

Dendritic cells and transmission of HIV-1

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Sexual transmission of HIV-1 requires that small amounts of virus at mucosal sites of inoculation gain access to replication-permissive cells. Recent observations have increased our understanding of the mechanisms by which this relatively inefficient virus can exploit the migratory nature of dendritic cells to establish infection within the host.

Dendritic cells (DCs) perform an essential role in the generation and regulation of adaptive immune responses¹. Immature DCs (iDCs) are widely distributed throughout the body and occupy sentinel positions in tissues such as epithelia, to which resting lymphocytes normally have restricted access. iDCs constantly sample their environment for antigens by phagocytosis, macropinocytosis and highly efficient receptor-mediated pinocytosis. In the presence of appropriate inflammatory 'danger' signals, iDCs undergo maturation characterized by the upregulation of cell surface MHC and lymphocyte costimulatory molecules. Subsequent migration to lymphoid tissue, a process orchestrated by complex chemotactic signals and tightly regulated expression of cognate receptors, results in the efficient presentation of optimally processed antigen to T cells. These specialized functions of DCs permit the rapid generation and maintenance of specific immune responses to invading pathogens, largely irrespective of access site. Recent work indicates that these exquisitely sensitive cellular interactions are exploited by HIV-1 to facilitate infection by this relatively inefficient virus.

DCs as Trojan horses

Sexual transmission of HIV-1 requires a means for small amounts of virus, at mucosal sites of inoculation, to gain access to cells that are permissive for viral infection. iDCs are located in the epithelial (Langerhans cells) and subepithelial (dermal DCs) layers of the genital tract. The migratory nature of DCs, together with their proficiency at recruiting numerous T cells within lymphoid tissue, identifies them as strong candidates for a role in the transmission of

HIV-1 (Ref. 2). Further support for this role emerged with the discovery that a DC surface protein, DC-SIGN, can capture HIV-1 and promote infection of permissive cells *in trans*³. This suggests a role for DCs as 'Trojan horses' and could explain some of the characteristics of HIV-1 transmission.

DC-SIGN, a type II membrane protein with an external C-type lectin domain, is exclusively and abundantly expressed on the surface of both mature and immature DCs (Ref. 4). The natural ligand for DC-SIGN appears to be intercellular adhesion molecule 3 (ICAM-3), although there is also a functional interaction with ICAM-2, which mediates DC transmigration across vascular endothelium⁵. Expression of ICAM-3 on resting T cells could provide the basis for early interactions that allow processed antigen to be scanned by large numbers of T-cell receptors (TCRs)⁴.

DC-SIGN is known to bind the HIV-1 envelope³. Further, it has been demonstrated that DC-SIGN-expressing cells can retain attached HIV-1 virions in an infectious state for several days and transmit them to replication-permissive T cells³. This observation explains previously reported discrepancies between susceptibility to productive infection and the ability of DCs to capture virus^{6,7}. Indeed, at low virus titre, HIV-1 infection of CD4⁺CCR5⁺ cells was not detected without the help of DC-SIGN *in trans*³. Although it has long been accepted that DCs perform a role in the transfer of antigens to lymphoid tissue, the DC-SIGN discovery, implicating a mechanism for the transfer of whole viruses *in vivo*, is something previously unconsidered. It is possible that DCs transfer other pathogens to lymphoid tissue via DC-SIGN or DC-SIGN-like molecules. As the highly organized forms of antigen found in viral envelopes are maximally efficient at inducing B cells and neutralizing antibody⁸, there is a theoretical advantage to a mechanism that transports whole pathogens from the periphery to where the immune system can best see them. This advantage becomes less clear if the transported pathogen, like HIV-1, is proficient at infecting lymphocytes.

