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A divergent myeloid dendritic cell response at virus set-point predicts disease outcome in SIV-infected rhesus macaques

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Abstract

Background—The mechanism for loss of myeloid dendritic cells (mDCs) from the circulation in HIV-infected individuals and its relationship to disease progression is not understood.

Methods—A longitudinal analysis of the mDC response in blood and lymph nodes during the first 12 weeks of infection was performed in a cohort of SIVmac251-infected rhesus macaques with different disease outcomes.

Results—Monkeys that rapidly progressed to disease or had long-term stable infection had significant losses or increases, respectively, in blood mDCs that were inversely correlated with virus load at set-point. The loss of mDCs from progressor animals was associated with evidence of an increase in CCR7-CCL19 dependent mDC recruitment to lymph nodes and an increase in mDC apoptosis.

Conclusions—mDC recruitment to and death within inflamed lymph nodes may contribute to disease progression in SIV infection, whereas mobilization without increased recruitment to lymph nodes may promote disease control.

Keywords

nonhuman primate; AIDS; cell dynamics; innate immunity

Introduction

Dendritic cells (DCs) are a heterogeneous family of innate immune system cells that secrete antiviral cytokines and induce adaptive immune responses to viral infections including HIV [33]. It has long been appreciated that DCs are lost from the blood of individuals with progressive HIV infection associated with an increase in virus load, whereas long-term non-progressors that control infection have relatively normal levels of blood DCs [1, 4, 12, 19, 22, 26, 31, 39, 44, 49]. Similarly, depletion of blood DCs has been described both in acute and end-stage SIV infection of rhesus macaques [9, 10]. These data support the long held notion that DCs are beneficial in HIV infection and that their loss compromises viral immunity and promotes disease progression [46]. However, recent comparative studies have demonstrated that SIV infection of African nonhuman primate species, which is generally nonpathogenic, is characterized by rapid resolution of innate immune responses, whereas

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progressive infection of rhesus macaques is characterized by persistent innate immune activation [7, 29, 34]. These and other studies [42, 43] suggest that chronic activation of innate immune cells plays a role in AIDS pathogenesis and have led to the hypothesis that the DC response may be pathologic depending on the stage of infection [6, 21, 28]. These contrasting roles of DCs either in facilitating control of virus infection or promoting disease progression have yet to be resolved and remain an important issue in the field.

While several recent studies have focused on the plasmacytoid DC (pDC) response in blood and tissues [10, 11, 27, 36, 41, 42], relatively little is known about the dynamics of the myeloid DC (mDC) response to HIV and SIV infection. A critical issue is the fate of mDCs that are lost from blood during progressive infection. In vitro studies with HIV and purified DC populations support the hypothesis that mDCs are activated via interaction with activated pDCs which leads to their recruitment to lymph nodes through increased chemotaxis [23]. However, findings relating to mDC in lymph nodes during HIV infection are inconsistent, with both accumulation and substantial loss being reported [5, 17, 32, 37]. mDCs are depleted from lymph nodes in rhesus macaques with end-stage SIV infection [9, 56], but data in the acute and chronic stages of infection in this tissue compartment are lacking. What is needed is a comprehensive study of the kinetics of the mDC response to infection in blood and tissues over time, but reports of this nature are absent from the literature. These studies are difficult to undertake in HIV-infected humans but are feasible and justifiable in nonhuman primates with SIV infection.

We have previously reported on an adenovirus-based immunotherapy study in rhesus macaques infected with SIVmac251 that was effective at boosting the strength of virus-specific T cell immunity but which had no discernable impact on virus load or disease outcome [48]. In a recent follow-up study [53] we found that monkeys in this cohort had differential survival and disease that was independent of immunotherapy but correlated with virus load at set-point, prior to any therapeutic intervention. Here we describe the dynamics of the mDC response to SIV infection up to virus set-point in this cohort that has allowed us to better define the relationship between mDC and disease progression and control.

Materials and methods

Animals, virus infection and therapy

21 adult Indian-origin rhesus macaques (*Macaca mulatta*) used in this study were enrolled in an immunotherapy trial the majority of which has been reported elsewhere [48]. Animals were infected by intravenous inoculation with 1,000 $TCID_{50}$ of uncloned, pathogenic SIVmac251. Animals were given two intervals of antiretroviral therapy (ART) beginning at week 12, and intramuscular injections of adenovirus serotype 5 and 35-based vaccines beginning at week16, as detailed elsewhere [48]. Analyses described here were done at or before 12 weeks post infection, prior to any therapeutic interventions.

