Innate Immune Activation in Primary HIV-1 Infection

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There is growing evidence that highlights the role of the immune response during acute human immunodeficiency virus type 1 (HIV-1) infection in the control or development of disease. The adaptive immune responses do not appear until after HIV-1 infection is already well established, so the role of earlier and faster-responding innate immunity needs to be more closely scrutinized. In particular, 2 aspects of innate immunity for which there are growing research developments will be examined in this review: the actions of type I interferons and natural killer cells. These two components of the innate immune response contribute to viral control both by killing infected cells and by modulating other immune cells that develop. However, the role of interferon \( \alpha \) in immune activation is a double-edged sword, causing recruitment of adaptive immune cells that can assist in viral control but concurrently contributing to immune activation–dependent disease progression. Understanding the complexity of how innate responses affect the outcome of HIV-1 infection will help in the development of vaccines that can use innate immunity to enhance viral control with minimal pathogenesis.

Viral infections result in a strong activation of the innate immune system that is followed by the development of adaptive immune responses. Studies in different models of viral infections, as well as studies of vaccination, have further demonstrated that the quality of the initial innate immune response is closely linked to, and in some studies predicts, the function of the subsequent adaptive immune responses to pathogens. This cross-talk between innate and adaptive immunity is exploited in vaccines by using adjuvants stimulating specific innate immune pathways.

Infection with human immunodeficiency virus type 1 (HIV-1) does not differ from other viral infections in activating the immune system, and several studies have now demonstrated significant activation of components of the innate immune system in primary HIV-1 infection, preceding the development of adaptive B and T cell responses. Very little is understood, however, about the role of innate immunity in HIV-1 pathogenesis and the consequences of the cross-talk between innate and adaptive immune responses in primary infection for immune control of HIV-1 infection. In this review, we will highlight some of the data presented at a recent symposium on acute HIV-1 infection in Boston, as well as published data on innate immunity in primary HIV-1 infection. Special focus is given to the role of type I IFNs and natural killer (NK) cells in HIV-1 disease, 2 areas of research that received considerable attention during the symposium.

HIV-1–INDUCED CYTOKINE AND CHEMOKINE PRODUCTION DURING ACUTE HIV-1 INFECTION

The innate immune system is the first line of defense against infection and consists of innate immune cells, which are able to recognize and respond to infections quickly through the recognition of pathogens by pattern recognition receptors. These receptors include Toll-like receptors (TLRs), which recognize conserved motifs.
unique to microorganisms; in viral infections they can detect double-stranded RNA and single-stranded RNA (ssRNA), as well as certain viral proteins [1, 2]. It has been shown that HIV-1 ssRNA encodes for multiple TLR7/8 ligands that can mediate direct activation of the immune system in vitro [3]. Likewise, TLR7 and TLR8 can also recognize simian immunodeficiency virus (SIV) infection in sooty mangabeys and rhesus macaques, leading to both innate immune activation and the activation of downstream adaptive immune responses [4]. Stimulation of TLR7/8 induces the production of several antiviral and immunomodulatory cytokines. In particular, interferon (IFN) α production after TLR stimulation has been shown to be up-regulated during acute infection with HIV-1 or SIV [5–8]. These early cytokines and the innate cells that produce them, such as dendritic cells (DCs), are pivotal in shaping the immune responses that develop in acute or early HIV-1 infection.

Recently, the cascade of cytokine production in the periphery has been thoroughly documented, showing an initial rapid increase and peaking of IFN-α production, followed by secondary tumor necrosis factor (TNF) α, inducible protein 10, and interleukin (IL) 18 secretion, and finally IL-10 and IFN-γ production, which was associated with the rise in virus-specific adaptive immune response [5, 9]. IFN-α, produced after plasmacytoid DC (pDC) recognition of HIV-1 ssRNA via TLR7, has been shown to have antiviral activities in other infections [10, 11], and is also used in the treatment of hepatitis B and C virus infections [12, 13]. The comprehensive mechanism of IFN-α inhibition of HIV-1 is not well characterized, but in vivo elevation of IFN-stimulated genes (ISGs) has been observed in both gene expression profiling of HIV-1 [14] and SIV infection [8]. The in vitro inhibitory effects of IFN-α on HIV-1 replication have been described in macrophages, monocytes [15], and humanized mouse models of HIV-1 infection [16]. Several in vitro studies have demonstrated that IFN-α is able to reduce HIV-1 replication by reducing the formation of late reverse-transcriptase products in infected cells [17]. This may be a consequence of IFN-α–dependent up-regulation of intrinsic host restriction factors, such as APOBEC3G [18], which can edit HIV-1 reverse transcripts, leading to the degradation of HIV-1 encoded DNA [19].