Tropism-specific transmission of HIV-1 Macrophage (M)-tropic strains of HIV-1 require the chemokine receptor CCR5, in addition to CD4, to gain entry into cells⁹, and are preferentially transmitted¹⁰. By contrast, T-cell (T)-tropic viruses classically use the chemokine receptor CXCR4 (Ref. 9). Differential surface expression of CCR5, CXCR4 and alternative chemokine coreceptors by CD4⁺ cells thus provides a mechanistic explanation for the phenomenon of cell-specific tropism. Examination of the phenotype of HIV-1 strains sampled at different times during the course of infection shows that isolates present early in infection are almost invariably M-tropic and use CCR5. This finding was made even more significant by the discovery that a homologous 32 base pair deletion in the CCR5 gene, which is present in ~1% of Caucasians and results in the expression of a nonfunctional receptor, confers resistance to the acquisition of HIV-1 infection¹¹. These observations suggest that either CCR5 bestows unique properties to cells that express it, or that this receptor is present on a key population of cells that are deficient in other chemokine receptors that could potentially be used by HIV-1. As DC-SIGN can convey both M- and T-tropic HIV-1 to T cells, it cannot account for the preferential transmission of M-tropic strains *per se*³. If the route of transmission is via the productive infection of DCs, then differential expression of CCR5 and CXCR4 on DCs present at sites of HIV-1 exposure might explain the selection of M-tropic strains^{12,13}. However, it is currently unclear exactly which DCs are the initial targets for HIV-1 and further work is required to address this issue.

Recent experiments that examine the chemotaxis of human iDCs towards HIV-1 are relevant¹⁴. Monocyte-derived iDCs were found to migrate towards the supernatant of T cells infected with M-tropic HIV-1, but not towards the supernatant of uninfected T cells or T cells infected with T-tropic viruses. These observations were substantiated using recombinantly expressed HIV-1 viral envelope glycoproteins (gp120)¹⁴. The recruitment of CCR5-expressing DCs along gradients of M-tropic HIV-1 might

