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Innate immune responses in primary HIV-1 infection

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Abstract

Purpose of review—Events occurring in acute HIV-1 infection are now recognized to be critical determinants of the subsequent disease course. Innate responses constitute the first line of defence against pathogens, and also play a key role in triggering the early adaptive response; as such, the innate responses activated in acute HIV-1 infection and their contribution to control of viral replication or disease pathogenesis are the focus of much current research. We review recent advances in this area.

Recent findings—Dendritic cell subsets can play pleiotropic roles in acute HIV-1 infection, with in-vitro studies illustrating that HIV–dendritic cell interactions may have outcomes as diverse as virion destruction, virus dissemination, T-cell triggering or subversion of dendritic cell functions. Natural killer cells can be activated in acute HIV-1 infection, and mounting evidence suggests that they contribute to determining the ensuing course of disease; however, much remains to be learned about how they mediate their effects.

Summary—The importance of innate responses as determinants of the outcome of HIV infection is increasingly evident, but more work is needed to understand how innate immunity can be harnessed to combat this infection.

Keywords

cytokine; dendritic cell; human immunodeficiency virus; innate immunity; natural killer cell

Introduction

Innate responses are rapidly activated in response to pathogen exposure or infection, and play dual roles in containment of early pathogen replication and induction of the adaptive response. The innate responses triggered on exposure to HIV type 1 (HIV-1) during acute HIV-1 infection (AHI) may thus be one of several factors involved in determining whether infection initially becomes established, and if so, how the subsequent disease course progresses. Many pathogens have evolved means of subverting innate responses to promote their replication, and increasing evidence suggests that HIV is no exception. Here, we discuss recent advances in understanding the nature and kinetics of innate responses activated in AHI and the roles they may play in protection or pathogenesis. We also review new insights into how HIV exploits components of the innate immune system during virus dissemination within the infected host.

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Pleiotropic roles of dendritic cell subsets in acute HIV-1 infection

Dendritic cells, sentinels of the immune system, are strategically located in skin, mucosal tissues and blood to monitor acquisition of infection. Through expression of a diverse array of receptors and signaling molecules, dendritic cells capture pathogens and trigger innate and adaptive immune responses. They are professional antigen presenting cells, and produce cytokines that mediate direct effector and immunoregulatory functions.

Distribution and characteristics of human dendritic cell subsets

In humans, there are two major dendritic cell subsets, conventional CD11c⁺ myeloid dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs, which are CD11c^{lo}). Located in skin (as Langerhans cells and dermal dendritic cells), genital/gut mucosa and in blood, cDCs are poised to encounter HIV-1 in the initial stages of infection. pDCs are found in blood, thymus, inflamed skin and mucosa and lymph nodes, and may first encounter HIV during early local viral replication/spread.

cDCs and pDCs serve as critical links between innate and adaptive immune responses through expression of pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) and C-type lectins, and intracellular pathogen sensors, which trigger specific signaling pathways that lead to host defense. cDCs express TLRs, 2–9, whereas pDCs express TLR7 and TLR9 [1•]. TLR ligation induces dendritic cell activation, illustrated by production of proinflammatory cytokines, upregulation of costimulatory molecules, acquisition of lymph node homing capacity, enhanced antigen presentation and efficient activation of T cells. Given their expression of a wider panel of TLRs, cDCs are equipped to respond to a more diverse range of pathogens, and are specialized to produce interleukin (IL)-12. By contrast, pDCs preferentially recognize viruses containing ssRNA (via TLR7) or unmethylated CpG motifs (via TLR9), and produce large amounts of type I interferons, a property unique to this dendritic cell subset.

