and *cis*-infection pathways [1*]. Efficient HIV-1 *trans*-infection mediated by DCs requires contact between DCs and $CD4^+$ target cells [7**]. The cell-cell junctions with concentrated HIV-1 are referred to as infectious/virological synapses (VS) [17,18], which facilitate HIV-1 transmission from DCs to $CD4^+$ T cells.

HIV-1 attachment factors expressed on DCs contribute to viral capture and transmission. The best studied factor is the C-type lectin DC-SIGN (DC-specific intercellular adhesion molecule 3-grabbing nonintegrin), which partially accounts for HIV-1 transmission by certain DC subsets (reviewed in [1*]). However, DC-mediated HIV-1 *trans*-infection occurs independently of DC-SIGN [1*,7**,19]. A recent study indicates that syndecan-3, a DC-specific heparan sulfate proteoglycan, binds HIV-1 through viral envelope glycoprotein (Env) and enhances HIV-1 *trans*-infection [20]. Accordingly, microbicides that block HIV-1 interactions with DC-SIGN and syndecan-3 might prevent DC-mediated viral transmission.

Cellular proteins and signaling pathways modulate DC-mediated HIV-1 transmission by interacting with DC-SIGN. Leukocyte-specific protein 1 (LSP1), an F-actin binding protein involved in leukocyte motility, binds to DC-SIGN and directs internalized HIV-1 to the proteasome in DCs for viral degradation [21]. Silencing LSP1 expression in DCs enhances HIV-1 transmission to $CD4^+$ T cells, suggesting that HIV-1 trafficking through the

cytoskeleton is important for viral transmission [21]. HIV-1 or DC-SIGN-specific antibodies activate DC-SIGN signaling through the leukemia-associated Rho guanine nucleotide-exchange factor (LARG), which increases Rho-GTPase activity [22]. Activation of LARG in DCs facilitates HIV-1 transmission to $CD4^+$ T cells by enhancing VS formation between DCs and T cells [22]. Moreover, interactions of DC-SIGN with different human pathogens including HIV-1 activate the Raf-1 kinase-dependent acetylation to modulate Toll-like receptor (TLR) signaling [23]. Given the importance of TLRs in DC-initiated adaptive immunity, this DC-SIGN-mediated signaling pathway may regulate the immune responses to various pathogens.

HIV-1 trafficking in DCs contributes to viral transmission and the formation of VS between DCs and T cells [7**,8,10,19,21,24–26]. We found that intracellular trafficking inhibitors partially block viral transmission [7**]. Our results indicate that both cell surface-bound and internalized HIV-1 contribute to DC-mediated *trans*-infection [7**]. Compared with immature DC-mediated HIV-1 transmission, viral trafficking in mature DCs appears to play a more important role in *trans*-infection [5,7**,8,10,24,26]. However, Cavrois *et al.* reported that DC-mediated HIV-1 *trans*-infection mainly derives from DC surface-bound viruses [14]. Although it is difficult to directly compare these results owing to the different experimental approaches, the dynamic trafficking and recycling of internalized HIV-1 to DC surfaces could also mediate viral transmission. This should be an important consideration in studying DC-HIV-1 interactions and in developing effective microbicides.

HIV-1-bearing DCs likely interact with different T cell subsets *in vivo* and mediate viral transfer. DCs may play a decisive role in differential susceptibility of HIV-1 infection in naïve and memory $CD4^+$ T cells [27]. R5 HIV-1 is most efficiently transmitted to effector memory T cells, which are the major targets for HIV-1 replication and abundantly present in mucosal tissues, while X4 HIV-1 is preferentially transmitted to naïve T cells by DCs. Thus, DCs may contribute to the initial burst of HIV-1 replication in effector memory T cells, and to the replication of X4 HIV-1 in naïve T cells at the late stage of infection [27].

