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Myeloid DCs in HIV-1 Infection

N. Derby[1], **E. Martinelli**[1], and **M. Robbiani**[1,*]
[1]Center for Biomedical Research, Population Council, New York, New York, USA

Abstract

Purpose of review—Myeloid dendritic cells (mDCs) are pivotal players in HIV-1 infection. They promote transmission and spread and at the same time are critical for recognizing HIV-1 and initiating immune responses to fight infection. Notably, their immunostimulatory capabilities can be harnessed to design better HIV-1 vaccines. In this review, advances in these areas of mDC-HIV-1 interactions are summarized.

Recent findings—New insights into HIV-1-induced dysfunction of mDCs and dysfunctional mDC effects on other cell types, as well as novel mechanisms of viral sensing by mDCs and their evasion by HIV-1 have been uncovered. These results emphasize the importance of mDCs in protection against HIV-1 infection. Targeting mDCs with vaccines and tailored adjuvants may improve the quality and anatomical location of elicited immune responses.

Summary—Understanding the multiplicity of HIV-1-DC interactions together with the numerous advances in targeted therapy and vaccination will help in the rational design of approaches to treat and block infection.

Keywords

Myeloid DC; HIV-1; pattern recognition receptors; dysfunction; immunity

Introduction

Dendritic cells (DCs) orchestrate innate and adaptive immune responses to infection. There are two major subtypes of human DCs: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). Unlike pDCs, which primarily drive innate inflammatory responses to pathogens by secreting large amounts of interferon-α (IFNα), mDCs are specialized for antigen presentation to direct adaptive responses. Residing at mucosal surfaces and skin ($CD11c^+$ mDCs, Langerhans cells [LCs] and $CD209^+$ dermal/submucosal DCs) they are sentinels to detect invading pathogens and are among the first leukocytes to encounter HIV-1 during sexual transmission [1]. Immature and mature mDCs capture and internalize virus, and immature mDCs are also infected by HIV-1 at a low level [2]. Direct transfer of captured and newly produced virus from mDCs to $CD4^+$ T cells promotes infection and spread [2].

Understanding how mDCs recognize and respond to HIV-1 is critical for improving antiviral approaches. Although HIV-1 subverts and manipulates signaling to favor viral replication [3], it may be possible to tip the balance towards an antiviral state through proper mDC activation. This review will cover recent advances in the dual roles of mDCs as pathogenic and protective in HIV-1 infection, as well as innovative strategies to harness them for

*Corresponding author: Melissa Robbiani, Senior Scientist and Director of Biomedical HIV Research, Center for Biomedical Research, HIV and AIDS Program, Population Council, 1230 York Avenue, New York, NY 10065, Tel 212 327 7794, Fax 212 327 7764, mrobbiani@popcouncil.org.

prevention and therapy. Studies of primary mDCs and LCs will be discussed alongside results obtained using the monocyte-derived DC (moDC) model.

HIV-1 modulation of mDC function

Impaired mDC function is a critical component of HIV-1 infection affecting most compartments of the immune system [4]. Abundant data indicate a loss of $CD11c^+$ mDCs from the blood of HIV-1 infected patients [5], yet the primary reason for this loss remains elusive. Depletion of circulating mDCs is detected during primary and chronic infection, and there continue to be reports on the ability of antiretroviral therapy (ART) to restore mDC numbers and function [6,7**,8*]. Macaque data show that loss of blood mDCs at virus set-point predicts disease progression, whereas an increase predicts long term absence of disease [7**]. However, these findings are not clearly correlated with viral load or $CD4^+$ cell counts [6,7**]. Disappearance of mDCs from blood can be partially explained by accumulation in lymph nodes (LNs) [7**], which seems to be offset by loss due to apoptosis during acute and chronic infection [7**,8*]. The expression of the anti-apoptotic factor BCL-2 and the frequency of $Caspase3^+$ mDCs are decreased and increased respectively in HIV-1 chronic infection patients [8*].

