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Dissecting the role of dendritic cells in simian immunodeficiency virus infection and AIDS

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Abstract

Human immunodeficiency virus (HIV) infection is associated with the loss of the two principal types of dendritic cell (DC), myeloid DC (mDC) and plasmacytoid DC (pDC), but the mechanism of this loss and its relationship to AIDS pathogenesis remain ill-defined. The nonhuman primate is a powerful model to dissect this response for several reasons. Both DC subsets have been well characterized in nonhuman primates and shown to have strikingly similar phenotypic and functional characteristics to their counterparts in the human. Moreover, decline of mDC and pDC occurs in rhesus macaques with end-stage simian immunodeficiency virus (SIV) infection, the model of HIV infection in humans. In this brief review, we discuss what is known about DC subsets in pathogenic and nonpathogenic nonhuman primate models of HIV infection and highlight the advances and controversies that currently exist in the field.

Keywords

Innate immunity; Nonhuman primate; Lymphoid tissue; In vivo; Pathogenesis

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Nonhuman primate models of human immunodeficiency virus infection

Nonhuman primate models are invaluable for advancing our understanding of virus–host interactions and disease pathogenesis, and none has been more informative in this regard than the simian immunodeficiency virus (SIV) model of human immunodeficiency virus (HIV) infection. Experimental SIV infection of rhesus macaques and other Asian nonhuman primate species results in progressive disease similar to HIV infection in humans, although with an accelerated course of decline; SIV infection of rhesus macaques is therefore a key model to study AIDS pathogenesis [1–5]. In contrast, SIV infection in "natural" African nonhuman primate hosts of SIV, such as the African green monkey and sooty mangabey, is nonpathogenic, and disease does not generally develop despite productive virus replication. This model has therefore been useful to dissect the mechanisms of disease control [6–9]. Acute SIV infection in both pathogenic and nonpathogenic models is defined by a rapid and strong type I interferon (IFN) response, similar to that observed in HIV-infected humans [10–12]. However, SIV-infected African green monkeys quickly and efficiently resolve this response, whereas SIV-infected rhesus macaques do not [8, 13–16]. Thus, development of AIDS in progressive disease models has been linked to continuous activation of the innate immune system during chronic infection [17, 18]. Indeed, chronic activation of the immune system is a reliable predictor of disease progression in both HIV-infected humans and SIV-infected macaques [19–22]. Because of the central role that dendritic cells (DC) play in the innate response to pathogens, these cells have recently come under the spotlight as potentially mediating chronic immune activation, but the picture is far from clear.

Identification and characteristics of DC in the primate

DC are antigen-presenting cells (APC) that form an indispensible bridge between the innate and adaptive immune responses. Human DC are grouped into two major subsets: myeloid DC (mDC) and plasmacytoid DC (pDC) [23]. Similarly, in rhesus macaques and other nonhuman primate species, we and others have identified mDC and pDC in blood, lymphoid tissues, and mucosal tissues [11, 24–29]. mDC are classically defined in monkey blood as MHC-class II + CD11c + CD123− cells lacking expression of the lineage markers CD3, CD14, and CD20, whereas pDC are identified as Lin–MHC-class II + CD123 + CD11c−, similar to the phenotype in humans [24, 26, 30]. Rhesus macaque mDC and pDC also have distinct morphologies, as is clear on cytospins of sorted cells (Fig. 1) [26]. Both cell types are resident in lymphoid tissues in the steady state, but during an inflammatory response, pDC and mDC are actively recruited to these tissues [31–33]. Recruitment of mDC is mediated by CCR7-CCL19/CCL21 interactions, whereas recruitment of pDC to inflamed lymph nodes is CXCL9- and E-selectin-dependent [32, 34]. An identifying feature of the pDC response to virus exposure is the production of the antiviral cytokine IFN-α, and this characteristic is seen in both human and monkey pDC [26, 27, 35–38].

Chronic HIV and SIV infection and the DC response

Relatively early in the AIDS epidemic, it was appreciated that HIV infection disrupts DC homeostasis. During chronic HIV infection, pDC and mDC are lost from the blood, and this depletion correlates with high plasma viral load and low CD4 + T-cell counts [39–52]. We confirmed that SIV-infected rhesus macaques with end-stage disease also have DC loss from both blood and lymphoid tissues [25]. Depletion of blood pDC is not thought to occur in nonpathogenic models of SIV infection [38, 53], and elevated blood pDC counts have been noted in HIV-infected individuals that have controlled infection, so-called long-term nonprogressors [52]. However, the relevance of pDC loss to disease progression is unclear, as it was recently reported that HIV-2 infection of humans, which is significantly attenuated relative to HIV-1 infection, is nevertheless associated with a substantial depletion of pDC

from blood [54]. Whether mDC accumulate in or are lost from lymph nodes in chronic HIV infection prior to AIDS is also a matter of debate, as both increases and decreases have been reported [55–57].