HIV-1 *cis*-infection of DCs and viral transmission

Similar to mucosal HIV-1 transmission, the selection for R5 HIV-1 strains occurs during parenteral transmission. However, the cell types responsible for this selection have not been defined. Using sorted blood mononuclear cells to model HIV-1 parenteral infection, Cameron *et al*. reported preferential HIV-1 infection of myeloid DCs and plasmacytoid DCs (pDCs) relative to monocytes and resting $CD4^+$ T cells [28*]. The selective infection of blood DCs by R5 HIV-1 and enhanced viral transmission to $CD4^+$ T cells suggest a potential mechanism of R5 HIV-1 selection during parenteral transmission.

HIV-1 infection of DCs can lead to virus production and long-term viral transmission, implying that HIV-1-infected DCs are viral reservoirs *in vivo* [1*,9**,16,29*]. To better understand HIV-1 *cis*-infection of DCs, it is important to define viral entry pathway that leads to productive infection in DCs. Previous studies [30–33] and our recent data [9**,34] indicate that productive infection of HIV-1 in DCs requires fusion-mediated viral entry. HIV-1 enters DCs predominately through endocytosis; however, endocytosed HIV-1 cannot initiate productive HIV-1 infection [4**,9**,34]. The majority of endocytosed HIV-1 in intracellular compartments in DCs will eventually be degraded [5,7**,30,35]; however, when HIV-1-bearing DCs encounter $CD4^+$ T cells prior to viral degradation, efficient HIV-1 *trans*-infection of $CD4^+$ T cells can occur *in vitro* [5–11]. Furthermore, we compared *cis*- and *trans*-infections of HIV-1 mediated by immature DCs and various stimulus-induced mature DCs, and found that these two infection pathways are dissociable [9**]. Therefore, various DC subsets *in vivo* may differentially contribute to HIV-1 dissemination via dissociable *cis*- and *trans*-infection.

HIV-1 proteins and host factors influence viral replication in DCs, and regulate viral transmission efficiency. We recently reported that HIV-1 Nef promotes HIV-1 transfer from DCs to $CD4^+$ T cells [29*]. Nef-induced CD4 downregulation in HIV-1-infected-DCs correlates with enhanced viral transmission. Interestingly, blocking CD4 on DCs with specific antibodies enhances DC-mediated HIV-1 *trans*-infection [29*]. These results suggest that CD4 and Nef can modulate HIV-1 transmission by DCs. Moreover, HIV-1 replication in DCs occurs through a tetraspanin-containing compartment enriched in adaptor protein 3 (AP-3), and viral production is dependent on AP-3 [26].

Host immune responses contribute to the attenuated disease progression of HIV-2 infection [36]. The lack of productive HIV-2 infection in DCs may help to explain the less pathogenic HIV-2 infection relative to HIV-1 infection. Duvall *et al*. showed that various HIV-2 isolates could not efficiently infect myeloid DCs or pDCs, and myeloid DCs failed to transfer HIV-2 to autologous $CD4^+$ T cells [37]. However, HIV-2-specific $CD4^+$ T cells contain more viral DNA than those of other specificities *in vivo* [37], suggesting that DCs are not an important contributor to infection of HIV-2-specific $CD4^+$ T cells *in vivo*.

HIV-1 cell-cell transmission by $CD4^+$ T cells and macrophages

HIV-1-infected $CD4^+$ T cells can initiate efficient cell-cell transmission to uninfected T cells through Env- and cytoskeleton-dependent VS [38*,39]. Cell-associated transfer of HIV-1 is estimated to be 92- to 18,600-fold more efficient than that of cell-free virus, and VS-mediated HIV-1 transfer is resistant to patient-derived neutralizing antisera [38*]. Cellular proteins that enhance immunological synapse formation, such as intercellular adhesion molecules and ZAP-70 kinase, also facilitate VS formation and HIV-1 transmission between $CD4^+$ T cells [40,41]. Interestingly, HIV-1-infected $CD4^+$ T cells can transfer viruses to uninfected T cells through intercellular membrane nanotubes [42*], suggesting that HIV-1 usurps intercellular connections between immune cells to enhance viral spread. Further studies are required to examine if these newly identified mechanisms also occur in DC- and macrophage-mediated HIV-1 transmission to $CD4^+$ T cells.