Together with fueling infection by transferring virus to $CD4^+$ T cells, mDCs can be infected by HIV-1 [2]. The substantial viral burden sustained by circulating mDCs in untreated patients [9] and the relatively long half-life of HIV-1 infected mDCs suggest a possible role in latency [10*].

Earlier studies demonstrated varying effects of chronic HIV-1 infection on mDCs [4,5]. Recent studies have focused on acute infection, revealing that despite their early reduction in circulation, the remaining mDCs display hyperfunctionality and can stimulate allogeneic T cell responses [11**], possibly contributing to chronic immune activation and T cell exhaustion. In fact, acute macaque SIV infection is associated with increased expression of a ligand for PD-1 (B7-H1) on mDCs which persists and correlates with PD-1 expression on T cells and impaired virus-specific T helper (Th) and cytotoxic T lymphocyte (CTL) functions [12*]. Moreover, mDCs from HIV-1 infected subjects upregulate expression of PD-1 on co-cultured T cells, inhibiting T cell activation and proliferation [13]. MoDCs generated from HIV-1 infected individuals exhibit a reduced ability to stimulate T cells and are altered in their production of IL-12 and IL-10 [6,14]. Many questions remain regarding the mechanism of mDC dysfunction and the relative contributions of direct HIV-1 infection vs exposure to viral products or even indirect effects by $CD4^+$ T cell dysregulation.

HIV-1-mediated mDC dysfunction also impacts the initiation of effective immune responses by other cell types. Direct infection of mDCs and interaction of mDCs with HIV-1 particles disrupts mDC-NK cross talk, resulting in decreased NK activation and lytic activity [4]. Both mDCs and moDCs derived from HIV-1 infected people are impaired in their ability to stimulate NK activity through poly(IC) [15] though they can still induce IFNγ secretion by NK cells when activated with LPS [6]. The impact of ART on mDC differentiation and the resulting aberrant mDC-NK communication may actually suppress hyperimmune activation related disease [16]. A role for HIV-1-induced mDC dysfunction in B cell disease has been attributed to increased expression of B lymphocyte stimulator and B cell growth factors during acute and chronic infection [17].

mDCs are essential in shaping the mucosal microenvironment and vice-versa. Interaction with other pathogens or pathogen-derived products results in dysfunctional DC activation, which can contribute to creating a tolerogenic environment and increase the number of susceptible target cells [18*,19**] at the initial stages of HIV-1 infection. HSV-2 infection is linked to HIV-1 acquisition epidemiologically [20] and mechanistically by recruitment of

activated $CD4^+$ T cells to sites of HSV-2-induced ulceration and the persistence of target cells at healed lesion sites following antiviral therapy [21]. HSV-2 has been shown to mature epidermal $CD1a^+$ LCs and decrease expression of CD207/Langerin [18*], which was associated with enhanced HIV-1 infection of LCs and transmission to $CD4^+$ T cells. Similar effects were achieved using live or UV-inactivated HSV-2, as well as an unrelated DC maturation stimulus, poly(IC) [18*]. We have demonstrated a direct link between HSV-2 infection of moDCs and increased HIV-1 replication in the DC-T cell milieu [19**]. Specifically, HSV-2 infected moDCs induced a retinoic acid (RA) dependent increase in α4β7 expression by $CD4^+$ T cells and HIV-1 replication in DC-T cell mixtures. This coincided with HSV-2 infected DCs expressing more aldehyde dehydrogenase ALDH1A, which is essential for RA production. Moreover, elevated percentages of $\alpha4\beta7^{high}CD4^+$ T cells were detected in the rectal mucosa, draining LNs, and blood of macaques rectally infected with HSV-2, even in the absence of obvious lesions. This further supports the role for α4β7 in facilitating mucosal HIV-1 infection [22*], especially in the presence of HSV-2, and emphasizes that mDCs are central to this biology. Importantly, blocking α4β7 was also shown to limit acute SIV infection [23]. Key aspects of the microenvironment that favor protection vs pathogenesis remain to be addressed.

