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A dendrite in every pie
Myeloid dendritic cells in HIV and SIV infection

Elizabeth R. Wonderlich[1,2] and Simon M. Barratt-Boyes[1,2,3,*]

[1]Center for Vaccine Research; University of Pittsburgh; Pittsburgh, PA USA; [2]Department of Infectious Diseases and Microbiology; University of Pittsburgh; Pittsburgh, PA USA; [3]Department of Immunology; University of Pittsburgh; Pittsburgh, PA USA

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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,[1,2] which differentiate from precursors found in the bone marrow and inhabit the periphery as immature cells.[3] 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.[1,2,4] 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.[1] 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.[2]

The effects of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection on pDC have been the focus of multiple reviews,[5-9] 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,[10-18] and comparing pathogenic and nonpathogenic nonhuman primate models of SIV infection can reveal insights into its cause.[19-21] 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.[22,23] 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.[22,24-27] 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.[4,28-33] 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.

*Correspondence to: Simon M. Barratt-Boyes; Email: smbb@pitt.edu
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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.[34-38] However, in the absence of direct infection, DC may form conjugates with T lymphocytes and facilitate their infection.[39] 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.[40] 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 if mDC do contribute to virus dissemination it is through these indirect mechanisms.[41] 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.[42] 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.[42]

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.[43-46] 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.[47] 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 8–12 weeks of ART increases the number of circulating mDC in infected individuals.[48,49] In conflicting studies, mDC populations were only partially recovered after 6–12 mo[50] or 2 years of ART.[51]

Longitudinal studies of circulating and tissue mDC cell counts after SIV infection in rhesus macaques reveal a marked depletion in progressively infected macaques[33,52,53] and ART significantly increases mDC circulating cell counts within 8 weeks of beginning the regimen.[53] Moreover, a link is evident between the rate of disease progression and the numbers of mDC found in the blood. This is observed in rapidly progressing HIV-infected patients that experienced low mDC frequencies despite ART as compared with long-term non-progressing patients that had elevated numbers of mDC.[54] In the blood of SIVmac251-infected rhesus macaques, low mDC frequencies at viral set point predicts rapidly progressing disease.[55] 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.[53] These studies indicate that mDC presence during infection could aid in controlling infection or may be a marker of a more fully constituted immune system.

It had been hypothesized that mDC are lost from circulation because they become infected by HIV and SIV and apoptose,[37] 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,[41] 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.[50,56] 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.[53] Furthermore, HIV is linked with imbalanced cytokine secretion in lymphatic tissue that causes increased cellular recruitment and retention leading to lymphadenopathy.[57]

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.[58] mDC can detect bacterial and viral infection through the expression of TLR 1, 2, 3, 4, 5, 6 and 8,[59,60] with TLR8 serving as the principle receptor for HIV single stranded RNA.[61,62] 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,[63] 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,[64] 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.[65] Because viremia in patients is positively correlated with TLR expression and ART is able to return TLR mRNA levels to normal,[66] the presence of HIV may be making mDC hypersensitive to TLR agonists. Increased spontaneous production of cytokines by mDC from HIV infected patients[67,68] 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

TLR7/8 agonists during primary and late stage HIV infection,[69,70] and throughout SIV infection and disease.[53] Importantly, this hyper-responsive phenotype is reversible with 12 weeks of ART in progressively infected rhesus macaques,[53] which may suggest that the presence of viremia may be causing hypersensitivity to viral RNA.

However, many of these studies have used ex vivo stimulation of mDC with potent synthetic agonists as opposed to biologically relevant TLR agonists such as viruses. We have used physiologically relevant stimuli to examine mDC function in SIV-infected macaques, including influenza virus and uridine-rich sequences of single stranded RNA from SIVmac251, based on similar approaches with HIV.[61] We found that mDC isolated from the blood and lymphatic tissue during acute SIVmac251 infection were hyper-responsive to both influenza virus and SIV-derived ssRNA oligonucleotides. We also discovered that mDC from SIV-infected macaques with progressive disease or stable infection had divergent responses, being hypo-responsive and hyper-responsive, respectively, to SIV-derived TLR8 agonists (Wonderlich and Barratt-Boyes, unpublished data). These studies using virus-encoded TLR ligands indicated that increased mDC function in SIV infection may in fact be beneficial.

