Dendritic cells (DC) are a heterogeneous population of innate immune cells that are fundamental to initiating responses against invading pathogens and regulating immune responses. Myeloid DC (mDC) act as a bridge between the innate and adaptive immune response during virus infections but their role in immunity to human immunodeficiency virus (HIV) remains ill-defined. This review examines aspects of the mDC response to HIV and its simian counterpart, simian immunodeficiency virus (SIV), and emphasizes areas where our knowledge of mDC biology and function is incomplete. Defining the potentially beneficial and detrimental roles mDC play during pathogenic and stable infection of humans and nonhuman primates is crucial to our overall understanding of AIDS pathogenesis.

**Introduction**

Dendritic cells (DC) are a heterogeneous cell population known to bridge the gap between the innate and adaptive immune responses. The family of DC includes myeloid DC (mDC) and plasmacytoid DC (pDC) subsets, which differentiate from precursors found in the bone marrow and inhabit the periphery as immature cells. In humans and nonhuman primates, DC are defined by the absence of T, B and monocytic cell lineage markers, the presence of major histocompatability complex class-II (MHC-II), and high expression of CD123 and CD11c on pDC and mDC, respectively. Upon exposure to invading pathogens, pDC migrate through high endothelial venules to lymphatic tissue and excrete copious quantities of antiviral type I interferon, which can slow viral replication and contribute to an inflammatory environment. Through a separate pathway, mDC recognize viral particles, mature, produce pro-inflammatory cytokines and migrate through afferent lymphatics to lymph nodes where they stimulate and polarize the antigen-specific adaptive immune response.

The effects of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection on pDC have been the focus of multiple reviews, but new studies have renewed interest in the complex role of mDC in these infections. As the focus of this brief review, mDC can be thought of as having a “dendrite in every pie” as they are active participants in multiple processes of the immune response including instigating, maintaining and controlling immunity and inflammation. We will consider each of these factors in discussing mDC in HIV and SIV infection, particularly those areas that remain controversial.

**Nonhuman Primate Models for HIV Pathogenesis**

In order to elucidate the mechanism of HIV pathogenesis and to test vaccines and treatment therapies, the use of a nonhuman primate infection model that mirrors the course of human disease is invaluable. Continued overactivation of the immune system is a key predictor of disease course in HIV-infected individuals, and comparing pathogenic and nonpathogenic nonhuman primate models of SIV infection can reveal insights into its cause. The SIV disease course in Asian nonhuman primate species such as rhesus macaques is comparable to HIV infection in humans in that it exhibits an early and strong type-I interferon response, which chronically persists ultimately contributing to immune dysfunction and progressive disease. In contrast, natural infection of African nonhuman primates such as the sooty mangabey and African green monkey is characterized by the rapid control of the type I interferon response and lack of manifestations of disease, despite high virus loads. Crucial to the use of nonhuman primates as models of AIDS, it has been determined that DC subsets from nonhuman primates are phenotypically and functionally comparable to DC of humans. Thus, the study of progressive and non-progressive models of SIV infection in nonhuman primates can be very informative in determining whether mDC play a beneficial role in controlling SIV infection, or a detrimental role in promoting immune activation and disease.
The Role of mDC in Disseminating HIV and SIV from the Site of Infection

The relative contribution of direct and indirect infection of mDC in virus dissemination in HIV infection is still not well understood. Throughout maturation and migration mDC express the required receptors for HIV and SIV entry and can become productively infected; thus mDC can potentially transport virus from the primary site of exposure in mucosal tissues to secondary sites of viral replication. However, in the absence of direct infection, mDC may form conjugates with T lymphocytes and facilitate their infection. In addition, mDC may trans-infect CD4+ T lymphocytes by engulfing viral particles associated with either CD4 or DC-SIGN and traveling to lymph nodes where the virus is then spread through virological synapses. In SIV-infected macaques, the proportion of mDC that are productively infected during the peak virus replication in lymph nodes at day 14 post infection is minor, suggesting that mDC do contribute to virus dissemination it is through these indirect mechanisms. In a recently updated model of viral dissemination, pDC are rapidly recruited to mucosal surfaces following vaginal exposure to SIV, where they secrete pro-inflammatory cytokines and chemokines that drive subsequent recruitment of CD4+ T lymphocytes to the site of infection, thus counter-intuitively creating a local expansion of target cells and viral replication. As an example of knowledge-directed therapeutics, local administration of the antimicrobial agent glycerol monolaurate inhibits the very cytokines and chemokines that are required to establish inflammation and SIV infection through vaginal inoculation of rhesus macaques.