The importance of mDC dysfunction in HIV-1 pathogenesis is underscored by findings from HIV-2, which is highly attenuated in comparison to HIV-1. Although there are not published reports on mDC numbers in HIV-2-infected patients, pDC loss has been reported [24], suggesting that DC preservation may not be a factor in the attenuated phenotype. However, mDCs are less susceptible to HIV-2 infection than HIV-1 *in vitro* [25], which may have implications for differences in latency or other aspects of disease progression. An important distinction between the viruses has been uncovered with respect to virus transfer between mDCs and $CD4^+$ T cells. HIV-1 can be transferred across the immunological synapse (IS), a part of the normal communication to promote an adaptive immune response. In contrast, HIV-2 Nef has been shown to block IS formation by downregulating the TCR-CD3 complex [26], potentially limiting T cell activation and thereby reducing virus amplification. Although HIV-1 Nef is known to hijack mDC functional activity, which may favor both infection and escape from immune surveillance [27], it does not modulate the formation of the IS, thereby promoting rapid systemic viremia. HIV-2 gp120 also has no effect on the differentiation or maturation of moDCs [28] while the interaction of HIV-1 gp120 with CD4 on mDCs impairs mDC responses to TLR ligands, secretion of cytokines and chemokines, and contributes to reducing proper activation of other cell types [4,29]. More studies of the impairment of mDC function in pathogenic vs attenuated or non-pathogenic (eg. HIV-2, SIV in natural hosts) infections will be crucial to understanding this biology and may lead to novel treatment strategies.

Sentinel role of mDCs and HIV-1 evasion

The profusion of strategies employed by HIV-1 to dysregulate mDC function underscores the significance of these cells in initiating effective immune responses. Normally, pathogen encounters stimulate mDCs through the triggering of their pattern recognition receptors (PRRs) by pathogen associated molecular patterns [30]. The cells migrate to secondary lymphoid organs where they present antigens to naïve T cells and initiate specific responses. While signaling through PRRs is critical to effective antiviral immunity [31], a growing body of evidence demonstrates that HIV-1 manipulates this signaling to favor its survival.

Several PRRs sense incoming RNA viruses, including TLRs, cytosolic helicases, and C-type lectins. TLR3, RIG-I, and MDA5 all recognize double-stranded RNA (dsRNA) while TLR7/8, and RIG-I sense single-stranded RNA (ssRNA) through different mechanisms [30]. CD207 and CD209 recognize HIV-1 with dissimilar outcomes. Unlike CD207 (above),

CD209 can promote HIV-1 transfer to $CD4^+$ T cells [3]. Glycoproteins have been identified in breast milk and seminal plasma that compete for HIV-1 binding to CD209 and block virus transfer [32,33]. MoDCs express TLR8, and viral hijacking of TLR8 signaling may be involved in the lack of mDC responsiveness to HIV-1 *in vitro* and *in vivo* [10*,34]. HIV-1 reportedly can signal through TLR8 in moDCs, as well as blood and dermal mDCs, engaging NF-κB to initiate transcription from integrated provirus [34*]. Transcription elongation is then facilitated by interaction of CD209 with gp120, which induces NF-κB phosphorylation by Raf-1 kinase [34*]. TLR8 signaling through NF-κB also activates latent HIV-1 in mDCs from infected patients [10*].