We have recently addressed this issue in the pathogenic SIV model. We found that animals with long-term stable infection of more than 1 year had average increases in blood mDC of 200% over pre-infection levels at virus set point (8–12 weeks post-infection), whereas animals that progressed rapidly to AIDS within 32 weeks had significant loss of mDC at set point. Progressive infection was associated with increased expression of CCR7 on blood mDC and an eightfold increase in CCL19 expression in lymph node tissues, consistent with increased mDC recruitment that was nevertheless offset by increased apoptosis [58]. These data suggest that the inflamed lymph node serves as a sink for mDC in progressive SIV infection beginning relatively early in infection before disease manifests, consistent with a role in disease pathogenesis [59].

The DC response in acute SIV infection

Studies of DC kinetics in acute HIV infection have been slow to emerge, perhaps because at these early stages, the majority of patients are unaware of their infection status. We have taken advantage of the rhesus macaque/SIV model to begin to initially define the pDC response in acute SIV infection. We have combined absolute blood cell counts with 5-bromo-2′-deoxyuridine delivery in vivo to label recently divided cells that have been mobilized from bone marrow into blood and tissues (Fig. 1) [24, 60]. We found that as early as 3 days after intravenous virus inoculation, pDC experience a significant mobilization resulting in a three- to sevenfold increase in pDC in blood [60]. This mobilization may be related to a systemic surge in proinflammatory cytokines such as TNF-α [61], which in mouse models causes rapid pDC mobilization [32]. The increase in pDC in blood tapers rapidly, and by 14 days post-infection, blood and lymph node pDC are depleted to levels that inversely correlate with plasma viral loads. Interestingly, while the absolute number of pDC in lymph nodes decreased in acute infection, the proportion of lymph node pDC that had recently divided based on 5-bromo-2′-deoxyuridine incorporation increased 10- to 20-fold above that seen in uninfected monkeys [60]. These data indicate that pDC death exceeds recruitment within these tissues, a condition that is not consistent with a pathologic role for pDC in disease [62].

The mechanisms responsible for pDC and mDC loss are still under investigation. Research suggests that depletion of pDC in the blood could be caused by direct infection [63–65] or by apoptosis as a result of pDC fusing with HIV-infected cells [66]. We have studied DC infection during the acute phase of SIV infection of macaques when virus load in blood and lymph nodes is at its peak. We found that lymph node mDC had a negligible level of infection, whereas around 4% of pDC were productively infected, based on a quantitative PCR assay for proviral DNA in sorted cells [60]. This frequency of pDC infection in vivo is not likely to account for the substantial cell loss seen at the same time. Interestingly, lymph node pDC uniformly upregulated expression of CD95 in lymph nodes at day 14 post-infection, and death of cells could potentially result from engagement of this receptor by ligands expressed in inflamed lymph nodes [60].

Effect of infection on DC maturation and its consequences

In addition to quantitative changes that have been observed in the blood and lymph nodes, disturbances in the quality of DC have also been reported. HIV infection causes pDC to have a diminished ability to migrate toward the CXCR4 ligand, CXCL12, while mDC retain their migratory ability [56]. HIV and SIV infection is associated with increased expression of immunostimulatory molecules CD40, CD80, and CD86 on mDC [39, 58] as well as the

regulatory molecule B7-H1, the ligand for PD-1 that is concomitantly upregulated on T cells [29].Expression of PD-1 on virus-specific T cells is associated with disease progression in HIV infection of humans [67]. Interestingly, we have observed that mDC from lymph nodes of macaques with stable long-term SIV infection have a less-activated, semi-mature phenotype relative to progressive infection or naïve individuals [58]. Semi-mature DC isolated from HIV-infected lymph nodes have been shown to induce CD4 + FoxP3 + T regulatory cells (Treg) in vitro [57]. Similarly, HIV-activated pDC stimulate Treg in vitro [68]. These effects have been interpreted as an immunosuppressive function that could dampen HIV immunity. Consistent with this possibility, increased proportions of FoxP3 + CD4 + T cells have been noted in progressive HIV infection [69]. However, in pathogenic SIV infection, we have noted a loss of Treg, which correlated with immune activation in vivo [70], and others have defined only a transient and delayed Treg response in pathogenic SIV infection as opposed to nonpathogenic infection of African green monkeys, associated with an imbalance with Th17 cells [71]. The capacity for DC to induce Treg or alternatively to polarize CD4 + T cells into Th1, Th2, or even Th17 cells and its relationship to early pathogenesis are a significant issue that needs to be addressed.

