HIV: **Dendritic cells as embers for the infectious fire**

Edward A. Clark

In people with HIV-1, most of the CD4-expressing T cells that produce virus are short-lived and vulnerable to anti-retroviral agents. But the initial 'fire' of HIV-1 infection may begin in, and be maintained by, cells of the dendritic cell lineage.

Address: Department of Microbiology and Regional Primate Research Center, University of Washington, Box 357242, Seattle, Washington 98195, USA.

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More than 99 % of HIV-1 in infected individuals is produced by recently infected and short-lived T cells which express the cell-surface marker CD4 [1–3]. Although anti-retroviral agents can effectively block the 'raging fire' [1] of HIV-1 replication in T cells, it is less clear how to prevent viral persistence in long-lived cell populations — potential reservoirs that could re-ignite the fire.

Several recent studies suggest that cells within the dendritic cell (DC) lineage may be a key reservoir for active HIV-1 replication. DCs are a heterogeneous family of highly efficient antigen-processing and antigen-presenting cells that interact with T cells. Like T-cell subsets, the different family members are classified on the basis of their characteristic expression of cellular markers. For instance, epidermal Langerhans cells (LCs) are classified as $S100^+$,$CD1a^+$,factor $XIIIa^-$; DCs found in the mucosal interstitium and epithelium are classed as $S100^+$,$CD1a^-$, factor $XIIIa^+$ [4]. DCs found in the regions of peripheral lymphoid tissues that are populated by T cells express costimulatory molecules, such as CD80 (B7-1) and CD86 (B7-2), which are required to activate resting T cells. The relationship between these cell types has not been defined precisely, but they are likely to be dendritic-lineage subsets at different stages of maturation. Upon exposure of skin LCs to antigen, the antigen is processed by the cells. Cytokines, such as tumor necrosis factor-α [5], then induce the LCs to mature into DCs, which then migrate into the lamina propria (the layer of connective tissue underlying the epithelium of a mucous membrane) or to the lymph nodes, where they encounter and activate antigen-specific T cells. Cells within the dendritic lineage express CD4, the receptor for HIV, and thus are potentially capable of binding HIV and/or being infected by it.

Precisely where the initial and active sites for HIV-1 replication lie remains controversial. It is clear that skin LCs can be infected with HIV-1, and it may well be that LCs are an initial target of HIV infection [6,7]. But it has been less clear whether DCs are efficiently infected by HIV-1 *in vivo*. Recently, by examining adenoidal lymphoid tissue from asymptomatic HIV-1-infected individuals, Frankel and coworkers [8] discovered 'giant cells' within, and just beneath, the mucosa that contained HIV-1 genomes and intracellular viral p24 antigen. These syncytia — which were actively replicating HIV-1 in otherwise asymptomatic people — expressed the DC marker, S100, and an actin-bundling protein, p55, which is known to be expressed in DCs. These results suggested that the syncytia may be made up of cells that include DCs. Because LCs may mature into DCs, and because LC preparations are likely to contain DCs as well, it is possible that some of the HIV-1 production previously ascribed to LCs may actually be attributable to DCs. And because DCs, unlike LCs, interact with T cells *in vivo*, Frankel and coworkers [8] proposed that interactions between DCs and T cells in mucosal lymphoid tissues ''may drive HIV-1 replication''.

These striking *in vivo* data are not sufficient by themselves to implicate DCs as a key reservoir of HIV-1 infection. Neither S100 nor p55 is found only in DCs; p55, for example, is also expressed in activated B cells. Although the authors suggest [8] that T cells may be contributing to the giant syncytia, they have not tested this directly (as yet). However, the model is also consistent with results from several previous studies. HIV RNA transcripts have been detected *in situ* within $CD4^+$,factor $XIIIa^+$ dermal DCs [9]. Cutaneous $CD4^+$ DCs can also be infected by HIV-1 *in vitro* [10,11]. Furthermore, a mixture of DC and $CD4^+$ T cells promotes extensive HIV-1 expression and spread [12–15] via a process that requires interactions between the DCs and $CD4^+$ T cells [13]. Interestingly, HIV-1-pulsed DCs may maintain HIV-1 longer than HIV-1-pulsed T cells or monocytes [10,14], consistent with a model suggesting that DCs are the 'embers' that can ignite or re-ignite the HIV-1 fire.