Another explanation for the absence of strong anti-HIV-1 immunity in mDCs is the fact that HIV-1 does not replicate efficiently in these cells (although this is overcome at high inocula [35]), so maturation and type I IFN production are not readily induced [36,37**]. While HIV-1 infection of moDCs does not induce type I or II IFN, a specific unusual group of IFN stimulated genes is induced [38] including marked upregulation of IRF1, which is suspected to promote HIV-1 replication as the LTR of most isolates contains an IRF-1/7 binding site [37**]. Poor HIV-1 replication in mDCs has been attributed to the lack of the accessory protein, Vpx, in the genome [39**,40**,41*]. An antiretroviral protein, SAMHD1, was shown to restrict HIV-1 infection of myeloid lineage cells during reverse transcription, and this was countered by the introduction of Vpx, which induced proteasomal degradation of SAMHD1 [40**]. By providing Vpx-mediated relief to this restriction in *trans* (using a VSV-G pseudotyped HIV-1 plus SIV virus-like particle co-infection system) and enhancing HIV-1 replication in moDCs, moDCs were found to upregulate CD86 and produce type I IFN [39**]. The potent innate response in these infected moDCs was mediated by the interaction of cellular cyclophillin A with the newly produced capsid through IRF3, which is an essential transcription factor in the pathway by which viruses and the synthetic dsRNA molecule poly(IC) induce IFNα/β [30]. These data support other findings that HIV-1 inhibits IRF3 activation in moDCs [37**] and that IRF3 is important in pDC recognition of HIV-1 infected lymphocytes [42]. Additionally, HIV-1 engineered to package and produce Vpx has been shown to replicate more efficiently in and induce a potent type I IFN response by moDCs, while also being more readily transmitted from moDCs to $CD4^+$ T cells than wild type virus [41*]. Together, these studies show that while ligation of PRRs should induce potent antiviral responses, HIV-1 either subverts or co-opts the first line defense to favor viral replication and spread.

APOBEC3G (A3G) is an innate intracellular defense against HIV-1, which is induced by type I IFN and poly(IC) in mDCs and $CD4^+$ T cells [43]. In a study of SIV infected macaques, A3G expression in mDCs and $CD4^+$ T cells was inversely correlated with viral load [44]. In moDCs, A3G activation was accompanied by the expression of small proteins that cross-react with A3G antiserum [45], which have been since identified as APOBEC3A (A3A; in primary monocytes and macrophages [46] and in moDCs, Derby, N, and Robbiani, M, unpublished observations). This agrees with previous data implicating A3A in the resistance of monocytic lineage cells to HIV-1 infection [43]. Poly(IC) treatment impedes HIV-1 replication through type I IFN secretion and APOBEC induction in moDCs [45], in the DC-T cell milieu (Derby, N, and Robbiani, M, unpublished observations), and in lymphoid tissue stimulated *ex vivo* [47]. These findings contrast the aforementioned enhancement of HIV-1 infection in poly(IC) matured LCs through CD207 downregulation [18*]. The timing of poly(IC) stimulation relative to virus exposure may play a role in these conflicting results. Alternatively, because poly(IC) can activate DCs through TLR3, RIG-I, and MDA5 [30], it is possible that varying expression of PRRs by different DC (and other cell) subsets and/or the method of delivering poly(IC) to the cells may affect downstream signaling and lead to distinct outcomes in the context of HIV-1 infection. Further

investigation is warranted to clarify the mechanisms behind PRR related virus amplification vs suppression.

Harnessing mDCs to boost anti-HIV-1 immunity

Although mDCs are dysregulated by HIV-1 to favor viral replication, proper stimulation can block infection of mDCs and interacting $CD4^+$ T cells. PRR ligands represent novel strategies to prevent HIV-1 replication and aid in the induction of multifunctional antigen-specific cellular immunity [48]. Poly(IC) and poly ICLC (stabilized to resist primate serum nucleases) have shown promise as adjuvants for preventative and therapeutic immunization [49,50,51*,52]. Targeting vaccines to mDCs is being explored to elicit more effective responses. Although proteins do not efficiently elicit CTLs [48], immunogenicity can be improved by targeted antigen delivery to mDC antigen uptake receptors specialized in cross-presentation [53,54]. A large body of work is accumulating on CD205/DEC-205 for delivery of HIV-1 antigens [53,55*]. Combining the DEC-gag immunogen (gag p24 incorporated into anti-CD205 antibody that targets the antigen to DCs in mice) with poly(IC) and a DNA boost, elicited potent $CD4^+$ and $CD8^+$ T cell responses, coincident with the accumulation of antigen specific $CD8^+$ T cells at the challenge site and enhanced protection [55*]. The $CD8^+$ T cell response required CD40 expression on mDCs [55*], strengthening the association between mDC targeting of the antigen, the involvement of mDC maturation, and the observed T cell responses to this vaccine. A parallel study demonstrated that Flt3L treatment significantly enhanced cross-presentation by the DEC-gag vaccine in mice [56]. mDC activation and mobilization by Flt3L was confirmed in SIV- and SHIV-infected macaques in the absence of any changes to viral load or $CD4^+$ T cell numbers [57], suggesting Flt3L could be added to mDC targeting vaccines without creating a more permissive environment for the virus. Incorporation of CD40L into vaccines may also induce mDC activation and boost antigen specific responses [58]. DEC-gag antibodies have now been optimized for humans [59**] and are moving into clinical trials for HIV-1 prevention [60]. The Phase 1 trial DCVax-001 is planned to evaluate safety and immunogenicity of DEC-gag co-administered with poly ICLC in HIV-1 negative individuals [60].