Insights from in-vitro studies into possible outcomes of HIV-1–dendritic cell interactions in acute HIV-1 infection

Dendritic cells at sites of pathogen exposure are thought to be among the first cells with which HIV interacts as infection occurs. HIV–dendritic cell interaction may involve contact of viral components with PRRs, capture of virions, or dendritic cell infection; and may have diverse consequences, including triggering of dendritic cell activation, impairment of dendritic cell maturation or modulation of dendritic cell behavior, and virion dissemination and amplification of infection [2] (Fig. 1). Although difficult to study *in vivo*, insight into the possible outcomes of HIV–dendritic cell interaction in AHI has been gained from in-vitro studies.

Dendritic cell infection—Both cDCs and pDCs express CD4 and CCR5/CXCR4, and can be productively infected with HIV-1 *in vitro*, although the frequency of cells producing virus is small (<5%). This fact may be because dendritic cells deploy viral restriction strategies to contain HIV replication. For example, cDCs can express apolipoprotein B mRNA editing enzyme catalytic polypeptides (APOBECs), proteins that deaminate cytidine to uridine in nascent minus-strand viral DNA, blocking HIV replication [3•]. Mature cDCs increase APOBEC expression, explaining their relative resistance to HIV-1 infection [4•]. APOBEC expression in the dendritic cells of HIV-infected patients has not been quantitated, but if substantial, may underlie the difficulty in consistently finding HIV⁺ dendritic cells in blood. Whether pDCs express APOBEC has yet to be determined, but type I interferons can promote its expression in myeloid cells [5].

HIV-1 transmission to T cells—Shortly after capture, cDCs transmit HIV-1 in *trans* to T cells [6] through virologic synapse formation or via exosomes and later, following direct viral replication. Transmission occurs preferentially to antigen-specific T cells [6] and is enhanced by dendritic cell maturation [7]. pDCs also transmit HIV to T cells, although production of type I interferons and other mechanisms limit replication in the latter [8,9].

Dermal and mucosal dendritic cells and monocyte-derived dendritic cells, but not circulating cDCs or pDCs, express dendritic cell-specific, intercellular adhesion molecule-grabbing nonintegrin (DC-SIGN), a C-type lectin thought to be prominent in capture of HIV-1 into specialized endosomes, from which virus can be routed to proteasomes or transmitted to CD4⁺ T cells in *trans*. DC-SIGN activation results in leukemia-associated Rho guanine nucleotide-exchange factor (LARG)-induced Rho-GTPase activation, required for virus T-cell synapse formation and increased virus replication [10]. Interestingly, ligation of DC-SIGN on monocyte-derived dendritic cells causes downregulation of major histocompatibility complex (MHC) class II molecules and interferon response genes [10]. By ligating and being sequestered via DC-SIGN, HIV-1 may simultaneously achieve dissemination and subversion of the host immune response.

Recent studies suggest that dendritic cells can capture, process or transfer virus through DC-SIGN-independent mechanisms [11–13]. One alternative HIV capture receptor is Langerin, a C-type lectin receptor expressed by Langerhans cells, a subset of cDCs that reside in the skin and in most mucosal epithelia. In contrast to HIV-1 captured by DC-SIGN, HIV-1 captured by Langerin is internalized into Birbeck granules and degraded [14•]. Unlike DC-SIGN⁺ cDCs in the subepithelium, Langerhans cells may thus effect clearance of captured virions rather than mediating HIV transmission to T cells.

Dendritic cell activation—In pDCs, endocytosis of HIV-1 after envelope–CD4 interactions is followed by ligation of TLR7 with viral RNA [15] and pDC activation. By contrast, HIV infection of cDCs does not lead to their activation, despite the fact that they also express TLR7 (although high doses of HIV-1 may induce phenotypic maturation of cDCs [16]). The paradox is that conventional TLR7 agonists such as resiquimod, or GU-rich sequences derived from genomic HIV RNA [17], activate both dendritic cell subsets. cDCs may route HIV-1 to endosomal compartments that do not intersect with those that contain TLR7. Notably, as discussed above, mucosal cDCs but not pDCs express DC-SIGN, virions captured by which are sequestered in specialized endosomes; and ligation of this C-type lectin also exerts immunomodulatory effects on cDCs [10].