Friend or foe: the innate immune response to HIV and SIV infection

pDC and mDC express distinct arrays of the Toll-like receptor (TLR) family of pattern recognition receptors, with pDC expressing TLR7 and TLR9 and mDC expressing TLR2, TLR3, TLR4, TLR5, TLR6, and TLR8 [72, 73]. Endocytosed HIV has been shown to directly activate pDC through TLR7 recognition of the viral RNA genome, leading to the production of IFN-α [74]. HIV particles do not appear to directly stimulate TLR8 in mDC; however, HIV-encoded TLR8 agonists are effective inducers of proinflammatory cytokines in these cells, suggesting mDC are susceptible to HIV-mediated activation [75, 76]. Whether DC activation is beneficial or deleterious in HIV infection is still a matter of debate [77, 78], and there are many downstream consequences of activation and recruitment that could conceivably lead to widely different clinical outcomes (Fig. 2).

pDC and pDC-derived IFN-α have a well-established role in the control of virus infection including HIV-1 (the latter demonstrated in vitro) [66, 79–82]. Our preliminary data indicate that pDC are recruited and accumulated within gut and lung mucosal tissues in acute infection (M. Kader and Z. Swan, unpublished data) where they could serve an antiviral function, as with other viral infections [80, 81]. In contrast, it has been suggested that continual IFN-α production by persistently stimulated pDC could cause chronic immune activation and subsequent dysfunction [18, 38, 83, 84]. Furthermore, products of the IFN-signaling pathway remain elevated throughout chronic infection, associated with increased CD4 + T-cell activation and apoptosis [85]. HIV appears to induce persistent pDC activation in vitro [86], and pDC derived from women (who progress more rapidly to AIDS than do men at a given virus load [87–89]) produce more IFN-α in response to HIV-1-derived TLR7 ligands [90]. Again, this is a controversial issue, as therapy with IFN-α has been shown to have a beneficial effect in chronic HIV infection, significantly reducing virus loads [91]. pDC have also been shown to induce immunosuppressive effects by expressing the tryptophan-catabolizing enzyme, indoleamine-pyrrole 2,3-dioxygenase (IDO) [17]. IDO has been shown to be immunosuppressive by inhibiting expansion of activated T cells [92] and furthermore by influencing naïve CD4 + T cells to become regulatory T cells [93]. In HIV-infected patients, high plasma levels of IDO correlate with increased plasma viremia and inhibit maturation of bystander mDC [94], suggesting that pDC activation is causing adaptive immune system suppression and inhibiting further antigen presentation.

Differential effects of infection of pDC and mDC responsiveness to stimulation

In vitro, DC that are activated for the first time with TLR agonists have a robust ability to induce Th1 polarization (production of IFN-γ), whereas cells that are repeatedly stimulated exhibit “exhaustion” which is reflected in Th2 polarization (production of IL-4) or nonpolarization [95–97]. Likewise, pDC from chronically HIV-infected individuals have been shown to be refractory to ex vivo stimulation with either ssRNA or HSV DNA [41, 48, 98]. These data suggest that pDC are bombarded with activating agonists leading to a chronic state of stimulation [99, 100], suggesting an exhausted, refractory phenotype, which could lead to impaired stimulation of Th1 responses and a preferential induction of Th2 responses. In contrast, mDC have been shown to remain relatively functional at producing proinflammatory cytokines in HIV infection [101, 102] and inducing a repertoire of NK-cell functions [103]. Our preliminary studies in SIV-infected macaques are consistent with this finding. We find that mDC remain responsive to virus-encoded TLR agonists in acute infection, while pDC and monocytes become rapidly refractory. Moreover, continued hyper-responsiveness of mDC appears to be linked with long-term stable infection, whereas mDC isolated from monkeys that progress rapidly to AIDS have reduced responsiveness at an earlier stage (E. Wonderlich, unpublished data). The relationship between mDC activation and disease control is an active area of investigation.

Summary

While considerable advances have been made to define the role of DC in HIV pathogenesis, the fundamental question of whether the DC response is good or bad remains unanswered. Clarity on this topic is essential if we are to effectively intervene in the innate response to the betterment of HIV-infected individuals. Studies in the nonhuman primate models of SIV infection, both pathogenic and nonpathogenic, have provided key insight into the DC response and its relationship to AIDS pathogenesis. We believe the ensuing years will see continued contributions of this model in defining the contribution of the different DC subsets to virus control and disease progression.