Peptides can also elicit mDC-mediated Th1 responses when properly delivered. In the Ligand Epitope Antigen Presentation System (LEAPS), peptides containing T cell epitopes are rendered immunogenic by covalent linkage to a peptide with T cell binding capability. LEAPS vaccines have demonstrated Th1 mediated protection against lethal HSV-1 challenge in mice [61*]. However, protection is actually mediated by mDCs. Immunization of mice with a peptide from gag p17 coupled to one from β2-microglobulin activated mDCs, inducing IL12p40 and p70 secretion, and promoted antigen specific IFNγ production by splenic T cells [61*]. *Ex vivo*, the vaccine matured mouse bone marrow DC precursors [61*] and human monocytes [62] into IL12 producing mDCs. Thus, LEAPS immunogens act both as antigen and adjuvant in the absence of a supplemental maturation stimulus, although the mDC responses are distinct from those induced by poly(IC); TNFα and IL6 are not induced by LEAPS [61*,62].

As potent antigen presenting cells, mDCs can be loaded with antigen *ex vivo* and administered as preventative or therapeutic vaccines [63]. A recent study showed that the T cell responses induced by gag mRNA loaded moDCs were polyfunctional and exhibited a memory phenotype [64]. The safety, feasibility, and immunogenicity of this approach in combination with CD40L are being evaluated in preclinical studies in HIV-1 infected patients [65]. mDCs and LCs loaded with HIV-1 peptides also induce polyfunctional virus-specific $CD8^+$ T cell responses [66]. Antigen loaded mDCs can be targeted to specific tissues. A recent study in mice found that silencing the ubiquitin-editing enzyme A20, an inducible feedback inhibitor of innate immune signaling pathways that controls the

activation of mDCs and their immunostimulatory capabilities, rendered the mDCs hyperactivated with gut-homing potential [67*]. When A20-silenced mDCs were loaded with HIV-1 env, matured *ex vivo*, and delivered systemically, they were superior inducers of proinflammatory mucosal and systemic antigen-specific immunity [67*]. Notably, these cells upregulated expression of α4β7 on T cells in an RA dependent manner, a characteristic than can create a permissive environment for HIV-1 replication (above). Since blocking α4β7 limits SIV infection [23], it seems unlikely that A20 silencing would make a good vaccine strategy. Nevertheless, such studies are important for teasing apart the complexities of eliciting desirable immune responses without enriching the pool of target cells.

Conclusion

HIV-1 modifies mDC signaling pathways designed to prevent viral infections, thereby creating a permissive environment. While it is possible to manipulate mDCs to induce a specific and highly effective targeted immune response, future work will need to improve the direction of such responses to mucosal sites since even a potent systemic response might still arrive too late to prevent spreading infection.

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Key Points/Phrases

- Myeloid dendritic cells (mDCs) promote HIV-1 infection by direct transfer of captured and newly produced virus to $CD4^+$ T cells.
- Although mDCs are dysregulated by HIV-1 to favor viral replication, proper stimulation can block infection of mDCs and their ability to fuel infection.
- This review will cover recent advances in better understanding how HIV-1 modulates mDC function and the role of mDCs in HIV-1 pathogenesis.
- Promising new strategies to harness mDCs for HIV-1 prevention and therapy will also be discussed.