Dendritic Cell Immune Responses in HIV-1 Controllers

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Abstract

Purpose of Review—Robust HIV-1-specific CD8 T cell responses are currently regarded as the main correlate of immune defense in rare individuals who achieve natural, drug-free control of HIV-1; however, the mechanisms that support evolution of such powerful immune responses are not well understood. Dendritic cells (DCs) are specialized innate immune cells critical for immune recognition, immune regulation, and immune induction, but their possible contribution to HIV-1 immune defense in controllers remains ill-defined.

Recent Findings—Recent studies suggest that myeloid DCs from controllers have improved abilities to recognize HIV-1 through cytoplasmic immune sensors, resulting in more potent, cell-intrinsic type I interferon secretion in response to viral infection. This innate immune response may facilitate DC-mediated induction of highly potent antiviral HIV-1-specific T cells. Moreover, protective HLA class I isotypes restricting HIV-1-specific CD8 T cells may influence DC function through specific interactions with innate myelomonocytic MHC class I receptors from the leukocyte immunoglobulin-like receptor family.

Summary—Bi-directional interactions between dendritic cells and HIV-1-specific T cells may contribute to natural HIV-1 immune control, highlighting the importance of a fine-tuned interplay between innate and adaptive immune activities for effective antiviral immune defense.

Keywords

HIV-1 controllers; Dendritic cells; Dendritic cell immune responses; CD8 T cells; HIV-1 immune defense

Introduction

Dendritic cells (DCs) represent a heterogeneous, multifunctional group of innate immune cells specializing in capturing and internalizing microbial pathogens and presenting foreign antigen to adaptive immune cells [1]. In addition, DCs also have important roles for regulating innate and adaptive effector immune cells through secretion of chemokines and

other soluble factors, for orchestrating and bridging innate and adaptive antimicrobial immunity and for direct killing and elimination of cells infected with microbes, specifically in the context of viral infections [2]. Circulating DCs can be subdivided in two main subgroups known as myeloid DCs (mDCs) and plasmacytoid (pDCs). DCs recognize antigens through innate pattern recognition receptors that include toll-like receptors (expressed on the cell surface or in the endosome), C-type lectin receptors (typically expressed on the cell surface), and cytoplasmic immune sensors [3–6]. However, the individual distribution of these receptors varies considerably between mDC and pDC, and contributes to their distinct functional profiles. Importantly, DCs are preferentially located in mucosal tissues interfacing with the environment, consistent with their role as sentinels of the immune system, but small proportions of both mDC and pDC also circulate in the peripheral blood.

Infection with HIV-1 elicits a multifaceted immune response that involves almost all effector components of the innate and adaptive immune system, and although these immune responses seem unable to prevent successful HIV-1 infection, they can, in many cases, modulate or attenuate HIV-1 disease progression. Effective immune control of HIV-1 infection is most obvious in rare HIV-1-infected individuals who are able to naturally restrict HIV-1 replication in the absence of antiretroviral therapy and maintain undetectable levels of viral replication as determined by commercial PCR assays. While HIV-1-specific T cells seem to represent the functional hallmark of spontaneous viral controllers and have been studied in a large number of prior studies [7–9], the precise role of DCs in developing viral control is still in the beginning of being more closely understood and represents an understudied area of investigation. Yet, given the overarching role of DCs for immune recognition, immune regulation, and immune induction, these cells are likely to contribute in several direct and indirect ways to mechanisms of HIV-1 immune defense in these specific patients. In this review, we briefly summarize recent advances in understanding the role of DCs for antiviral immune control.

Myeloid Dendritic Cells

mDCs can be phenotypically identified based on the expression of CD11c and HLA-DR, in the absence of lineage-specific markers [6]. These cells seem intrinsically involved in many aspects of HIV-1 pathogenesis and immune defense and can simultaneously act as target cells for HIV-1 replication, as sites for antigen recognition, presentation and immune induction, and as mobile vehicles for HIV-1 particle capture and dissemination [10–12, 13••, 14]. Due to the exquisite rarity of these cells in the peripheral circulation, analyzing primary mDC from HIV-1 controllers tends to be remarkably complex and requires large amounts of available cell samples. Nevertheless, a number of recent studies have addressed the specific contribution of mDC to antiviral immune defense in controllers, as discussed below.