Enumeration and characterization of cells by flow cytometry

Identification of mDCs was done by flow cytometric analysis following antibody staining of peripheral blood mononuclear cells (PBMCs) and lymph node cell suspensions as described [53]. mDCs were identified as cells lacking expression of lineage markers CD3 (antibody clone SP34-2), CD20 (2H7) and CD14 (M5E2) and expressing HLA-DR (G46-6) and CD11c (S-HCL-3) [8, 9]. mDCs were analyzed for activation by labeling with cross-reactive antibodies to CCR7 (150503), CD40 (5C3), CD80 (L307.4) and CD86 (FUN-1). Apoptosis was determined by labeling fixed and permeabilized cells with antibody to active caspase-3 (C92-605), as described [53]. The absolute number of blood $CD4^+$ T cells was determined using a precise volume of blood stained with antibodies to CD3 and CD4 in the absence of

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any wash step in tubes that contained a known number of fluorescent beads to provide internal calibration (TruCOUNT, BD Biosciences), as described [48]. The number of mDCs was calculated based on the ratio of mDCs to $CD4^+$ T cells in PBMC at the same time point. All flow cytometric analysis was performed on an LSR II cytometer with FACSDiva software (BD Bioscience).

Detection of chemokine expression in tissues

Lymph nodes were harvested at 12 weeks post infection and total RNA was isolated from cell suspensions. Real time PCR analysis of CCL19, CCL21 and β-glucuronidase was done using primers and probes from Taqman human gene expression arrays as described [53].

Results

Changes in blood mDCs but not $CD4^+$ T cells at set-point are predictive of disease outcome

Animals in this cohort were distinguished on the basis of disease progression, with one group of 11 monkeys remaining healthy until elective sacrifice at a mean of 60 weeks post infection (‘stable’ group) and the other group of 10 animals succumbing to AIDS-defining illnesses at a mean of 32 weeks (‘progressor’ group)[53]. This differential outcome was independent of immunotherapy and was inversely proportional to virus loads at set-point, defined as the mean plasma virus titers from weeks 8–12 post infection, consistent with previous reports [50, 52]. When we monitored mDC numbers in blood in these groups of animals over the first 12 weeks of infection, we found a divergent response. While both stable and progressor animals had an initial decline in circulating mDCs at week 2 post infection, progressor animals had a continued decline to week 12, whereas stable animals had a significant increase in the number of blood mDCs over this period [53]. When individual animals were evaluated over time we found that mDCs dropped to 30% of pre-infection levels in some progressor animals (mean=60%) but increased to nearly 500% in some stable animals (mean=206%). This change in the number of mDCs over the first 12 weeks of infection had an inverse relationship with virus load ($P = .0054$, $r = -.6264$). In contrast, changes in $CD4^+$ T cell counts over this time were not predictive of ultimate disease outcome [53]. These data suggest that a divergent mDC response in blood during primary infection predicts whether SIV infected animals go on to control infection or to progress rapidly to disease (Fig. 1).

Evidence for increased mDC recruitment and death in lymph nodes in progressive SIV infection

To investigate the dynamics of the mDC response further we first analyzed the phenotype of mDCs in blood. mDCs were rapidly activated following SIV infection regardless of outcome, with CD80 and CD86 expression on blood mDCs increasing by 2 weeks in all animals [53]. However, at 12 weeks post infection there was a differential expression of the chemokine receptor CCR7 on blood mDCs in the two groups, with substantially more upregulation on mDCs of animals in the progressor but not the stable group [53]. CCR7 is the ligand for chemokines CCL19 and CCL21 and mediates DC recruitment to lymph nodes [24]. To investigate whether these ligands were upregulated in lymphoid tissues we performed quantitative analyses of mRNA. Expression of CCL19 in lymph node cell suspensions was 8-fold greater in monkeys with progressive infection relative to naive animals as determined by real time PCR, whereas expression in stable animals was unchanged. Minor differences were noted in expression of CCL21 [53]. These findings raise the possibility that the loss of mDCs from blood in progressor animals could be the result of enhanced recruitment to lymph nodes via CCR7-CCL19 interactions. Surprisingly, there was no difference in the proportion of mDCs in lymph nodes are week 12 post infection in

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either stable or progressor animals relative to uninfected monkeys, although mDCs from progressor animals had increased apoptosis based on expression of active caspase-3 [53]. The overall findings from the study are summarized in Table 1. The data are consistent with an increase in mDC recruitment from blood to inflamed lymph nodes in progressive SIV infection that is offset by an increase in cell death within tissues.