The Dynamics of the mDC Response in HIV and SIV Infection

Many aspects of mDC biology in HIV and SIV infection remain poorly defined or controversial, including the dynamics of circulating mDC with and without anti-retroviral therapy (ART). During chronic and late-stage infection, mDC are depleted from the blood of infected patients. A conflicting study argues that mDC are only depleted in patients with high viral loads, as depletion was only detected in patients with viral loads of > 5,000 copies/ml and ART diminished this defect. Likewise, a general consensus remains to be agreed upon regarding effective treatment aiding in circulating mDC reconstitution. Administration of the nucleoside analog reverse-transcriptase inhibitor AZT or 8 weeks of ART increases mDC frequencies to 3.5-fold higher than pre-infection levels. It had been hypothesized that mDC are lost from circulation because they become infected by HIV and SIV and apoptose, but as discussed above the overall magnitude of mDC loss in the periphery does not match their low rate of infection, at least in SIV-infected macaques, suggesting other factors may contribute to mDC disappearance. Certainly a likely factor in loss of mDC from blood is increased migration of mDC to inflamed lymphatic tissue. In fact, mDC taken from progressively infected rhesus macaques express more of the lymph node homing receptor CCR7 while lymph node tissues express significantly higher levels of the CCR7 ligand CCL19. Furthermore, HIV is linked with imbalanced cytokine secretion in lymphatic tissue that causes increased cellular recruitment and retention leading to lymphadenopathy.

Innate Function of mDC when Responding to Infection

mDC engulf extracellular pathogens and recognize generic pathogen associated molecular patterns through pattern recognition receptors like members of the Toll-like receptor (TLR) family. mDC can detect bacterial and viral infection through the expression of TLR 1, 2, 3, 4, 5, 6 and 8 with TLR8 serving as the principle receptor for HIV single stranded RNA. The effect that HIV and SIV infection has on the ability of mDC to respond to invading pathogens and the impact this has on immune activation remains controversial. A correlative study suggests that reconstitution of IL-12 producing mDC after ex vivo TLR8 stimulation allows for CD4+ T lymphocyte stabilization in the blood, suggesting that functional mDC are required for appropriate maintenance of the CD4+ T lymphocyte population. Furthermore, PBMC from HIV infected individuals stimulated with a TLR8 synthetic agonist produce more IL-10 and less IL-12, suggesting that mDC from infected individuals are driving immune modulation rather than activation. Perpetual TLR7/8 activation through either R-848 or single-stranded RNA oligonucleotide administration in mice creates a disease resembling HIV disease. Because viremia in patients is positively correlated with TLR expression and ART is able to return TLR mRNA levels to normal, the presence of HIV may be making mDC hypersensitive to TLR agonists. Increased spontaneous production of cytokines by mDC from HIV infected patients suggests that the presence of virus is chronically stimulating the TLR pathway leading to persistent immune activation and creating a chronically enflamed environment. Furthermore, mDC are shown to be hyper-functional when responding to patients that experienced low mDC frequencies despite ART as compared with long-term non-progressing patients that had elevated numbers of mDC. In the blood of SIVmac251-infected rhesus macaques, low mDC frequencies at viral set point predicts rapidly progressing disease. Additionally, a separate group of animals in the same cohort experiencing stable infection exhibit elevated numbers of mDC in the blood, and ART further boosts mDC frequencies to 3.5-fold higher than pre-infection levels. These studies indicate that mDC pressure during infection could aid in controlling infection or may be a marker of a more fully constituted immune system
The HIV protein Nef down-modulates MHC-I molecules on the lymphocytes, although more work in this area is urgently needed. There is evidence that HIV infection has a significant impact on immune system, such as mDC and cause killer cells (NK) to proliferate, secrete IFN-γ, and induce cytolysis.71-75 NK cells are active effectors of the innate immune system that provide immediate antigen independent mechanisms to control viral infection.76,77 Importantly, at early stages of infection NK cells are implicated in partially controlling HIV replication prior to cell-mediated immune responses.78 NK cells can kill HIV-infected cells and inhibit viral entry and replication through ample secretion of IFN-γ, TNF-α, and CCR5 binding chemokines.79,80 Although HIV is shown to affect the interplay between pDC and NK cells,81,82 infection does not affect NK cell induction by mDC.83