Infection of cDCs with HIV not only fails to activate these cells, but may also interfere with their maturation in response to other activation stimuli. HIV-1-exposed cDCs elicit IL-10, are defective in IL-12 production and may adversely regulate T-cell function [18].

Immunoregulation by dendritic cells—cDCs capture and process HIV-1, and present associated antigens to T cells [13]. It is not yet known if pDCs display this capacity, although they present viral antigens to T cells following infection with influenza virus [19]. Nevertheless, pDC-derived interferon (IFN)-α participates in T-cell priming and cross presentation [1•]. HIV-1-activated pDCs also express indoleamine 2,3-dioxygenase (IDO) [20•]. This indirectly impairs CD4⁺ T-cell proliferation [20•] through tryptophan metabolism and has been implicated in the induction of T-regulatory cells.

In addition to its adjuvant effects, IFNα mediates direct antiviral activity against HIV [21]. Type 1 interferons may help to restrict viral replication by other means; for example, HIV-1-induced IFNα induces tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas/Fas ligand on CD4⁺ T cells, leading to T-cell apoptosis [22], which may limit virus

spread from infected cells; however, pDC-derived IFN α may also induce apoptosis of uninfected CD4⁺ T cells, contributing to generalized T-cell loss [23].

In-vivo studies of the dendritic cell response in acute HIV-1 infection

Although HIV–dendritic cell interactions at the initial sites of virus infection and in lymphoid tissues are difficult to study in infected patients, some insight has been gained into the systemic dendritic cell response during AHI from analysis of plasma cytokine levels and peripheral blood dendritic cell subsets in recently infected individuals.

Cytokines—The earliest perturbations in plasma cytokine levels detectable in AHI include increases in IFN α and IL-15, both of which are transiently elevated prior to the peak in acute plasma viraemia [24–26]. Elevations in levels of circulating tumor necrosis factor (TNF) α , IFN γ and other cytokines rapidly follow, temporally correlating with the increase in plasma viraemia [27,28]. The source of cytokine production is likely to be a combination of dendritic cells, monocytes, natural killer (NK) cells and possibly T cells, with IFN α probably being derived from pDCs, supporting the concept that this dendritic cell subset undergoes activation as plasma viraemia increases in AHI.

Dendritic cell subsets—There is a paucity of data on the activation or infection status of dendritic cell subsets in the blood during AHI, although in-vitro studies indicate that dendritic cells are initially preferentially infected compared with other blood leukocyte populations [29]. One study prospectively examined blood pDC and cDC frequencies in 88 therapy naïve patients undergoing AHI [30], and found that pDC, but not mDC, levels were reduced by almost half. Another study confirmed the decline in pDC counts [31], and showed that type I interferon production on in-vitro stimulation with herpes simplex virus type 1 was substantially impaired, albeit transiently. Interestingly, pDCs ligated with gp120 display impaired maturation, IFN α secretion and NK cell activation following stimulation via TLR9 [32]. This ‘refractory’ state of pDCs may mimic the natural unresponsiveness that occurs *in vivo* during AHI.

The mechanism behind the decline in pDC numbers in AHI is not clear, but this could be due to apoptosis as a direct result of infection [9] or mediated by TRAIL and Fas ligand–Fas interactions; may be a consequence of compromised production of pDC precursors due to bone marrow infection; or may reflect pDC migration to lymphoid tissues after HIV-induced activation. An accumulation of DC-SIGN⁺, CD40⁺ dendritic cells has been reported in lymph nodes of acutely infected patients [33].

The natural killer cell response in acute HIV-1 infection: a critical determinant of control of early viral replication?

