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Innate Immune Activation in Primary HIV-1 Infection

J. Judy Chang and **Marcus Altfeld**
Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02129, USA

Abstract

There is growing evidence highlighting the role of the immune response during acute HIV-1 infection on the control or development of disease. The adaptive immune responses do not appear until after the HIV-1 infection is already well established and as such the role of the earlier and faster responding innate immunity needs to be more closely scrutinized. In particular, two aspects of the innate immunity with growing developments will be examined in this review; type I IFNs and NK cells. Both innate immune responses contribute to viral control by the killing of infected cells and also the modulation of other immune cells that develop. However, the role of IFNα in immune activation is a double edged sword driving recruitment of adaptive immune cells that can assist in viral control but also concurrently driving immune activation dependent disease progression. Understanding the complexity of how the innate responses affect the outcome of HIV-1 infection will open opportunities for vaccine development that can utilize the innate immunity to enhance viral control with minimal pathogenesis.

Introduction

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 during vaccinations, 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 during vaccinations by using adjuvants stimulating specific innate immune pathways.

Infection with HIV-1 does not differ from other viral infections in activating the immune system, and several studies have now demonstrated a 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 however understood 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 review some of the data presented at a recent symposium on Acute HIV-1 Infection in Boston, as well as published data assessing innate immunity in primary HIV-1 infection. Special focus is given to the role of Type I IFNs and NK cells in HIV-1 disease, two areas of research that received considerable attention during the symposium.

*Corresponding Author: Marcus Altfeld, MD/PhD, Associate Professor, Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Bldg. 149, 13th Street, 6th floor, Charlestown, Navy Yard, MA, 02129, Tel: 617-724-2461, Fax: 617-724-8586, maltfeld@partners.org.

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HIV-1 induced cytokine and chemokine production during acute HIV-1 infection

The innate immune system is the first line of defense 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 (PRRs). The PRRs include Toll-like receptors (TLRs) which recognize conserved motifs unique to microorganisms and in viral infections they can detect dsRNA, 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 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 IFNα production following TLR stimulation has been shown to be up-regulated during acute infection in HIV-1 and SIV infections [5–8]. These early cytokines and the innate cells such as dendritic cells that produce them are pivotal in the shaping of the immune responses that develop in acute/early HIV-1 infection.

Recently the cascade of cytokine production in the periphery has been thoroughly documented, showing initial rapid increase and peaking of IFNα production followed by secondary TNFα, IP-10 and IL-18 secretion and finally IL-10 and IFNγ production which was associated with the rise in virus-specific adaptive immune response [5,9]. IFNα is produced following 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 HBV and HCV infections [12,13]. The comprehensive mechanism of IFNα inhibition of HIV-1 is not well characterized, however, *in vivo* elevation of interferon stimulated genes (ISG) has been observed in both gene expression profiling of HIV-1 [14] and SIV infection [8]. The *in vitro* inhibitory effects of IFNα 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 IFNα 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 IFNα–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 IFNα–dependent initiation of intracellular pathways, type I IFNs are also able to regulate other immune cells such B cell/antibody development [20] and both $CD4^+$ and $CD8^+$ T cell survival by inhibiting apoptosis [21]. IFNα modulation of $CD4^+$ T cell survival seems to have differential effects with preferential apoptosis occurring in antigen-experienced $CD4^+$ T cell potentially through the induction of TRAIL expression on infected $CD4^+$ T cells [21,22]. Furthermore, IFNα is also a pro-inflammatory cytokine activating both adaptive and innate cells including NK cell cytolytic activity against infected cells [23]. Taken together IFNα can contribute both to viral control by inhibiting viral replication via intracellular mechanisms and to the initiation of the adaptive antiviral immune response (Table 1).

While IFNα might play an important role in the control of viral spread during acute/early HIV-1 infection, persistent stimulation by IFNα 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 non-pathogenic SIV infection in sooty mangabeys or African green monkeys as compared to the persistent immune activation in pathogenic SIV infection in rhesus macaques [4,6,26,27]. Recent studies now demonstrate that differences in IFNα 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 with most

studies showing IFNα being elevated in both natural hosts (sooty mangabeys and African green monkeys) and non-natural host (rhesus macaques) [6,26,27] while one study has observed no elevation in IFNα [4]. Examination of ISGs expressions supports the observation of elevated IFNα with ISG expression peaking and declining concurrently with the plasma IFNα levels in acute infection [26]. In the subsequent chronic infection, however, significantly higher levels of ISG expression persist in SIV infected rhesus macaques compared to sooty mangabeys and African green monkeys [26]. Similar to this, ISGs also remain elevated in chronic HIV-1 infections and are associated with immune activation, particularly in individuals with progressive HIV-1 disease [25].