Discussion

The loss of mDCs from blood in HIV-infected individuals was first reported more than 20 years ago [39], yet the mechanism for this loss and its relationship to disease progression remain unclear. SIV infection of rhesus macaques provides a powerful model to understand mDC depletion in HIV infection, as mDCs in this species are similar to mDCs in humans [8, 14], and the pathobiology and clinical syndrome associated with SIV and HIV infection are analogous, although the disease course of SIV infection in macaques is accelerated [35]. We have used this model to monitor the mDC response to infection with a pathologic isolate of SIV in animals that have divergent disease outcomes. Our data reveal that readily discernable differences in the kinetics of the blood mDC response occur early in the course of infection that reflect whether animals will have long-term stable infection without disease or will progress relatively rapidly to AIDS. The finding that the mDC response in both blood and tissues differs from a relatively early stage as a function of disease outcome may help to explain the apparent inconsistencies in the literature regarding mDC dynamics in HIV and SIV infection (Table 2).

In all animals in our study SIV infection rapidly led to activation of blood mDCs based on increased expression of costimulatory molecules, consistent with previous reports in HIV infection [4, 26, 30]. However, only in progressor animals were there substantial increases in the proportion of blood mDCs expressing CCR7 together with an increase in the corresponding ligand CCL19 in lymph nodes. Increased lymph node expression of homeostatic chemokines including CCL19 has been described previously in SIV-infected lymph nodes, although a distinction was not made between stable and progressive infection [13]. Interestingly, increased expression of CCL19 and CCL21 has been detected in serum of HIV-infected patients and shown to be correlated with virus load and disease progression [15]. Whether these systemic increases in chemokines are reflective of even greater increases in lymphoid tissues in HIV-infected individuals is not known. Collectively, the data suggest that in progressive SIV and HIV infection mDC migration from blood to lymph nodes is promoted by an increase in the CCR7/CCL19 axis. Within inflamed lymph nodes, mDCs are prone to undergo apoptosis through an indirect mechanism that may involve the CD95-CD95 ligand pathway [53]. Direct infection is unlikely to be a contributing factor as negligible numbers of lymph node mDCs contain proviral DNA [10]. The lymph node in progressive infection therefore has a sink effect, continuously pulling in mDCs that rapidly die. These changes in mDC occur prior to disease progression raising the possibility of a causal relationship between mDC decline and disease development, although this has not formally been shown.

In contrast to progressive SIV infection, animals with long-term stable infection had a steady increase in blood mDCs over time that was associated with a lack of high-level expression of CCR7 and homeostatic expression of CCL19 in lymph nodes. Coupled with evidence of increased production of mDCs in bone marrow in acute infection (Wijewardana and Barratt-Boyes, unpublished data), these findings suggest that mDCs are mobilized in SIV infected monkeys with relatively low virus loads and build up in blood due to the absence of any increased recruitment to tissues. Similarly, in SIV infection of cynomolgus macaques, which is less pathogenic than the SIV/rhesus macaque model, an increase in circulating mDCs has been noted [40]. It is interesting to speculate that the increased level

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of mDCs in blood could be a factor in the establishment of more effective T cell responses to opportunistic infections in stable infection.

There are several outstanding questions that remain to be answered before we fully understand the nature of the mDC response during SIV and HIV infection. One consistent finding is that lymph node mDCs in HIV infection have a relatively immature phenotype with lower level expression of costimulatory molecule expression than lymph nodes from naïve individuals [17, 32]. We also found lymph node mDCs that are relatively immature with lower expression of MHC class II, CD40, CCR7 and CD86 relative to naïve monkeys, but interestingly this phenotype was restricted to animals with stable infection rather than progressive infection [53]. This restriction implies that reduced activation of lymph node mDCs may be beneficial in SIV infection. The function of immature mDCs in HIV-infected lymph nodes is not known, but there is evidence that these cells may preferentially activate regulatory T cells [32]. Such regulatory T cells could reduce the function of virus-specific T cells but could also contribute to control of immune activation which is a hallmark of nonpathogenic SIV infection [7, 29].

A second unanswered question is whether mDC recovery in progressive SIV and HIV infection can be promoted by ART. Data on the efficacy of ART in HIV infection are contradictory, with numerous reports indicating positive effects on mDC recovery [2, 4, 12, 20, 25] and still others indicating that ART has no beneficial effect on mDC dynamics [3, 22, 44]. Our own investigations into the impact of ART on mDC responses in SIV infection indicate that ART given at 12 weeks post infection promotes recovery of blood mDCs in progressor animals and stabilizes the number of blood mDCs animals that control infection [53]. These findings need to be verified but imply that ART may have differential effects on mDCs depending on disease severity.

These studies highlight the value of the nonhuman primate model in dissecting the DC response to HIV infection and defining the DC's role in disease control or progression. Continued studies in this model are likely to provide a better understanding of the nature and function of immature mDCs in stable SIV infection, the potential effects of ART on mDC recovery and the role of mucosal tissues in mDC recruitment and loss. The most informative approaches are likely to utilize attenuated virus strains as well as well-defined cohorts of non-progressive and progressive infection with a single pathogenic virus. Studies in nonpathogenic hosts such as the African green monkey and sooty mangabey are likely to also contribute to our understanding of DC biology in HIV infection in the near future.