NK cells are a subset of innate lymphocytes, capable, when mature, of responding rapidly to the presence of infection without the need for prior antigen exposure. They perform direct effector and immunoregulatory functions in the early response to many virus infections [34], acting via cytotoxicity and production of cytokines/chemokines. Triggering of NK cell effector functions on contact with target cells is controlled by the balance of signals received through cell-surface activating and inhibitory receptors [35,36•]. NK cell activity, however, is also modulated by accessory cells, via contact-dependent interactions and soluble factors including IFN α , IL-12, IL-15 and IL-18 [37•].

Historically, most studies of NK cells in HIV-1 infection have focused on analysis of NK cell numbers and function in chronic infection. The consensus from these is that NK cell activity is enhanced during viraemic HIV infection, but that in the context of chronic

infection NK cell numbers are reduced, the NK cell subset composition is perturbed and there are alterations in NK cell functions [38,39•]. The contribution made by NK cells to control of infection has thus not been clear. Recent work, however, has begun to address the NK response in AHI, showing that NK cells are activated at this time and may play an important role in control of early virus replication.

Natural killer cell activation and functions in acute HIV-1 infection

As reviewed above, a transient elevation in plasma levels of IFN α and other innate cytokines occurs prior to the peak in plasma viraemia in AHI [24–26], likely reflecting systemic activation of dendritic cells at this time. Plasma levels of cytokines including TNF α and IFN γ increase shortly thereafter [25–28], providing suggestive evidence that systemic dendritic cell activation is rapidly (and most likely causally [40•]) followed by activation of other cell types including NK cells. Consistent with this, an increased percentage of NK cells has been observed in the blood in AHI in some [41], but not all [42], studies, with longitudinal analysis demonstrating that NK cell populations are expanded around the time of peak plasma viraemia, prior to HIV seroconversion and the development of HIV-specific CD8⁺ T-cell responses [43•].

During AHI, there is an increase in the proportion of CD3⁺CD56^{dim} NK cells in the peripheral blood NK pool, while the proportion of CD3⁺CD56^{bright} NK cells is reduced [41,42]. The former is likely due to expansion of the CD3⁺CD56^{dim} NK cell population, which possesses cytolytic activity and is postulated to be the principal ‘direct effector’ NK subset [44]. Peripheral blood NK cells exhibit enhanced activity (degranulation and IFN γ production) during AHI [43•]. The reduced proportion of CD3⁺CD56^{bright} NK cells in the blood during AHI may reflect recruitment of these cells, to which immunoregulatory functions are ascribed [44], into lymphoid tissues, where they could potentially play a role in activation of the adaptive response. The number/activity of NK cells present in lymph nodes during AHI, however, has not been addressed.

Evidence that natural killer cells impact on the control of viraemia in early HIV infection

The observation that NK cells are activated during AHI [41,42,43•] suggests that they may contribute directly or indirectly to control of primary viraemia. Likewise, reports of elevated NK cell activity in HIV-exposed, seronegative (ESN) individuals [45,46] imply that these cells may also play a role in preventing the establishment of infection. Further indirect evidence for a role for NK cells in combating HIV is that this virus possesses strategies for reducing NK cell activation on contact with infected cells – for example, although the HIV-1 Nef protein mediates downregulation of human leukocyte antigen (HLA)-A/B alleles from the surface of infected cells to impair recognition by virus-specific CD8⁺ T cells, expression of HLA-C/E, ligands for inhibitory NK cell receptors, is retained [47]; however, the strongest evidence for the importance of NK cells in HIV infection comes from genetic studies.

In 2002, a significant association was found between coexpression of killer inhibitory receptor (KIR)3DS1 (an allotype of the *KIR3DL1* gene encoding a putative activating NK cell receptor), with HLA-Bw4 alleles having an isoleucine residue at position 80 (HLA-B Bw4-80Ile) (ligands for the inhibitory KIR3DL1 allotypes, which may also be involved in KIR3DS1 binding), and slower HIV disease progression [48]. Importantly, the strongest synergistic effect between these loci was on progression to depletion of CD4⁺ T cells, suggesting that a protective NK response involving KIR3DS1 and its class I ligands may begin soon after HIV infection. Likewise *KIR3DS1/Bw4-80Ile* was subsequently found to be associated with a low viral load in early HIV infection [49•]. Recent studies have given more insight into the expression, function and ligand specificity of the previously poorly

characterized *KIR3DS1* gene product, demonstrating that it is expressed on peripheral blood NK cells and when ligated, activates NK cell cytotoxicity and IFN γ production, plus suggesting that its interaction with HLA-Bw4 ligands may be peptide dependent [50•,51•].

