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### Commentary

Langerhans cells (LCs) are likely among the first targets of HIV-1 infection due to their localization in mucosal tissues. In their recent work, Pena-Cruz and colleagues were able to study HIV-1 infection in vaginal epithelial DCs (VEDCs), termed CD1a<sup>+</sup> VEDCs. They show that VEDCs are distinct from other blood- and tissue-derived DCs or LCs because they express the protein langerin but not the lectin receptor DC-SIGN, and they do not have Birbeck granules. The results from this study indicate that HIV-1 using CXCR4 replicates poorly in VEDCs but that a higher replication for HIV-1 using CCR5 strains is supported by VEDCs. Furthermore, Pena-Cruz and colleagues demonstrate that VEDCs can represent a viral reservoir in HIV-1-infected virologically suppressed women. As such, VEDCs may represent another sanctuary of viral persistence and can be an additional obstacle to viral eradication.

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# Vaginal epidermal dendritic cells: defense against HIV-1 or a safe haven?

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Langerhans cells (LCs) are likely among the first targets of HIV-1 infection due to their localization in mucosal tissues. In their recent work, Pena-Cruz and colleagues were able to study HIV-1 infection in vaginal epithelial DCs (VEDCs), termed CD1a<sup>+</sup> VEDCs. They show that VEDCs are distinct from other blood- and tissue-derived DCs or LCs because they express the protein langerin but not the lectin receptor DC-SIGN, and they do not have Birbeck granules. The results from this study indicate that HIV-1 using CXCR4 replicates poorly in VEDCs but that a higher replication for HIV-1 using CCR5 strains is supported by VEDCs. Furthermore, Pena-Cruz and colleagues demonstrate that VEDCs can represent a viral reservoir in HIV-1-infected virologically suppressed women. As such, VEDCs may represent another sanctuary of viral persistence and can be an additional obstacle to viral eradication.

## DCs and their subsets

DCs, the key initiators of the immune response, are located on the skin and the inner lining of various organs. Because of their primary location, they are in first line of contact with external injuries and infections. Despite their low susceptibility to HIV-1 infection, the ability of DCs to interact with multiple cell types of the naive and adaptive immune system makes them an ideal target during the early steps of HIV-1 infection (reviewed in refs. 1–3). During later stages of infection, DCs have the ability to migrate to proximal draining lymph nodes and spread the virus through its most susceptible target: CD4<sup>+</sup> T cells. Thus, because of their very early exposure to HIV-1, potential to become infected, and natural potential to activate the immune system, DCs and their subsets represent cell types that are of great interest to control and eradicate HIV-1 infection. DCs and their subsets are complex, however, and unbiased single-cell RNA sequencing has led to the identification of no less than six subsets of DCs in human blood alone

(4). Skin subsets of DCs are also complex, despite having been studied for many years (reviewed in refs. 5–7). Much less is known of LCs, a unique subset of DCs in mucosal squamous epithelium and skin epidermis, and their specific variants. In addition to DCs and their subsets, microenvironments such as chemokine levels in mucosal tissues correlate with HIV acquisition in men (8). Making progress in the identification of new DC subsets exposed to HIV-1 during the early stages of infection can ultimately either open new therapeutic opportunities to block the infection or represent unexpected obstacles to eradication.

## Understanding DCs to design strategies to prevent sexual transmission of HIV-1

DCs specifically express the C-type lectin receptor that binds HIV-1, called DC-SIGN (9). In contrast, LCs express the C-type lectin receptor langerin. LCs also express CD4, CCR5, and CXCR4 (the key molecules required for HIV-1 entry), although at levels lower than those in CD4<sup>+</sup> T cells

(10). HIV-1 viral proteins and nucleic acids can be detected in DCs and their subsets by pattern-recognition receptors such as TLRs and C-type lectins. For instance, the HIV envelope can activate conventional DCs through mTOR signaling, impairing autophagy, and TLR4 pathways (11). Interestingly, LCs seem relatively resistant to HIV infection, in part due to entry and postentry mechanisms. This includes blocks induced by Langerin (12), as well as restriction factor Trim5a (13, 14) and TGF- $\beta$ -mediated postentry restrictions to HIV infection (15).

Low levels of HIV-1 viremia not only have a role in early HIV infection, but those levels can be maintained and detected in the plasma of patients for many years during the later phase of HIV-1 infection. The low division rate of DCs may account for the long-term maintenance of the virus and the establishment of a latent reservoir that can persist despite antiretroviral treatment. The ability of HIV-1 to propagate from DCs to CD4<sup>+</sup> T cells via infectious or virological synapses (16 and reviewed in ref. 17) make DCs ideal candidates for intervention during both the initial and late stages of infection.

In high-risk populations, pre-exposure prophylaxis (PrEP) has shown promising results by treating noninfected individuals with antiretroviral drugs to prevent early HIV-1 infection, particularly in men at high risk (18). In contrast, tenofovir-based PrEP for HIV infection among African women was unable to reduce the rates of HIV-1 acquisition in an intention-to-treat analysis, probably due to low adherence to study drugs (19). Understanding early events of HIV-1 infection, including infection in vaginal subsets of DCs, may hold answers to some of the challenges of preventing sexual transmission of HIV-1.