Interestingly, different TLR pathways in DC are affected by HIV infection differently, as TNF-α production by mDC in response to TLR8 stimulation is directly correlated with viral load whereas TLR2 responses appear unaffected.[69] In addition, HIV infection does not interrupt ex vivo responsiveness to the TLR3 stimulant poly I:C.[68]

Changes in the innate immune sensing ability of mDC could have far reaching effects on stimulating effecter cells of the immune system, such as mDC's ability to directly activate natural killer cells (NK) to proliferate, secrete IFN-γ and cause 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 T_H17 Cells

The literature on whether induction of regulatory T cells (T_{reg}) is beneficial or detrimental to HIV disease outcome is conflicting. Natural SIV infection of African green monkeys reveals an early induction of T_{reg} including TGF-β and IL-10 elevations during acute infection.[91] Data in pathogenic SIV infection of macaques is conflicting, as T_{reg} depletion[92] and accumulation[93] have both been reported. In HIV-infected individuals depletion of T_{reg} results in a greater anti-HIV-specific immune response, thus suggesting that T_{reg} suppress the normal anti-HIV response and promote persistence of viremia.[94-96] In contrast, premature induction during acute infection and accumulation of T_{reg} in lymphoid tissue and mucosal tissue during chronic infection is found in rhesus macaques and humans.[93,97-99] Moreover, the products of T_{reg} induction including TGF-β and indoleamine 2,3-dioxygenase are more abundant in the tonsils of untreated HIV infected individuals[100] 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 nodes[102-104] and these cells are implicated in inducing T_{reg}. 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 T_{reg} and this is further confirmed in the mesenteric lymph nodes of humans.[105,106] $CD103^+$ DC are lost from the gut mucosa in SIV-infected macaques, providing a potential mechanism for disruption to T_{reg} 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 T_{reg}, this is unrelated to expression of CD103.[108] Found in the gut mucosa and opposing T_{reg} in the balance between regulation and inflammation, T_H17 $CD4^+$ T lymphocytes function to promote inflammation to fight infection of bacteria and fungi.[109,110] An imbalance of T_H1 and T_H17 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 T_H17 induction, and whether this is altered in HIV and SIV infection, remains to be determined.

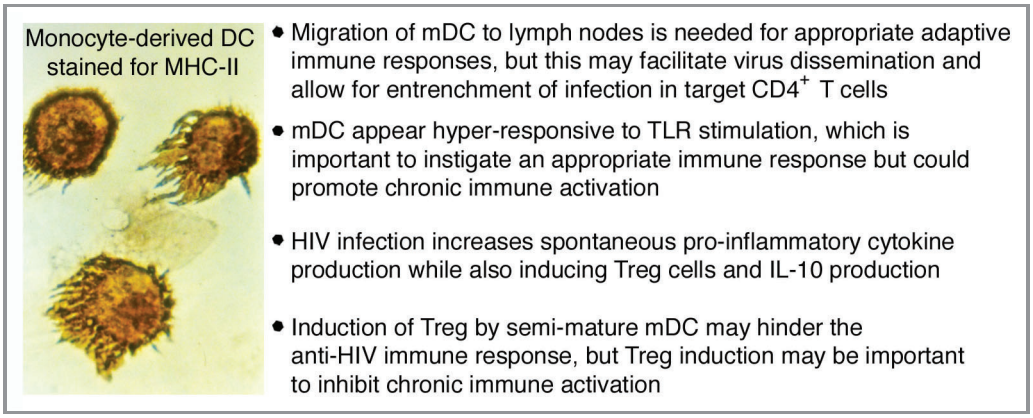

Figure 1. Opposing capacities of mDC influence HIV and SIV immunity.

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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