In addition to this IFN-α–dependent initiation of intracellular pathways, type I IFNs are also able to regulate other immune cells, regulating B cell and antibody development [20] and also regulating both CD4+ and CD8+ T cell survival by inhibiting apoptosis [21]. IFN-α modulation of CD4+ T cell survival seems to have differential effects, with preferential apoptosis occurring in antigen-experienced CD4+ T cells, potentially through the induction of TNF-related apoptosis-inducing ligand expression in infected CD4+ T cells [21, 22]. Furthermore, IFN-α is also a proinflammatory cytokine, activating both adaptive and innate cells, including NK cells cytolytic activity against infected cells [23]. Considering all its effects, IFN-α can contribute both to viral control, inhibiting viral replication via intracellular mechanisms, and to the initiation of the adaptive antiviral immune response (Table 1).

Although IFN-α might play an important role in the control of viral spread during acute or early HIV-1 infection, persistent stimulation by IFN-α in chronic HIV-1 infection can contribute to HIV-1–associated pathology [24, 25] (Table 1). This is most apparent in the lack of chronic immune activation observed in nonpathogenic SIV infection in sooty mangabeys or African green monkeys, compared with the persistent immune activation in pathogenic SIV infection in rhesus macaques [4, 6, 26, 27]. Recent studies have demonstrated that differences in IFN-α production and activation of ISGs are associated with varying SIV chronic disease progression in rhesus macaques and sooty mangabeys or African green monkeys [4, 6, 26–28]. In the setting of acute SIV infection, however, there is some controversy; most studies show IFN-α elevated in both natural hosts (sooty mangabeys and African green monkeys) and nonnatural hosts (rhesus macaques) [6, 26, 27], but 1 study ob-

### Table 1. Positive and Negative Effects of Interferon (IFN)–α during Human Immunodeficiency Virus Type 1 (HIV-1) Infection

<table>
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<tr>
<th>Phase of infection</th>
<th>Effects of IFN-α</th>
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<tr>
<td>Acute</td>
<td>Transiently expressed in acute infection; activates intracellular antiviral pathways; activates cytopathic natural killer cells; initiates adaptive immune response</td>
</tr>
<tr>
<td>Chronic</td>
<td>Induces apoptosis of infected cells</td>
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**NOTE.** Positive effects show the role of IFN-α in HIV-1 control; negative effects, contributions to the pathogenesis of HIV-1 infection.
served no elevation [4]. Examination of ISG expression supports the observation of elevated IFN-α, with ISG expression peaking and declining concurrently with plasma IFN-α levels in acute infection [26]. In the subsequent chronic infection, however, significantly higher levels of ISG expression persist in SIV-infected rhesus macaques than in sooty mangabeys and African green monkeys [26]. Similarly, ISGs also remain elevated in chronic HIV-1 infections and are associated with immune activation, particularly in individuals with progressive HIV-1 disease [25].

IFN-α is encoded by several different genes, and expression of the varying IFN-α genes changes over disease progression, with certain subtypes expressed only in individuals with progressed disease and depleted CD4+ T cells [29]. The discordance between IFN-α levels and ISG expression could therefore result from differences in the quality rather than the quantity of type I IFNs produced. Furthermore, greater responsiveness to HIV-1 in pDCs from women, compared with those from men, resulting in stronger IFN-α production in vitro, has been associated with higher levels of immune activation in HIV-1–infected women than in men for the same level of viral replication [30]. These findings indicate that differences in HIV-1–induced IFN-α production in chronic infection might be associated with differential HIV-1 disease progression. Despite these potentially detrimental properties of IFN-α, its use to treat HIV-1 in vivo has been examined in several studies of chronic HIV-1 infection, and it can lead to a slowing of disease progression [31] and decreases in HIV-1 p24 levels [32]. The role of IFN-α in chronic HIV-1 infection is therefore controversial, and many questions still need to be addressed. For example, what regulatory mechanisms reduce chronic IFN-α production in nonpathogenic SIV infection in sooty mangabeys or African green monkeys, and can detrimental chronic immune activation in progressive SIV and HIV-1 infection be reduced by reducing TLR7/8 stimulation?