HIV-1-infected macrophages act as viral reservoirs, and play an important role in HIV-1 pathogenesis. HIV-1-infected macrophages transmit viruses to $CD4^+$ T cells through VS [43, 44**]. Studying HIV-1 assembly in macrophages may aid in development of novel antivirals or microbicides. HIV-1 assembles mainly at the plasma membrane [45,46] or into an intracellular plasma membrane domain in macrophages [47]. HIV-1 can also bud and accumulate in nonacidic endosomes of macrophages [48*], suggesting that HIV-1 survives within a nonacidic assembly compartment by preventing intracellular degradation. HIV-1 may use the same strategy to survive in infected-DCs. In fact, DCs have mechanisms to control phagosomal acidification to preserve antigen cross-presentation [49].

Inhibitors that block HIV-1 infection in macrophages might be potential candidates for microbicides or antivirals. Carbohydrate-binding agents have been shown to inhibit HIV-1 infection in macrophages and prevent viral transmission to $CD4^+$ T cells [50]. Moreover, HIV-1 protects infected macrophages from apoptosis by viral Env-induced signaling; therefore, pharmacological restoration of apoptotic sensitivity for HIV-1-infected macrophages could be a potential therapeutic strategy [51]. Since HIV-1 infection elevates Akt kinase activity in macrophages, PI3K/Akt inhibitors might be used as novel antivirals to block HIV-1 infection in macrophages [52].

Host factors influencing HIV-1 mucosal transmission

Host factors can promote or inhibit HIV-1 infection and transmission, thereby influencing viral infection and AIDS progression [53*]. In the screen of host factors that affect the efficiency

of sexual viral transmission, Münch *et al*. identified that human semen-derived amyloid fibrils dramatically enhance HIV-1 *in vitro* infection [54**]. The semen-derived amyloid fibrils might play an important role in sexual transmission of HIV-1, and could represent a new target of microbicide development. By contrast, Sabatté *et al.* reported that human seminal plasma markedly inhibits HIV-1 transmission to $CD4^+$ T cells mediated by DCs and DC-SIGN-expressing cells [55]. These discrepant results might derive from the different experimental approaches and procedures, which require further investigation.

DC restriction of HIV-1 infection reflects innate antiviral immunity. HIV-1 replication in $CD4^+$ T cells is inhibited by pDCs through the secretion of interferon alpha (IFN-α) and other unidentified antiviral factors [56,57*]. High levels of viral replication *in vivo* are associated with cell death of pDCs, and pDCs from HIV-1-infected individuals, who maintain low levels of viremia without antiretroviral therapy, suppress HIV-1 replication *ex vivo* [57*]. Moreover, HIV-1 infection in monocytes, monocyte-derived DCs, and pDCs can be partially blocked by the antiretroviral factor APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G) and its family molecules [58–60], suggesting that DCs, particularly pDCs, could be imyportant mediators of innate anti-HIV immunity. However, HIV-1 gp120 inhibits TLR9-mediated activation in pDCs, resulting in a decreased secretion of IFN-α and inflammatory cytokines [61*]. Further studies of anti-HIV mechanisms in DCs may help to develop new strategies against HIV/AIDS.

HIV-1 exploits the cytoskeletal network to facilitate viral infection and dissemination [62]. We observed that an intact cytoskeleton network is required for efficient DC-mediated HIV-1 transmission (Wang JH and Wu L, unpublished data). It might be worth exploring if cytoskeleton inhibitors can be developed as reversible or topical agents to block HIV-1 transmission *in vivo*. The actin cytoskeleton also contributes to T cell activation by forming immunological synapses (IS) between antigen-presenting cells and T cells [63]. The IS appear to share structural similarities with the VS, and may play a role in HIV-1 pathogenesis [64]. HIV-1 facilitates cell-cell transmission by promoting VS formation, whereas HIV-1 infection impairs IS formation [65]. Theoretically, blocking the formation of VS may prevent DC-mediated HIV-1 transmission to $CD4^+$ T cells; however, the structure and function of IS should be protected to maintain anti-HIV immunity.