Impact of HIV Infection on Induction of Adaptive Immunity by mDC

There is evidence that HIV infection has a significant impact on the capacity of mDC to prime and stimulate antigen-specific T lymphocytes, although more work in this area is urgently needed. The HIV protein Nef down-modulates MHC-I molecules on the surface of DC, which impacts antigen presentation to CD8+ T lymphocytes. Nef also specifically inhibits cytotoxic T cell lysis of infected CD4+ T lymphocytes and DC.84-86 Furthermore, Nef specifically restricts the peptides being presented by MHC-II molecules, thereby inhibiting CD4+ T lymphocyte activation through antigen presentation.87 There is also evidence that DC from HIV infected individuals have a reduced capacity to stimulate naïve CD4+ T lymphocytes.40 DC taken from lymph nodes of HIV infected individuals have decreased expression of co-stimulatory markers CD80 and CD86,88 and splenic DC have decreased expression of the maturation marker CD83,89 potentially providing a link between a lack of DC maturation and an inability of mDC to stimulate T cells. HIV-specific CD4+ T cell proliferation is substantially impaired in infected patients during early stages of infection,90 but whether suppressed mDC function plays any part in this failure of CD4+ T cell function has yet to be explored.

Potential Involvement of mDC in Imbalance between Regulatory T Cells and TH17 Cells

The literature on whether induction of regulatory T cells (Treg) is beneficial or detrimental to HIV disease outcome is conflicting. Natural SIV infection of African green monkeys reveals an early induction of Treg including TGF-β and IL-10 elevations during acute infection.91 Data in pathogenic SIV infection of macaques is conflicting, as Treg depletion92 and accumulation93 have both been reported. In HIV-infected individuals depletion of Treg results in a greater anti-HIV-specific immune response, thus suggesting that Treg suppress the normal anti-HIV response and promote persistence of viremia.94-96 In contrast, premature induction during acute infection and accumulation of Treg in lymphoid tissue and mucosal tissue during chronic infection is found in rhesus macaques and humans.97-99 Moreover, the products of Treg induction including TGF-β and indoleamine 2,3-dioxygenase are more abundant in the tonsils of untreated HIV infected individuals100 and in the spleen and gut mucosa of progressively infected macaques.101 This accumulation could lead to immune suppression, thus inhibiting an appropriate response to HIV and opportunistic diseases.

HIV causes semi-mature, pro-apoptotic mDC to accumulate in lymph nodes102-104 and these cells are implicated in inducing Treg. In addition, recent advancements in the research of the gut mucosa in the small intestine of mice reveal a population of CD103+ mDC that are particularly suited for inducing Treg and this is further confirmed in the mesenteric lymph nodes of humans.105 CD103+ DC are lost from the gut mucosa in SIV-infected macaques, providing a potential mechanism for disruption to Treg induction.107 However, the issue is likely to be complicated, as while mature mDC from mesenteric lymph nodes of SIV infected rhesus macaques can stimulate Treg, this is unrelated to expression of CD103.108 Found in the gut mucosa and opposing Treg in the balance between regulation and inflammation, TH17 CD4+ T lymphocytes function to promote inflammation to fight infection of bacteria and fungi.109,110 An imbalance of TH1 and TH17 cell types noted in pathogenic SIV infection, which is absent in nonprogressive disease models, is implicated in the loss of integrity of the gut mucosa,110-112 and this in turn could contribute to microbial translocation, persistent plasma lipopolysaccharide, and immune activation.110 Whether DC found in the gut mucosa of humans and nonhuman primates...
are linked with direct T₃₁⁷ induction, and whether this is altered in HIV and SIV infection, remains to be determined.

**Conclusions and Future Perspectives**

As summarized in Figure 1 and discussed throughout this review, mDC functions after HIV and SIV infection can have opposing contributions to disease control or progression. For several functions of mDC the impact of HIV and SIV infection are yet to be fully determined. Continued studies in HIV infected individuals and particularly in nonhuman primates with progressive and non-progressive SIV infection may reveal insights into the more favorable actions of mDC that may limit virus burden and immune activation and promote T cell immunity. A more complete understanding of mDC biology may also lead to development of therapeutics designed to either enhance or suppress aspects of the mDC response to ultimately control HIV and SIV infection.

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