Susceptibility of mDC to HIV-1 Infection—It is well established that owing to surface expression of CD4 [15], DCs are susceptible to HIV-1 infection and support all necessary steps of the HIV-1 life cycle. Yet, the dynamics of viral replication in myeloid dendritic cells seems to differ considerably from those of CD4 T cells, and the specific cellular microenvironment of DCs is a lot more restrictive to HIV-1 infection, for reasons that have

only partially been unraveled. Most importantly, restriction of HIV-1 replication in mDC seems to be mediated by SAMHD1, a host protein that is highly expressed in myeloid cells and capable of limiting HIV-1 replication at the level of reverse transcription by depleting endogenous intracellular pool of dNTPs [16] and by directly degrading viral RNA [17••]. Notably, this restriction factor can be effectively antagonized by the viral accessory gene Vpx, which is included in the genome of SIV and HIV-2, but not HIV-1, and its activity is regulated by phosphorylation mediated through host cyclin-dependent kinase 1 [18]. Based on prior studies showing a reduced susceptibility of macrophages from controllers to HIV-1 [19], two recent studies have analyzed the viral permissiveness of mDC from controllers, using ex vivo infection assays [20, 21••]. These investigations demonstrated that in comparison to cells from HIV-1-uninfected individuals, mDCs from controllers have reduced abilities to support viral replication, yet, paradoxically, the susceptibility of mDC from progressors to HIV-1 was even more limited, indicating that immune protection against HIV-1 at the organismal level does not correlate with cellular resistance of mDC to HIV-1. To some extent, the more limited susceptibility of mDC from progressors to HIV-1 seems related to upregulation of SAMHD1, which is known to be inducible by IFN- , a cytokine more abundantly secreted in HIV-1 progressors, as a result of increased generalized immune activation in these patients. Yet, several studies have failed to draw a direct correlation between expression of SAMHD1 and/or phosphorylated SAMHD1 and corresponding susceptibilities of mDC to HIV-1 [22], suggesting that a number of as of yet undefined host restriction factors may also influence and regulate viral replication patterns in mDC. On a conceptual level, questions have been raised whether restriction of HIV-1 in mDC by SAMHD1 truly benefits the host, in which case preservation of Vpx or a functionally equivalent accessory protein would be expected in HIV-1 from an evolutionary development perspective. Indeed, the restriction of HIV-1 replication in mDCs may allow the virus to avoid viral immune recognition and the subsequent evolution of cell-intrinsic type I IFN responses in mDC, which may disrupt coordinated immune induction through a fine-tuned interplay between innate and adaptive immune mechanisms (see below). As such, the paradoxically increased HIV susceptibility of mDC from controllers, relative to the susceptibility from progressors, may benefit the host by allowing for improved viral immune recognition and more efficient induction of antiviral effector cell responses, even though it may be achieved on the expense of a larger total reservoir of virally infected mDC. The latter aspect may be more prominently visible when HIV-1 controllers are started on suppressive antiretroviral therapy and may distinguish treatment-naive HIV-1 controllers from those who develop undetectable levels of HIV-1 replication after an initial course of antiretroviral therapy (the so-called post-treatment controllers). Clearly, future studies would be informative to better comprehend the contribution of mDC to viral reservoirs and persistence in patients with immune-mediated and pharmacological control of HIV-1.