Further to this, a large study addressing the effects of inhibitory *KIR3DL1* subtypes in combination with *HLA-B* allelic groups on HIV disease progression and viral load provided evidence for an important role for epistatic effects of distinct *KIR3DL1* and *HLA-B Bw4* combinations in HIV infection [52••]. Notably, highly expressed, highly inhibitory *KIR3DL1* alleles were found to strongly enhance the protection conferred by *Bw4-80Ile* alleles [52••]. This observation, which is seemingly inconsistent with the protective effect of *KIR3DS1/Bw4-80Ile* in HIV infection, may be explained by a model in which NK cells bearing the highly expressed *KIR3DL1* allotypes are strongly inhibited in the presence of their Bw4 ligands, resulting in these cells being potent effectors against HIV-infected cells with reduced surface HLA-B expression. *KIR3DS1*-expressing NK cells may, by contrast, be stimulated by HIV-infected cells if the residual surface Bw4-80Ile presents viral or stress peptides, generating their cognate ligand.

Two recent studies have also documented patterns of NK receptor or ligand expression that could lower the threshold for NK cell activation in ESN individuals [53•,54•], supporting the hypothesis that NK cells may be involved in mediating resistance to HIV infection.

Natural killer cell recognition of HIV-infected cells

NK cells could combat HIV replication and spread both directly, via lysis of infected cells or production of antiviral cytokines (e.g. IFN γ) and coreceptor-blocking CC-chemokines; and indirectly, via activation of adaptive responses. The contribution of these different mechanisms to NK cell-mediated protection in AHI, however, is not known. In-vitro studies have demonstrated the capacity for NK cells to suppress HIV replication in infected cells via noncytolytic mechanisms [55,56]. By contrast, it is less clear how well NK cells are able to lyse HIV-infected cells [57].

The receptor–ligand interactions involved in determining whether target cell lysis is triggered following the interaction of an NK cell with an HIV-infected cell (Fig. 2) are currently under investigation. One set of interactions involved are those between class I molecules on the target cell and cognate inhibitory NK receptors: as mentioned above, surface levels of HLA-A/B are reduced on infected cells, whilst HLA-C/E expression is maintained [47] (or HLA-E may be upregulated [58]), resulting in inhibition of target cell lysis by NK cells expressing inhibitory receptors that interact with HLA-C/E (certain KIRs and NKG2A/CD94), but giving the potential for lysis by NK cells inhibited via receptors that interact with HLA-A/B [47,58]. Recent studies have also shown that ligands for activating receptors are expressed on HIV-infected cells, including a ligand for the natural cytotoxicity receptor NKP44 induced by a motif in the HIV envelope gp41 protein [59] and the NKG2D ligands UL-16 binding protein (ULBP)-1, 2 and 3 [60•] plus, as discussed above, a *KIR3DS1* ligand.

HIV possesses a variety of strategies for impairing NK cell activation by infected cells. In addition to the Nef protein modulating surface class I levels [47], Nef was also recently reported to reduce the upregulation of cell-surface expression of MHC-I related chain (MIC)A and ULBP-1 and 2, ligands for the activating NK receptor NKG2D [61•]. Expression of NK-T-B cell antigen (NTB-A) and CD48, ligands for the NK cell coreceptors NTB-A and 2B4, is also downmodulated on HIV-infected cells [60•]. Other mechanisms by which HIV may interfere with the NK cell response include inhibition of NK cell functions by HIV-1 gp120 [62] and an indirect effect of the HIV-1 Nef protein on NK cell activity mediated via impairment of NK/dendritic cell cross-talk [63].