Biography

Simon M. Barratt-Boyes

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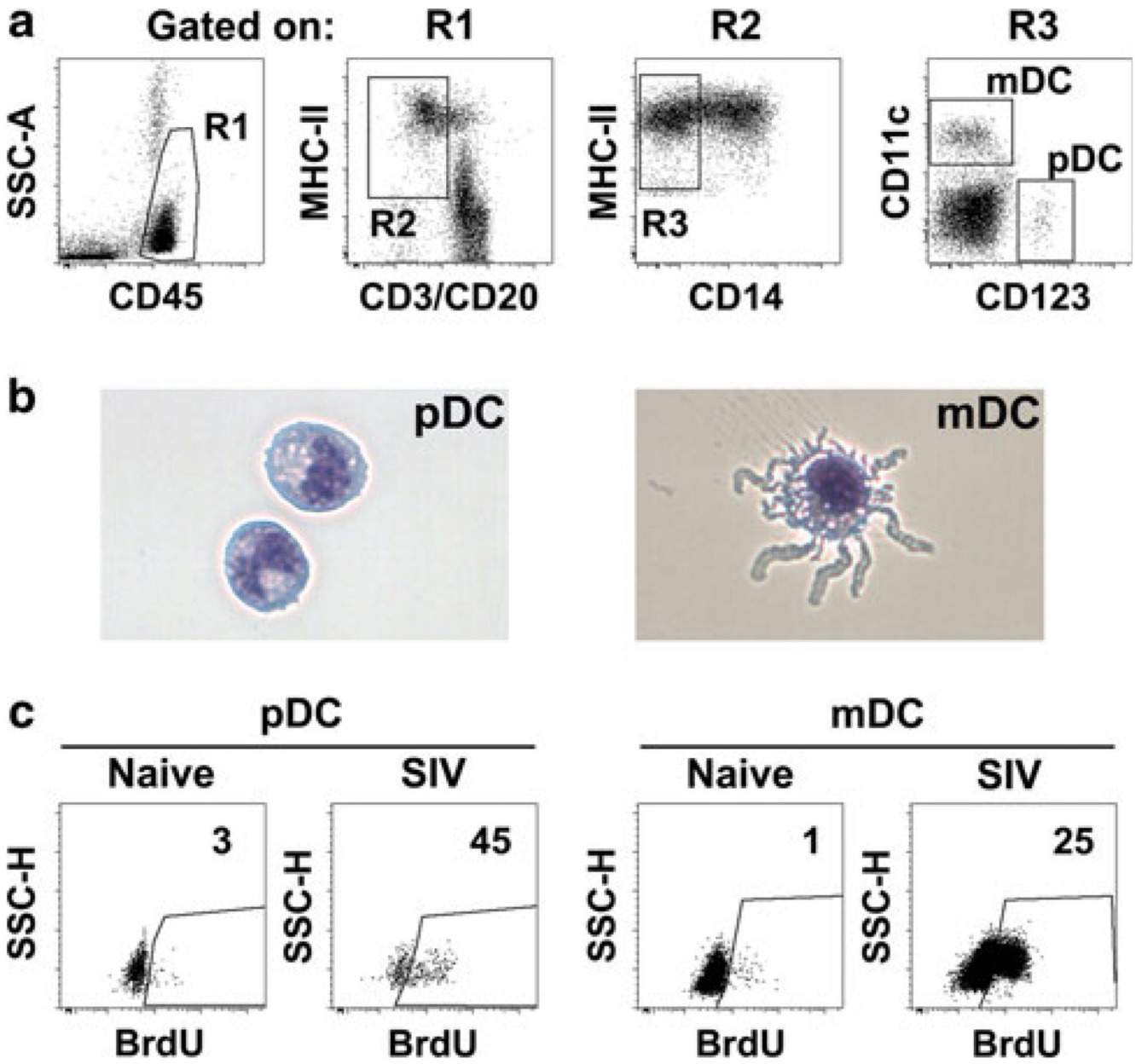

Fig. 1.