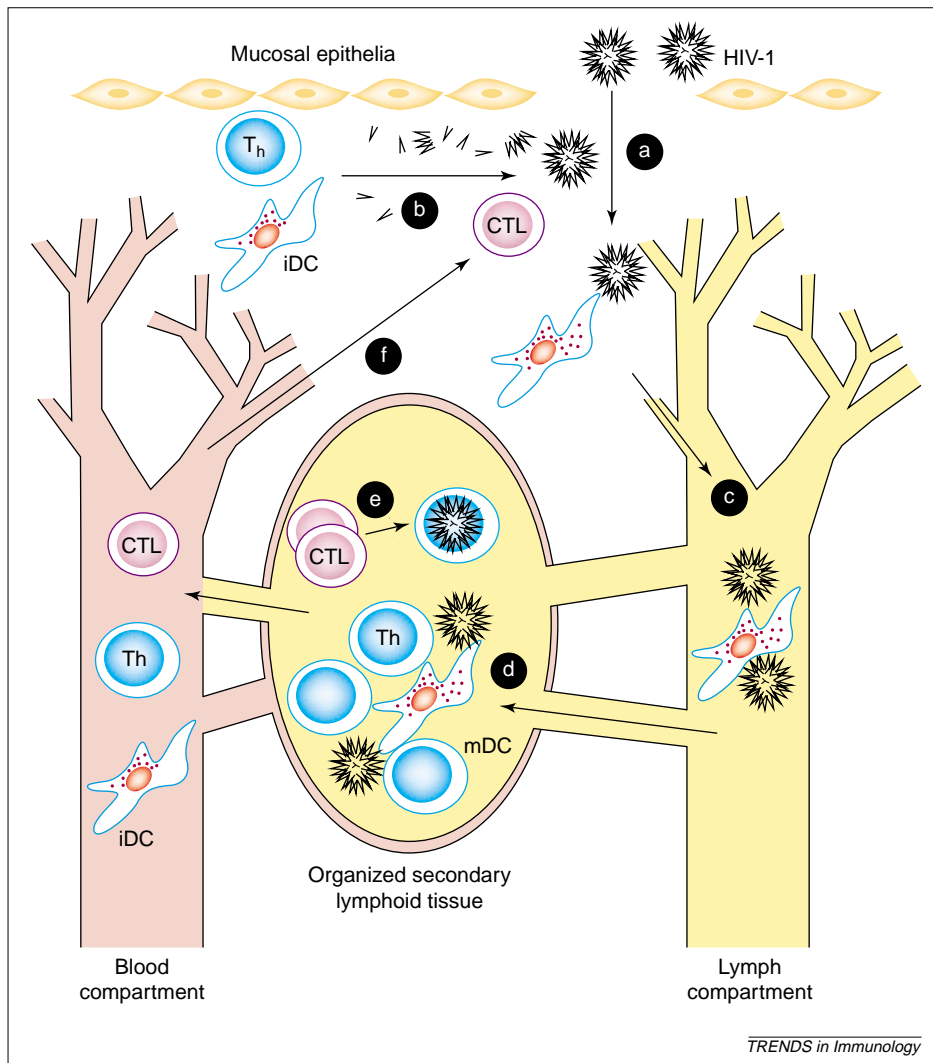


Fig. 1. HIV-1 exploits multiple stages of the intercellular processes responsible for the generation and regulation of adaptive immune responses. (a) Sexual transmission of HIV-1 requires viral entry through mucosal epithelia. (b) Immature dendritic cells (iDCs) and CCR5⁺ CD4⁺ T helper (Th) cells migrate towards macrophage (M)-tropic HIV-1 (Refs 14, 19, 20). Productive infection of CCR5⁺ Th cells and DCs, and the binding of M-tropic virions to DC-SIGN, are facilitated by this chemoattraction. Virus bound to DC-SIGN remains infectious for longer periods than free virus³; this might enable more-efficient transfer of HIV-1 locally at the site of a low titre inoculum, as well as maintaining virus infectivity during transport to lymphoid tissue. (c) Activated DCs carry HIV-1 to lymphoid tissue. This migration is accompanied by a switch from CCR5 to CXCR4 usage by DCs (Ref. 21). (d) Interactions between mature DCs (mDCs) and CD4⁺ CCR5⁺ cells lead to efficient propagation of infection within lymphoid tissue. Similar events might occur outside the environment of organized lymphoid tissue²². HIV-specific CD4⁺ Th cells recognize virus-derived human MHC HLA class II-restricted antigen on the surface of DCs, and might therefore become preferentially infected as a function of this interaction. (e) Generation of HIV-specific cytotoxic T lymphocytes (CTLs). Immune-mediated destruction of infected HIV-specific Th cells and DCs selectively impairs further generation of CTLs specific for HIV-1, facilitating viral persistence. (f) Migration of HIV-specific CTLs to peripheral sites of infection. The known natural ligands for CCR5 include the CC chemokines RANTES, macrophage inflammatory protein 1α (MIP-1α) and MIP-1β. iDCs exhibit chemotaxis towards all these ligands²¹. Antigen encounter triggers CTLs to release CC chemokines that normally act to optimize the localization of immune responses²². In the case of HIV-1, this process might operate to recruit further CCR5⁺ target cells to propagate the infection. As M-tropic HIV-1 gp120 is a ligand for CCR5 and can generate a signal similar to that generated by natural ligands^{19,20}, it seems that HIV-1 has hijacked the migration of CCR5-expressing iDCs and Th cells to recruit these cells (see b).

favor the transmission of these viral strains independent of whether the route is via the direct infection of DCs or DC-SIGN-mediated *trans*infection of CD4⁺ T cells.