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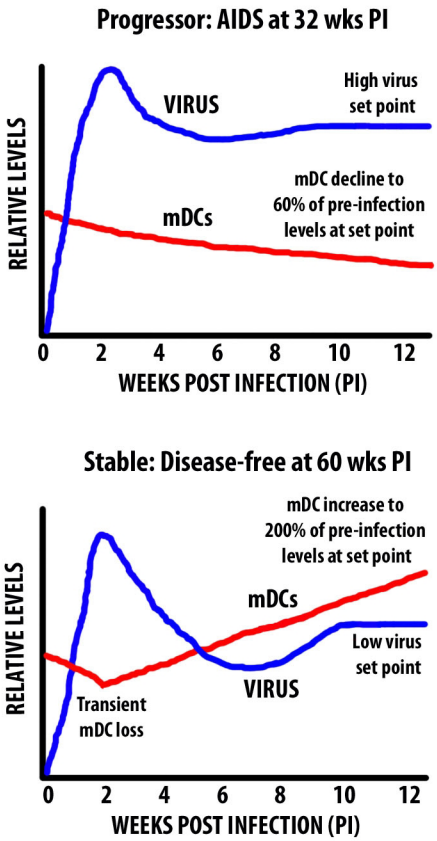

Figure 1.
Relationship between virus load and mDCs in blood in the early stages of SIV infection of monkeys with different disease outcomes.

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Table 1

Changes in mDCs and chemokines at virus set-point in SIV-infected rhesus macaques with different disease outcomes[1]

Parameter	Stable SIV infection[2]	Progressive SIV infection[3]
Number of mDCs in blood	Increased to ~200% of pre-infection levels[4]	Decreased to 60% of pre-infection levels
Activation of mDCs in blood	Minor increase in CCR7; CD80/86 elevated	Major increase in CCR7; CD80/86 elevated
Proportion of mDCs in lymph node	Similar to naïve	Similar to naïve
Activation of mDCs in lymph node	CCR7, CD40, CD86, MHC class II low	CCR7, CD40, CD86, MHC class II normal
Expression of CCL19 mRNA in lymph node	Similar to naïve	8-fold higher than naïve
Apoptosis of mDCs in lymph node	Similar to naïve	3-fold higher than naïve

[1] Data adapted from [53]

[2] Healthy at elective sacrifice at a mean of 60 weeks post infection (range 56 to 63 weeks)

[3] Sacrificed due to AIDS-defining illness at a mean of 32 weeks post infection (range 11 to 43 weeks)

[4] Blood mDCs in stable infection had initial decline at 2 weeks post infection

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Table 2

Impact of SIV and HIV infection on mDCs in vivo

Stage of infection	Tissue	Finding[1]	Reference(s)
Acute	Blood	Reduced mDCs in primary HIV infection and acute SIV infection of RMs	[39, 44, 45, 53]
	Lymph node	Evidence for mDC accumulation in HIV infection	[37]
Chronic	Blood	mDC depletion is inversely correlated with virus load in HIV infection	[1, 4, 12, 19, 22, 26]
		mDC from HIV-infected individuals have reduced allostimulatory function	[18, 38, 39]
		Evidence for mDC hyperresponsiveness to stimulation in HIV infection	[45]
		Increased mDC apoptosis in HIV infection	[16]
		mDC loss predicts disease progression in SIV-infected RMs	[53]
		mDC activation in HIV infection and SIV-infected RMs	[4, 26, 30, 53]
		mDC numbers unchanged in SIV-infected Chinese RMs	[53, 54]
		mDC increased in SIV-infected CMs and RMs with stable SIV infection	[40, 53]
		Increased expression of B7-H1 in HIV infection and SIV-infected RMs	[51, 55]
	Lymph node	Accumulation of partially activated mDCs in HIV infection and stable SIV infection of RMs	[17, 32, 53]
		Increased mDC apoptosis in progressive SIV infection of RMs	[53]
		mDC loss in HIV infection	[5]
		Increased tissue chemokine expression in progressive SIV infection of RMs	[13, 53]
		Evidence for increased mDC responsiveness in SIV-infected RMs	[53]
AIDS	Blood	Loss of mDCs in simian AIDS	[9]
	Lymph node	Apoptosis and loss of mDCs in simian AIDS	[9, 56]
		Impaired DC maturation in simian AIDS	[47]

[1] RM=rhesus macaque, CM=cynomolgus macaque