Recently, over 250 cellular proteins required for HIV-1 replication have been identified through a functional genomic screen, and only 36 of them are previously associated with HIV-1 infection [66**]. A cell-membrane protein that inhibits HIV-1 release has been recently discovered and termed tetherin (also called CD317, BST-2 or HM1.24), whereas HIV-1 Vpu counteracts tetherin's antiviral function [67**,68]. These new findings shed light on the development of potential strategies for anti-HIV interventions.

Host immunity and HIV-1 mucosal transmission

DCs play a crucial role in the generation and the regulation of adaptive immunity [69]. DCs efficiently present HIV-1 antigens to T cells via MHC-I- and MHC-II-restricted pathways [35,70,71]. However, HIV-1 and host proteins can mediate viral immune evasion and affect AIDS pathogenesis. For example, gp120 mannoses induce immunosuppressive responses from DCs [72], and DCs capture and transfer antibody-neutralized HIV-1 to $CD4^+$ T cells via DC-SIGN [73]. A recent study identifies that the HIV-1 coreceptor CCR5 and its chemokine agonist CCL3L1 (also called macrophage inflammatory protein 1alpha, or MIP1α) are major determinants of cell-mediated immunity to HIV-1, suggesting these host factors influence viral pathogenesis through cell-mediated immunity and viral entry-independent mechanisms [74**].

Chronic activation of the immune system is a hallmark of progressive HIV-1 infection and AIDS. Microbial translocation can be a cause of systemic immune activation in chronic HIV-1 infection [75], suggesting chronic immune activation during HIV-1 infection is associated with a compromised gut mucosal surface. HIV-1 replication in gut-associated lymphoid tissue mediates massive depletion of gut $CD4^+$ T cells, which contribute to HIV-1 immune pathogenesis. A recent study reports that HIV-1 Env binds to and signals through integrin $\alpha_4\beta_7$, the gut mucosal homing receptor for peripheral T cells [76*]. Engagement of $\alpha_4\beta_7$ on CD4+ T cells via HIV-1 gp120 activates leukocyte function-associated antigen-1 [76*], which can facilitate VS formation and HIV-1 transmission.

Conclusion

A better understanding of the biology of HIV-1 mucosal transmission can facilitate the development of prophylactic and therapeutic approaches against HIV-1 infection. Recent research advances in HIV-1 mucosal transmission provide new insights into the design of effective microbicides, antiviral drugs, and vaccines. Although laboratory-adapted HIV-1 strains and monocyte-derived DCs/macrophages are commonly used in studies, these *in vitro* systems cannot fully recapitulate the physiological conditions in HIV-1 infection. Thus, clinical HIV-1 isolates, blood/mucosal DCs, tissue macrophages, and animal models should be used for confirming studies.