IFNα is encoded by several different genes and expression of the varying IFNα genes change over disease progression with certain subtypes only expressed in individuals with progressed disease and depleted $CD4^+$ T cells [29]. The discordance between IFNα levels and ISG expression could therefore be a result of differences in quality rather than quantity of Type I IFNs produced. Furthermore, higher responsiveness of pDCs from women, compared to pDCs from men, to HIV-1, resulting in stronger IFNα production *in vitro*, have been associated with higher levels of immune activation in HIV-1-infected women compared to men for the same level of viral replication [30]. These studies indicate that differences in HIV-1-induced IFNα production in chronic infection might be associated with differential HIV-1 disease progression. Despite these potentially detrimental properties of IFNα, the use of IFNα to treat HIV-1 *in vivo* has been examined in several studies of chronic HIV-1 infection and can lead to a slowing of disease progression [31] and decreases in HIV-1 p24 levels [32]. The role of IFNα in the setting of chronic HIV-1 infection is therefore controversial, and many questions need to be addressed: What are the regulatory mechanisms reducing chronic IFNα production in non-pathogenic SIV infection in sooty mangabeys or African green monkeys? 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. IFNα 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 IFNα 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 IFNα and IFNβ 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 capabilities of modulating T cells [22,36].

Furthermore, Dr Nina Bhardwaj from NYU 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 (IDO) which drives a pDC-dependent differentiation of naive $CD4^+$ T cells into Tregs [37]. These Tregs are found to have suppressive functions that can potentially limit anti-HIV-1 immune responses [37]. At the same meeting, Dr Jacob Estes from NCI furthermore reported that secretion of IFNα following mucosal SIV exposure in female macaques results in the production of pro-inflammatory 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 manipulate with pDCs and Type I IFNs may contribute both to an 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 driven by the high levels of proinflammatory cytokines secreted by dendritic cells and monocytes, including IL-15 and IFNα. Initial studies demonstrated a significant expansion of NK cell numbers in acute HIV-1 infection, in particular prior to 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 $CD56^{low}$ 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 cells clones that are characterized by differential receptor expression profiles, including different activating and inhibitory 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 it's putative HLA class I ligands, HLA class I molecules of the HLA-Bw4-80I family (including HLA class I alleles such as HLA-B57 and -B51) has been associated with slower disease progression [41]. In addition, the presence of subtypes of the inhibitory receptor KIR3DL1 that are 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 family [42]. Furthermore, a SNP associated with higher expression levels of HLA-C, the principal ligand for receptors of the KIR2DL and KIR2DS family, has been shown to be associated with lower viral setpoint and slower disease progression [43].

These epidemiological studies strongly suggest that specific subsets of NK cells from individuals expressing particular receptor/ligand genotypes are able to mediate better control of HIV-1 replication. Functional studies demonstrating the $KIR3DS1^{+}$ NK cells can strongly inhibit HIV-1 replication in $CD4^{+}$ T cells expressing HLA-Bw4-80I *in vitro* provide further support for this model [44]. Interestingly, the KIR/HLA class I compound genotypes also appear to modulate the ability of specific NK cell subsets to preferentially expand during acute HIV-1 infection. Recent data show that $KIR3DS1^{+}$ NK cells, and to a lesser extend $KIR3DL1^{+}$ NK cells, are over-proportionally expanded in primary HIV-1 infection, but only in individuals that also encode for HLA class I molecules of the HLA-Bw4-80I family, but not $HLA\text{-}Bw4\text{-}80I^{neg}$ individuals [45]. Further studies need to investigate whether the preferential expansion of these NK cells expressing KIRs associated with better HIV-1 disease outcome represent a functional correlate of protective immunity. However, apart from their role in eliminating HIV-1 infected cells, NK cells might also be involved in killing uninfected $CD4^{+}$ T cells expressing ligands for activating NK cell receptors as a consequence of bystander activation [46,47], and thereby contribute to $CD4^{+}$ T cell decline.

Apart from their direct antiviral activity, NK cells play an important role in modulating DC function. NK cells are involved in the rapid elimination of immature DCs, that aberrantly enter the peripheral circulation, while sparing mature DCs, due to differences in MHC class-I expression[48,49]. This NK cell mediated quality control of DC populations ensures that only immunogenic mature DCs are able to gain access to inductive sites. Recent studies have demonstrated that the ability of NK cells to eliminate immature DCs is severely

impaired in chronic HIV-1 infection [50], and this impairment of the quality control function of NK cells might have significant impact on the ability of DCs to induce antiviral T cell responses. These data suggest that NK cells play an important role in modulating of DC function, and thereby potentially in the modulation of adaptive immune function. Further studies will be needed to investigate this cross-talk between innate and adaptive immune effector cells in order to exploit this adjuvant function of NK cells for vaccine design. Overall, our understanding of the NK cell functions that contribute to the control of viremia in HIV-1 infection and slower disease progression are still very limited, and ongoing research in this area is needed to determine which NK cell functions are important in HIV-1, and how these functions can be modulated.

Conclusions

As with other viral infections, HIV-1 infection results into 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 it's adjuvant effect on adaptive immunity, is still very limited, and needs to be expanded in order to enable strategic interventions aimed at enhancing immune control of HIV-1 by modulating innate immunity, while avoiding immunopathogenesis resulting from overactivation of innate immunity.

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Table 1

Dichotomy of IFNα duringHIV-1 infection

	Positive effects **Role of IFNα on HIV-1 Control**	**Negative effects** **Contributing to HIV-1 pathogenesis**
Acute HIV-1 Infection	• Transiently expressed in acute infection • Activation of intracellular antiviral pathways • Activate cytopathic natural killer cells • Initiation of the adaptive immune response	• Recruitment of target cells to mucosal sites
Chronic HIV-1 Infection	• Induce apoptosis of infected cells	• Persistently expressed in chronic infection • Drive CD4+ T cell depletion • Induce chronic immune activation