Innate Immune Responses in mDC—DCs are, in principle, capable of inducing secretion of type I IFNs upon recognition of viruses, which subsequently leads to transcription of interferon-stimulated genes (ISGs) and upreg-ulation of class II HLA and costimulatory molecules. However, the ability of conventional DCs to induce secretion of IFNs in response to HIV-1 has been highly controversial, and initial studies found no evidence for cell-intrinsic type I IFN secretion in mDC in response to HIV-1 [23]. In

monocyte-derived dendritic cells (MDDC), an in vitro cell model based on the generation of DC-like cells from primary monocytes with recombinant cytokine support, HIV-1 seems to be able to induce several IFN-related genes in the absence of actual production of IFN/ due to induction of IRF1, which transiently induces expression of ISGs, while activation of IRF3, the necessary factor for transcription of IFN [24], is deficient. Moreover, experimental introduction of Vpx into MDDC can dramatically alter the ability of cells to mount IFN type I immune responses, indicating that at least in MDDC, a sufficient machinery to recognize viral antigen is present [25, 26]. In subsequent studies, this cryptic sensor was identified as cyclic GMP-AMP synthase (cGAS), a cytoplasmic host molecule that can effectively recognize reverse transcribed HIV-1 DNA [27••, 28••] and, following antigen recognition, synthesize cyclic GMP-AMP dinucleotide as the second messenger leading to activation of STING and induction of IFN production [29, 30]. Although initially demonstrated in MDDC, further investigations indicated that the cGAS-STING immune recognition pathway is also active in primary mDC isolated directly ex vivo and may represent an active component of the antiviral immune responses mounted against HIV-1 infection in humans [21••, 27••, 28••, 31, 32]. In fact, recent studies have shown that mDCs from HIV controllers have improved abilities to induce type I IFN responses upon exposure to HIV-1, an observation that may, among other factors, result from specifically altered cytoplasmic immune recognition by cGAS [21••]. Yet, these observations do not exclude the possibility that alterative mechanisms may facilitate the induction of type I IFN secretion in response to HIV-1 in controllers. Moreover, HIV-1 might have developed specific strategies to minimize cGAS-based mechanisms of viral DNA recognition, since Vif and Vpr are capable of inactivating the downstream effectors of the cGAS-STING pathway TBK1 [33]. In addition, it is important to recognize that the beneficial effects of antigen-specific IFN release in response to viral antigen recognition may to some extent be antagonized by generalized, unspecific increase of type I IFN secretion, which can occur as a result of elevated immune activation in controllers and may have multiple detrimental effects when persisting for prolonged periods of time. A more detailed exploration of mutual viral-host interactions contributing to cytoplasmic HIV-1 immune recognition and antiviral immune defense in HIV-1 controllers represents an important priority for future investigations.

Immune Induction and Antigen Presentation—The induction and fine-tuning of pathogen-specific adaptive immune responses arguably represent the most critical functional role of mDC, and an accumulating set of data suggests that the improved antiviral properties of effector immune cells in HIV-1 controllers result from specific interactions with mDC. A unique profile of circulating mDC in HIV-1 controllers was first reported by Huang et al., who demonstrated elevated antigen-presenting properties of mDC from such patients, while secretion of pro-inflammatory cytokines was reduced [34]. Subsequent work indicated that the ability of mDC from controllers to capture viral antigen is abnormally increased, again suggesting that a superior ability for immune induction and antigen presentation of mDC may represent a key aspect contributing to natural control of HIV-1 [20]. While cross-presentation of viral antigen in mDC may certainly contribute to induction of HIV-1-specific immune responses and specifically regulate the immuno-dominance patterns of such responses [35••], more recent studies have investigated how direct viral infection of mDC from controllers influences their ability to prime and expand HIV-1-specific CTL [21••].

These studies showed that increased secretion of type I IFN in mDC from controllers in response to viral antigen improved the functional profile of mDC, consistent with the hypothesis that innate immune recognition supports the quality of emerging innate and adaptive effector cells. Similarly, DCs infected with HIV-1 can also use multiple endogenous pathways to present viral MHC class II restricted peptides and induce HIV-1-specific CD4 T cell responses [36]; however, whether such mechanisms contribute to the strong and effective CD4 T cell-mediated immune responses typically seen in controllers [37–40] remains to be determined. Accumulating data also suggest that mDCs shape and structure the emergence of HIV-1-specific B cell responses. Based on prior studies, this may occur through direct release of B cell-tropic cytokines such as BAFF or BLYs, which are induced upon exposure to HIV-1 in vitro [41], or indirectly result from mDC-mediated induction of T follicular helper cell responses. Finally, DCs have a critical impact on natural killer (NK) cell activation and function [42] and improved DC function may also be critical to preserve NK cell-mediated control of HIV-1 infection [43••].