Dendritic cell identification in rhesus macaques. **a** Representative flow cytometry dot plots revealing the gating strategy used to define pDC and mDC within peripheral blood mononuclear cells of an SIV-naïve macaque. **b** Representative images of pDC and mDC sorted from lymph node cell suspensions of a rhesus macaque. Cells have been stained with modified Wright–Giemsa. **c** Representative dot plots demonstrating increased blood pDC and mDC incorporation of 5-bromo-2′-deoxyuridine in vivo in acute SIV infection of rhesus macaques relative to pre-infection. *Numbers* represent percentage of cells in the indicated gate

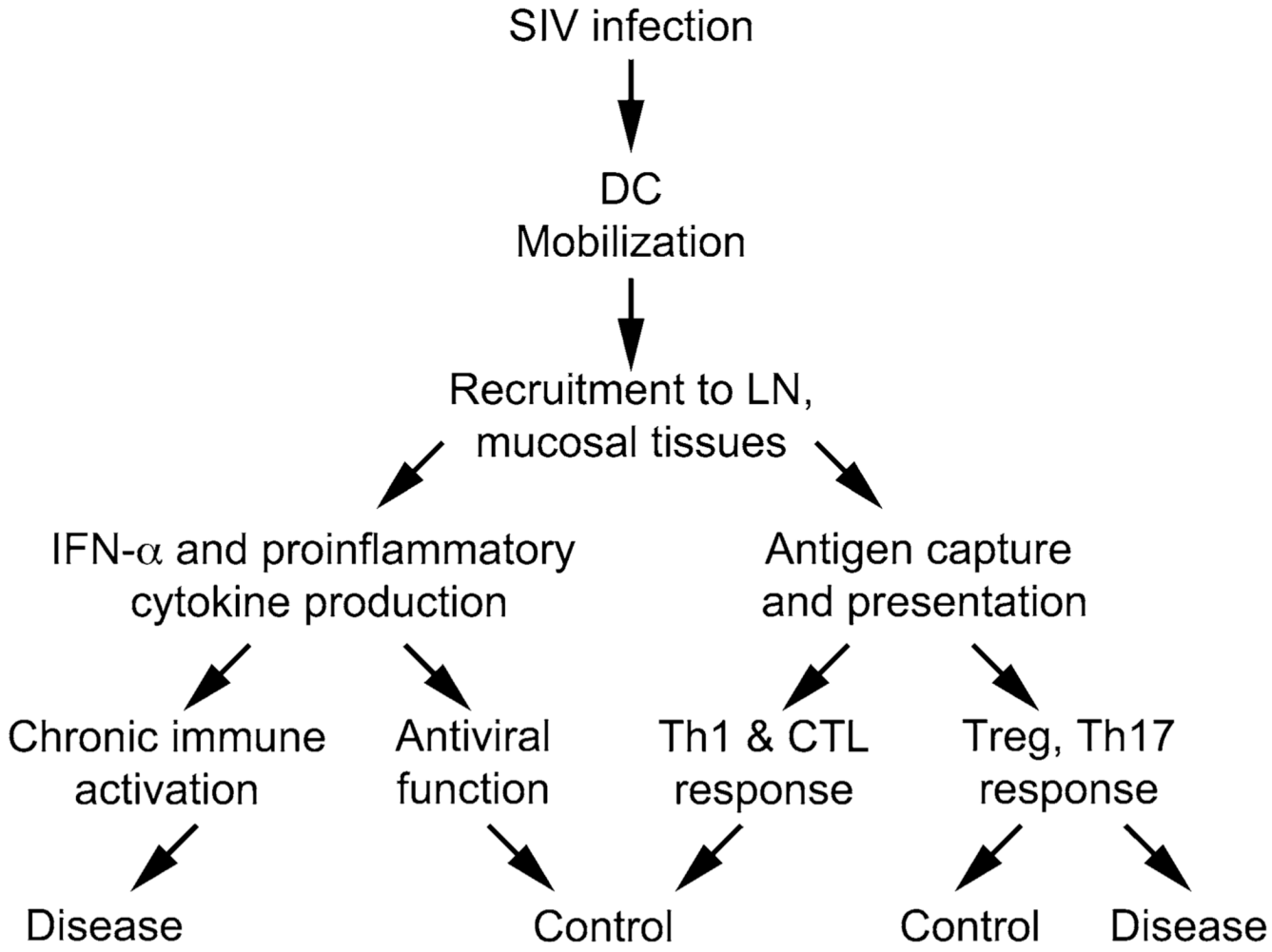

Fig. 2.

Potential beneficial and detrimental outcomes of the DC response to SIV infection. The mobilization and recruitment of DC to lymph nodes and mucosal tissues could be related to beneficial immune responses, which could control virus replication and mitigate disease progression. In contrast, chronic stimulation of DC and subsequent cytokine production could promote disease development through establishment or maintenance of deleterious chronic immune activation