DCs may also be an initial target early in simian immunodeficiency virus (SIV) infection. Spira and coworkers [15] found that within days of inoculating macaques intravaginally with SIV, SIV-infected cells were present in the vaginal lamina propria that appeared to be non-lymphoid cells expressing S100 and major histocompatibility complex class (MHC) II molecules. The cells were most probably DCs, because although LCs express the same markers, they do not reside in this site [15]. There is also evidence for the involvement of dendritic-lineage cells early in HIV-1 infections. Sexual transmission of HIV-1 seems to be subtype-selective, because certain relatively rare variants are preferentially transmitted sexually (see [15]). For

example, a recent study [16] suggests that HIV-1 infection may be most efficiently transmitted via heterosexual routes by isolates that grow preferentially in dendritic lineage cells. In this study [16], the authors compared HIV-1 subtypes isolated from American homosexuals with those isolated from Thai heterosexuals [16]. All of the isolates from the heterosexuals were subtype E and grew efficiently in LCs, whereas all of the typed isolates from the homosexuals were subtype B and grew less well in LCs than the subtype E isolates. In Thai heterosexual couples where one partner was HIV-1-positive and the other was HIV-1-negative, transmission was more efficient where subtype E viruses were involved [17]. The selective tropism for LCs measured *in vitro* may reflect a similar tropism for DCs; indeed, it is likely that the LC preparations of Soto-Ramirez *et al.* [16] also contain DCs. Transmission by homosexual routes could also involve DCs, as functional dendritic-lineage cells are present in the colonic epithelium (see, for example [18]). It remains to be determined whether HIV-1 subtypes differ in their ability to infect LCs and DCs, or in their requirement for these cells during the infection of $CD4^+$ T cells.

Why might DC-containing syncytia in particular be especially productive sites of HIV-1 replication *in vivo*? Studies *in vitro* suggest that a syncytium of DCs and T cells might express a combination of factors promoting efficient HIV replication that is not produced by either cell alone. Granelli-Piperno *et al.* [19] found that DCs do not express the transcription factor Sp1 but that T cells do; in contrast, resting T cells do not express NF-κB-related proteins such as p50 and p65, but DCs do. The syncytia contain both Sp1 and NF-κB, implying that they may express a combination of transcriptional activators capable of stimulating HIV-1 replication, and that this combination is not produced by T cells or DCs alone. But further analysis is needed to determine whether the HIV-producing syncytia found *in vivo* [8] are a fusion of DCs and T cells — and any model proposing that such syncytia are vital for the spread of HIV-1 must consider that syncytia may be 'terminal' cells with relatively short life spans.

What signals might 'stoke' DCs and lead them to produce HIV-1 efficiently, or to be more effective antigen-presenting cells in promoting HIV-1 spread? Culturing DCs alone with HIV-1 leads to little or no viral production, whereas culturing HIV-1-pulsed DCs together with $CD4^+$ T cells leads to significant viral production [11–13,20]. Interactions between DCs and T cells that occur during antigen presentation may be critical for HIV activation and transmission, as suggested by the finding that PPD (purified protein derivative of tuberculin) [20] or specific antigen [21] can significantly augment HIV-1 production mediated by DCs and T cells. Stimulating DCs via the CD40L–CD40 accessory receptor pathway [13] has a similar effect. The stage of maturation may also affect the ability of DCs to retain or replicate HIV-1; Weissman *et al.* [14], for instance, found that one blood DC subset could be infected with HIV-1, whereas another subset could not, even though both subsets could bind HIV. Conversely, agents that reduce DCs' antigen-presenting activity, arrest DC maturation, or induce apoptosis of DCs, may prevent DC-dependent HIV-1 production. For example, the antigen-presenting function of LCs is downregulated by an epidermal nerve product, calcitonin gene-related peptide [22]. Furthermore, blocking the DC–T-cell interactions mediated by CD80 and CD86 *in vitro* also blocks DC-dependent HIV-1 production [12]. Interleukin-10 (IL-10) can also block the interaction between DCs and T cells by downregulating the expression of the key CD86 costimulatory molecule on DCs [23]; IL-10 can also accelerate apoptosis in DCs [24].

Thus, dendritic-lineage cells may not only act as a latent reservoir for HIV genomes, but upon contact with antigen-specific T cells, they may also initiate a process dependent on DC–T-cell interactions, leading to bursts of HIV production, particularly in DC–T-cell syncytia. According to this model, latently infected DCs may be the 'embers' and DC–T-cell interactions the 'bellows' that fuel active short-lived production of HIV. Clearly, defining more fully how the life span and antigen-presenting activity of dendritic-lineage cells are regulated will be key areas of future investigation for those hoping to put the HIV fire out completely.

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