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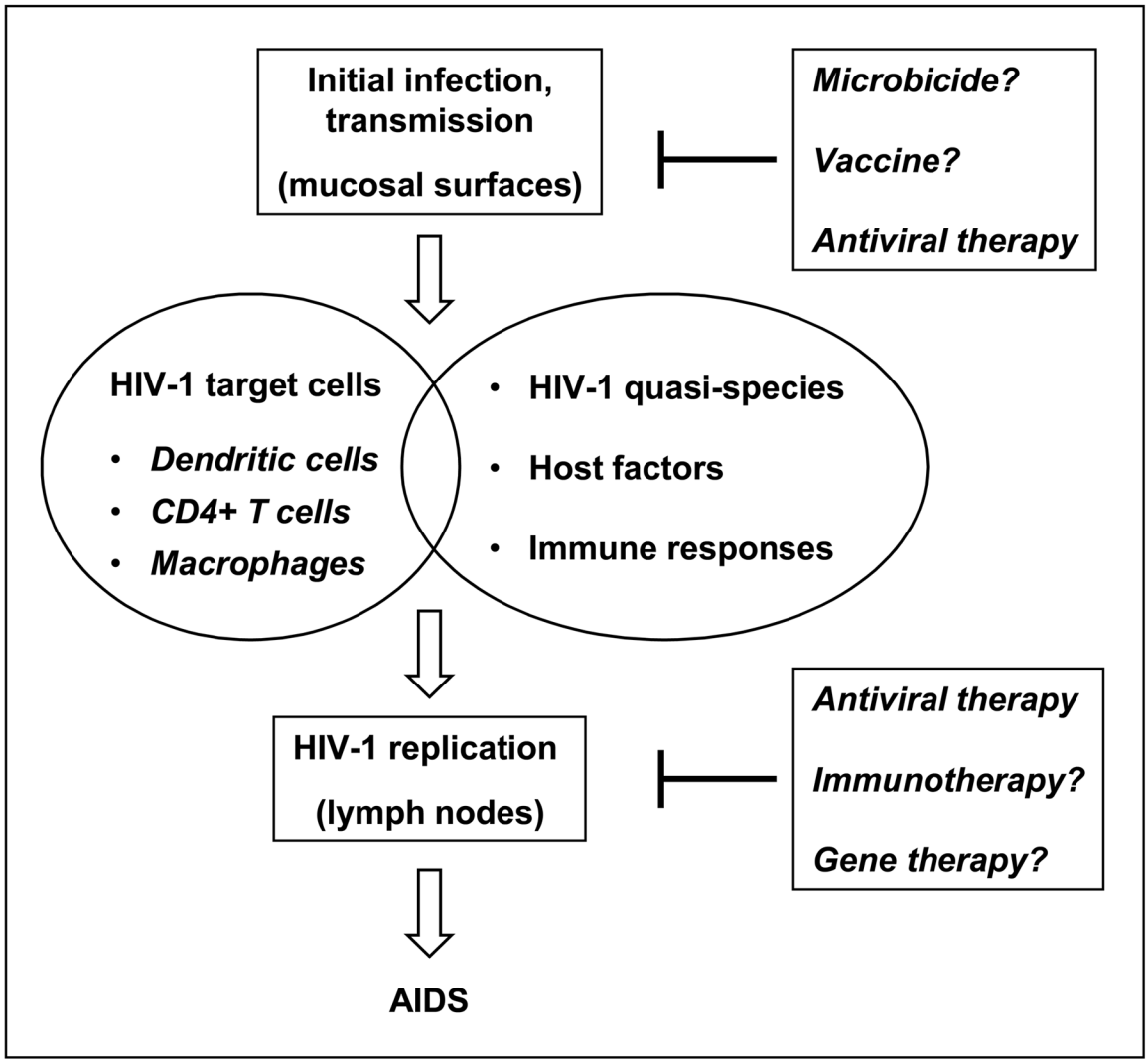

Figure 1. Schematic representation of HIV-1 mucosal transmission

HIV-1 mucosal transmission is a multifaceted process of virus-host interactions. Initial HIV-1 infection mainly occurs at the mucosal surfaces, involving epithelial cells, dendritic cells, $CD4^+$ T cells, and macrophages. Migration of HIV-1-infected immune cells to lymph nodes spreads virus and establishes robust viral replication. Interactions between HIV-1 quasi-species, host factors, and immune responses contribute to the disease progression. Without an antiretroviral therapy, the vast majority of HIV-1-infected individuals eventually develop AIDS. Current antiretroviral treatment cannot eradicate HIV-1, and no effective vaccine is achievable soon. Thus, it is important to develop new interventions such as microbicides to prevent HIV-1 infection.