Implications of recent advances

In addition to providing a possible explanation for tropism-specific

transmission of HIV-1, the recruitment of iDCs by M-tropic viral isolates might have other important implications. First, infectivity might be increased. The reverse transcriptase of HIV-1 is highly error prone. Even conservative estimates suggest that each 10 kb genome contains at least one error. This combines with the

extremely short half-life of HIV-1 virions *in vivo* to ensure that perhaps less than 1 in 1000 viral particles are capable of a productive round of infection. The chemotaxis of iDCs along gradients of virions, virion fragments or gp120 *in vivo* will ensure a greater likelihood of either their productive infection or the capture of an infective virion by cell surface DC-SIGN. HIV-1 can then exploit the migration of DCs as they mature to gain access to lymphoid tissue. Second, productivity might be increased. It has been demonstrated that DC-T-cell syncytia are actively formed *in vivo*¹⁵. The fusion of these two cell types, potentially mediated by the migration of one cell towards the other along gradients of virus, brings together transcription factors that act in synergy to drive the HIV-1 promoter¹⁶. Third, HIV-1-specific cellular immunity might be preferentially impaired. It is becoming clear that HIV-1-infected individuals mount a vigorous virus-specific CD4⁺ T helper (Th) cell response during primary infection^{17,18}. This response appears to dwindle within a few months¹⁷ and could result from the selective infection of HIV-specific CD4⁺ Th cells by HIV-1, leading to cytotoxic T lymphocyte (CTL)-mediated clearance or direct viral destruction. Although this could be caused by the preferential infection of activated Th cells, it seems likely that HIV-specific Th cells will preferentially interact with HIV-antigen-bearing DCs. As these DCs are likely to be productively infected with HIV-1 or bear DC-SIGN-bound virions, such interactions could be very dangerous liaisons.

Conclusions

Recent findings have combined to produce substantial conceptual advances in our understanding of the role of DCs in HIV-1 infection^{3,14}. The implications of this research are profound. It seems that the intricate intercellular interactions necessary for effective adaptive immunity provide the basis for efficient transmission and dissemination of HIV-1 (Fig. 1). Further research focusing on the cellular events that occur immediately after mucosal exposure to HIV-1 is clearly important. A detailed understanding of DC-HIV-1 interactions could provide the basis for the development of effective prophylactic and therapeutic interventions.

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Bypassing IgE and targeting T cells for specific immunotherapy of allergy

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Specific immunotherapy (SIT) is a common treatment for allergic diseases. Despite its usage in clinical practice for nearly a century, more-rational and safer allergen preparations are required. Here, the underlying mechanisms and principles of allergen modification for the future use of SIT in the treatment of allergy are discussed.

IgE-mediated allergy is an immune disorder affecting almost one-third of the population in some countries. Although immediate and late symptoms can be ameliorated by pharmacological treatment, specific immunotherapy (SIT) is the only curative approach against this type of allergy. However, some major problems related to this approach remain to be solved. Currently, SIT is performed with allergen extracts that usually

contain insufficiently characterized allergen mixtures that are not designed for an individual patient's allergen profile and that contain nonallergenic or unwanted toxic proteins. Most importantly, administration of native allergens can cause severe, often life-threatening, anaphylactic reactions. Therefore, the optimally efficient high dose of allergen required for successful SIT can often not be reached. Recent knowledge of the immunological mechanisms underlying SIT should allow such problems to be overcome in the future^{1–3}.

Mechanisms of antigen focusing

The first essential steps in SIT involve the specific recognition of allergen by T cells and the induction of peripheral anergy^{1–3}. Therefore, a basic requirement in

achieving successful SIT without risk of anaphylaxis is for the allergen to express T-cell epitopes that induce T-cell tolerance and lack antibody-binding sites that would otherwise facilitate IgE-mediated allergic responses. An intact three-dimensional structure of an allergen is pivotal in the development of distinct immune response profiles by the preferential usage of particular antigen-presenting cells (APCs) (Fig. 1). Whereas specific B cells most efficiently present conformational allergens at low concentrations, APCs that utilize phagocytosis or pinocytosis for antigen uptake, such as monocytes, macrophages and/or dendritic cells, internalize allergen molecules independently of their structural features^{4,5}. If B cells present low concentrations of antigen to T cells, high interleukin 4 (IL-4) but very little or