Plasmacytoid Dendritic Cells

Plasmacytoid dendritic cells (pDCs) represent a highly specialized subpopulation of DCs with distinct phenotypic and functional characteristics [44]. Phenotypically, these cells are characterized by surface expression of the C-type lectin BDCA2 (CLEC4C) and the immunoglobulin superfamily receptor immunoglobulin-like transcript 7 (ILT7; also known as LILRA4) [45]. Human pDCs also express CD4, CD68, ILT3 (LILRB4), and high levels of the alpha chain of the receptor for interleukin-3 (CD123), a cytokine required to maintain pDC survival. The functional hallmark of pDC is the production of large amounts of type I interferon in response to microbial infection, which can play a critical role in antiviral immune defense during acute HIV-1 infection but contributes to chronic inflammatory changes that favor immune dysfunction and viral persistence during chronic stages of the disease [46, 47]. Interestingly, the less pathogenic HIV-2 induces lower levels of type I IFN in pDCs compared to HIV-1, suggesting that lower levels of pDC activation could facilitate immune control of infection [48]. In addition to IFN- secretion, pDCs also execute a wide spectrum of additional effector functions that include antigen presentation via HLA class I and II molecules [44, 49], immune cell recruitment through secretion of chemokines, and direct elimination of virally infected cells through upregulation of TRAIL and granzyme B [47, 50]. Notably, available data suggest that many HIV controllers are able to maintain normal levels of circulating pDC, as opposed to progressors who typically have severely reduced number of circulating pDC [51]; the underlying reasons for this observation remain unknown. Nevertheless, circulating pDC from both controllers and progressors upregulated the gut-homing marker a4b7, suggesting preferential trafficking to mucosal intestinal tissue where the majority of HIV-1-infected cells reside [52]. From a functional perspective, levels of IFN- secretion in pDC from controllers and HIV-1-negative individuals are not noticeably different, but clearly exceed those of HIV progressors, which downregulate the CD4 receptor and may become refractory to antigenic stimulation due to elevated plasma levels of IFN- and other pro-inflammatory cytokines [53, 54]. In line with these observations, three-dimensional microscopic imaging indicated that pDCs from controllers and healthy donors, but not from progressors, contained high levels of intracellular TRAIL that is recycled to the membrane after HIV exposure and can induce apoptosis in virally infected CD4 T cells in a

process that was recently described to be regulated by the alarmin HMGB1 [53, 55]. In contrast, pDCs from viremic patients appeared to constitutively express TRAIL on the cell surface without any viral stimulation, which may contribute to unspecific induction of cell death in CD4 T cells and may by this mechanism aggravate CD4 T cell losses and cellular immune deficiency. Overall, these data indicate that pDCs from controllers maintain a functional profile that is frequently not different from those of normal HIV-negative persons. In contrast, pDCs from progressors exhibit what appears to be a hyperactivated condition characterized by constitutive TRAIL upregulation and a reduced ability to produce IFN-, most likely as a result of generalized immune over-activation that makes cells refractory to stimulation with microbial pathogens. The normal functional profile of pDC in controllers therefore seems more likely to be a consequence, rather than a cause of viral immune control. Notably, currently available data suggest that the decline in pDC frequency and function typically observed in progressive infection does not normalize during antiretroviral therapy, suggesting that prolonged periods of uncontrolled viremia cause an irreversible defect in pDC physiology in progressors [56].