Activation of other innate cell subsets in acute HIV-1 infection

In addition to dendritic cells and NK cells, other innate cell subsets also become activated in AHI, although relatively little is known about the kinetics with which this occurs or the contributions that these subsets may make to protection or pathogenesis.

For example, studies carried out in macaques have shown that peripheral blood monocyte counts increase prior to the peak in plasma viraemia in acute simian immunodeficiency virus (SIV) infection, and that circulating monocytes exhibit an increased functional capacity at this time [64,65•]. Monocytes may contribute directly or indirectly to control of infection via their ability to produce cytokines, chemokines and other soluble factors; but conversely may also act as a substrate for viral replication and may contribute to spread of virus within the infected host, including transport of virus into the brain [65•].

CD3⁺CD56⁺ natural T cells and CD1d-restricted natural killer T (NKT) cells (most of which express a restricted T-cell receptor repertoire consisting of a V α 24 chain preferentially paired to V β 11) are also thought to be activated in AHI. These are lymphocyte subsets that possess features of both NK cells and T cells, and are capable of mediating immunoregulatory and effector functions via production of T helper type 1 (Th1) and Th2 cytokines and via cytotoxicity. Peripheral blood NKT cell numbers are known to be reduced from early HIV infection onwards [66], which may be due in part to the susceptibility of CD4⁺ NKT cells to infection and destruction by HIV. Recent studies have shown, however, that administration of antiretroviral therapy results in recovery of (predominantly CD4⁺) NKT cells with kinetics similar to those of the increase in peripheral blood T cells [67•,68]. The latter is thought to reflect the return of cells previously sequestered in lymphoid tissues back into the circulation. The initial decrease in peripheral blood NKT cell numbers during AHI may thus be due to a combination of cell death and sequestration of NKT cells into tissues. NKT cell numbers in lymphoid tissues, however, remain to be addressed, as do the role(s) that these cells may be playing in control of viral replication or regulation of other innate or adaptive responses.

Conclusion

Although understanding of the innate responses activated in AHI is rapidly increasing, there is still much to be learned. Dendritic cell subsets exhibit a pleiotropic response to encounter with HIV, mediating effects that may be beneficial (e.g. capture and destruction of HIV by Langerhans cells; activation of HIV-specific T-cell responses by cDCs), detrimental (e.g. dissemination of infection to HIV-specific T cells by subepithelial cDCs), or perhaps a combination of the two (e.g. pDC production of IFN α , which may mediate antiviral effects but also drive CD4 T-cell apoptosis). Recent evidence suggests that NK cells may play an important role in mediating both resistance to HIV infection and containment of viral replication in infected individuals – but the mechanisms by which they mediate these effects and viral strategies for subverting NK control remain poorly understood. More work is thus required to dissect beneficial and detrimental aspects of innate responses in AHI, so that prophylactic and therapeutic strategies can be designed to exploit the former and block the latter.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 82–85).

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Figure 1. Pleiotropic functions of dendritic cell (DC) subsets in response to HIV encounter

The figure illustrates the range of effects that HIV has on conventional CD11c⁺ myeloid dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs) and their potential consequences. APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide; IFN, interferon; IL, interleukin; NK, natural killer; TNF, tumor necrosis factor.

Figure 2. Diagram to illustrate some of the putative interactions between ligands on (a) an uninfected cell and (b) an HIV-infected cell and activating/inhibitory natural killer (NK) cell receptors

The signals NK cells receive following interaction with uninfected cells are likely to be predominantly inhibitory (-); but on HIV-infected cells expression of ligands for inhibitory NK cell receptors is postulated to be reduced, whilst ligands for activating NK cell receptors are thought to be induced, resulting in many NK cells receiving a greater proportion of activating (+) signals and hence being triggered into functional activity.