Given the important role of innate immune responses in HIV-1 pathogenesis, the virus has developed several mechanisms to evade or alter the innate immune responses, and some are discussed below. IFN-α and pDCs both decrease in early HIV-1 infection, and, although some of this down-regulation has been attributed to pDC migration to the lymph nodes, direct HIV-1 infection of IFN-α-producing cells may further exacerbate this depletion [33, 34]. Fusion of HIV-1 with pDCs can induce their apoptosis [34], and even without direct infection the presence of exogenous Vpr can reduce IFN-α and IFN-β production by promoter disruption [35]. Impairment of pDCs can have important consequences for innate and adaptive immune responses, and indeed HIV-1–infected DCs have been shown to have reduced ability to modulate T cells [22, 36]. Furthermore, Nina Bhardwaj from New York University presented data at the recent acute HIV-1 meeting in Boston, demonstrating that stimulation via the TLR7 pathway can induce pDC production of indoleamine 2,3-dioxygenase, which drives pDC-dependent differentiation of naïve CD4+ T cells into regulatory T cells [37]. These regulatory cells are found to have suppressive functions that can potentially limit anti–HIV-1 immune responses [37]. At the same meeting, Jacob Estes from the National Cancer Institute also reported that secretion of IFN-α after mucosal SIV exposure in female macaques results in the production of proinflammatory cytokines and chemokines that might drive the recruitment of CD4+ T cell targets to the sites of infection. Taken together, these various mechanisms by which HIV-1 can interact with pDCs and type I IFNs may contribute to both impairment of the adaptive immune response and subsequent chronic immune activation.

**SIGNIFICANT AND SPECIFIC EXPANSION OF NK CELLS IN ACUTE HIV-1 INFECTION**

In addition to the activation of pDCs through innate pattern recognition receptors, acute HIV-1 infection also results in the activation and expansion of NK cells. In part, this activation of NK cells might be caused by the high levels of proinflammatory cytokines secreted by DCs and monocytes, including IL-15 and IFN-α. Initial studies demonstrated a significant expansion of NK cell numbers in acute HIV-1 infection, in particular before the development of any detectable antibody responses [38]. After this initial expansion of highly activated NK cells, NK cells become increasingly impaired, with persisting viral replication and disease progression. This impairment of NK cell function with progressive HIV-1 disease is associated with an accumulation of CD56dim NK cells that are anergic to stimulation [39, 40].

NK cells constitute a highly heterogenic cell population in a given individual, consisting of multiple different NK cell clones characterized by differential receptor expression profiles, including different activating and inhibitory killer cell immunoglutulin-like receptors (KIRs). The combination of activating and inhibitory KIRs, in conjunction with their HLA class I ligands, determines the functionality of NK cells and their ability to respond to virally infected target cells. Recent studies have shown that specific combinations of KIR genotypes, in combination with their HLA class I ligand genotypes, are associated with better control of HIV-1 replication and slower HIV-1 disease progression. In particular, the expression of the activating receptor KIR3DS1 in conjunction with its putative HIV class I ligands, HLA class I molecules of the HLA-Bw4–80I family (including HLA class I alleles, such as HLA-B57 and HLA-B51) has been associated with slower disease progression [41]. In addition, the presence of subtypes of the inhibitory receptor KIR3DL1 associated with higher expression levels of KIR3DL1 on NK cells has been shown to fine-modulate the protective effect of HLA class I alleles of the HLA-Bw4–80I
CONCLUSIONS

As with other viral infections, HIV-1 infection results in an initial activation of innate immunity, followed by the development of adaptive immune responses. Innate immune responses to HIV-1 can contribute directly to the control of HIV-1 replication, might play an important role in modulating the function of the subsequent HIV-1–specific adaptive immune response, and can contribute to HIV-1 disease progression. Our understanding of the direct antiviral activity of innate immunity, and its adjuvant effect on adaptive immunity, is still very limited and needs to be expanded, to enable strategic interventions aimed at enhancing immune control of HIV-1 by modulating innate immunity while avoiding immunopathogenesis resulting from its overactivation.

References

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