Due to expression of the viral receptors CD4, CCR5, and CXCR4, pDCs are susceptible to HIV infection, but patterns of viral replication, molecular host restriction factors, and HIV immune recognition pathways in pDC remain an understudied area of investigation. Detailed prior investigations have shown that pDC can recognize HIV-1 in the early endosome through TLR7, and that viral recognition skews pDC to a partially immature phenotype with signs of cellular over-activation, suggesting that direct viral-cell interactions may contribute to dysfunction of pDC described above [57]. Interestingly, cGAS was also found to be able to trigger activation in response to intracellular DNA in pDCs, independently of TLR9 [32, 58], although the specific relevance of cGAS-dependent HIV-1 immune recognition in pDC still requires deeper investigation. Importantly, no studies have yet analyzed the impact of pDC on the priming of HIV-specific CTL responses in controllers. In fact, very little is currently known about the role of pDC in inducing cellular immune responses mediated by CD8 T cells, although it is generally well recognized that pDCs can activate CD8 T cells through cross-presentation [49]. Moreover, the specific influence that HIV-1 infection of pDC has on the functional polarization of CD4 T cell responses requires more investigation, as initial studies suggested that infection of pDCs with HIV-1 seems to efficiently drive the differentiation of CD4+ T cells into regulatory T cells [59]. It is also tempting to speculate that improved function of pDC in controllers may contribute to preserved NK function, given that an association between the frequency of pDC and cytotoxic activities of NK cells has been postulated in a prior work [60].

Immunogenetic Associations

Immunogenetic variations in the MHC class I locus represent the best predictor of natural HIV-1 immune control. These immunogenetic associations have led to the classification of certain HLA class I alleles such as HLA-B57 and HLA-B27 as "protective," while others, in particular specific HLA-B35 subtypes, are described as disease-promoting [61, 62]. Mechanistically, these immunogenetic linkages between HIV-1 disease progression and variations in MHC class I alleles have largely been attributed to effects of HIV-1-specific CD8 T cells, which are restricted by HLA class I molecules [63–66]. Yet, more recent

studies suggest that associations between HIV-1 disease outcomes and specific HLA class I polymorphisms may also be related to interactions between HLA class I isotypes and specific types of innate HLA class I receptors expressed on dendritic cells, termed leukocyte immunoglobulin-like receptors (LILRs). These receptors show a distinct expression profile on mDC from HIV-1 controllers and can regulate DC maturation and antigen presentation through inhibitory and activating signals [67, 68]. Interestingly, recent studies suggest that the binding affinity between HLA class I molecules and the inhibitory receptor LIRB2 (ILT4) on mDCs is critically influenced by polymorphisms in HLA class I molecules. Moreover, subsequent studies demonstrated that the specific statistical influence of a given HLA class allele on HIV-1 progression is closely associated with binding strength of the respective HLA isotype to LILB2, across a large spectrum of different HLA class I alleles expressed in individuals of Caucasian and African descent [69]. In essence, these data showed that HLA class I isotypes associated with accelerated HIV-1 disease progression have more pronounced binding strength to LILR2, which functionally translated into increased inhibitory signals on mDC that caused weaker functional antigen-presenting properties. Interestingly, a new recent study has shown that LILRs can also modulate pDC function in the context of HIV infection [70].

Conclusions

In this review, we have summarized recent advances in understanding the complexity of dendritic cells in contributing to HIV-1 immune control. These studies reveal a remarkably diverse array of mechanisms by which mDCs may support natural control of HIV-1, while unique functional properties of pDCs that contribute to HIV-1 immune defense in controllers are less obvious, at least based on current experimental results. That said, the closer investigation of DC biology in the context of HIV-1 controllers still represents a vastly understudied area of investigation, and multiple as of yet unknown mechanisms of DC-mediated immune recognition and immune induction pathways may be discovered in HIV-1 controllers in future studies. In addition, it is possible that DCs may also play a role in specific subgroups of HIV-1 controllers (frequently termed post-treatment controllers), who maintain undetectable viral loads after an initial period of suppressive antiretroviral therapy, likely through a distinct set of immunological and virological alterations (ref). A closer understanding of DCs in the context of HIV controllers may ultimately contribute to inducing spontaneous HIV-1 immune control in larger populations of patients who currently depend on lifelong adherence on suppressive antiretroviral therapy as their only treatment modality.

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