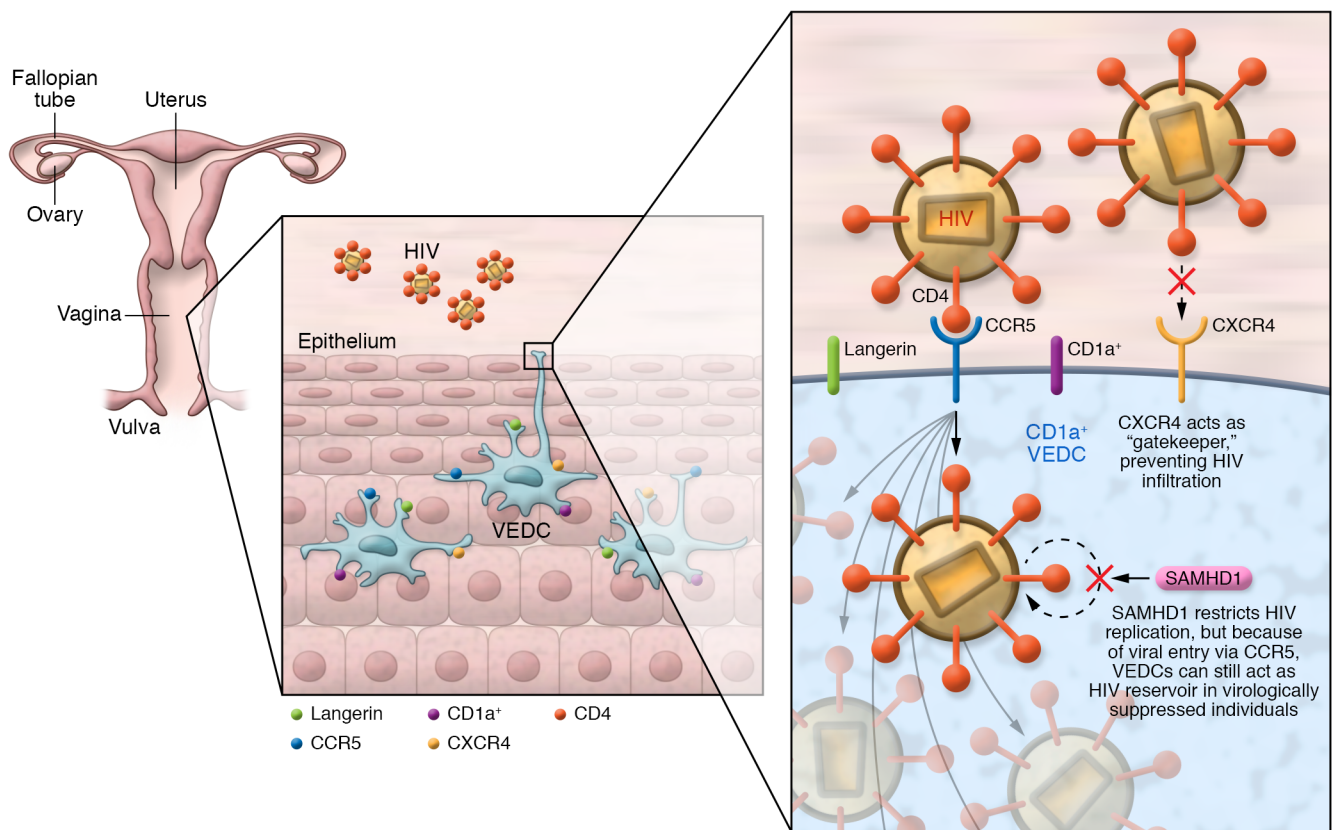
## Identification of a unique DC subtype opens up doors toward new therapeutic strategies

In the current issue of the *JCI* (20), Pena-Cruz and colleagues have identified and

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**Figure 1. VEDCs and HIV-1.** CD1a<sup>+</sup> VEDCs are purified from the vaginal epithelium. VEDCs preferentially replicate HIV-1 using CCR5. VEDCs express SAMHD1, which acts as a cellular restriction to HIV-1. However, although VEDCs can be gatekeepers by not being infected efficiently by CXCR4-using HIV-1 strains, they can contain virus even in virologically suppressed women and are therefore potential reservoirs for the virus.

described an apparently unique subset of VEDCs that shares characteristics found in skin DCs and in LCs but which remains distinct from the other well-known DC and LC subsets. These cells, labeled CD1<sup>+</sup> VEDCs, display a unique phenotype wherein they express langerin and CD1a, but not DC-SIGN, and do not harbor Birbeck granules like LCs do. VEDCs express the HIV-1 coreceptors CXCR4 and CCR5 just like mucosal-derived DCs and LCs, yet they are more susceptible to HIV-1 infection by CCR5-using strains as compared with CXCR4-using strains. Furthermore, the authors show that VEDCs express host restriction factors to HIV-1 infection, such as dendritic and myeloid cell-specific HIV-1 restriction factor SAMHD1 (21). Importantly, the authors also show that the HIV-1 DNA was detectable in VEDCs isolated from two HIV-1-infected virologically suppressed women, thereby indicating that VEDCs may act as a potential reservoir during latency.

These intriguing observations open up a number of questions for the field.

Are VEDCs a unique cell type? Do they differ from LCs in the male foreskin? Perhaps new techniques such as unbiased single-cell RNA sequencing would shine light on these questions. Another problem with *ex vivo* human cell systems such as the one used in the study by Pena-Cruz et al. is that extraction and purification of the LCs will potentially alter their phenotype. How much of the process has affected the results obtained? Are these cells truly different from their more-studied counterpart, skin-derived LCs? Additionally, although the authors show that SAMHD1 plays a role as a restriction factor in VEDCs, the contribution of additional potential restrictions such as langerin, Trim5a, and others needs to be explored. Preventing HIV transmission remains a great unmet challenge, particularly in women (19). Are VEDCs another obstacle to HIV-1 infection or do they represent a viral reservoir that has already been accounted for? Only by having clear answers to these questions will we be able to develop novel therapies to prevent HIV infection at its earliest stages.

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