Current HIV/AIDS Reports (2019) 16:224–229
https://doi.org/10.1007/s11904-019-00444-7

HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

Pathogenic Role of Type I Interferons in HIV-Induced Immune Impairments in Humanized Mice

Lishan Su[1]

Published online: 4 May 2019

Abstract

Purpose of Review Recent findings on the critical pathogenic role of type 1 interferons (IFN-I) in HIV-1 persistence in humanized mice suggest that inhibiting IFN-I signaling transiently will reverse HIV-induced inflammatory diseases and rescue anti-HIV immunity to control HIV-1 reservoirs.

Recent Findings In both humanized mice and in monkeys, IFN-I signaling is functionally defined to play an important role in suppressing early HIV-1 and SIV infection. During persistent infection in humanized mice, however, IFN-I signaling is revealed to induce T cell depletion and impairment. Interestingly, in HIV-infected mice with effective combination antiretroviral therapy (cART), blocking IFN-I signaling reverses HIV-induced inflammation, rescues anti-HIV T cells, and reduces HIV-1 reservoirs.

Summary These findings functionally define the role of IFN-I in HIV-1 reservoir persistence and suggest that blocking IFN-I signaling will provide a novel therapeutic strategy to (i) reverse inflammation-associated diseases in HIV patients under cART, (ii) rescue host anti-HIV immunity, and (iii) reduce or control HIV-1 reservoirs.

Keywords IFNAR · ISG · pDC · Inflammation · T cell exhaustion · HIV-1 reservoirs

Introduction

HIV-1 persistence is associated with hyper-inflammatory activation [1]. Despite efficient suppression of HIV-1 replication and increased survival with highly active or combination antiretroviral therapy (HAART or cART, respectively), HIV-1 rebounds in all patients post-cART cessation due to the "cART-resistant" viral reservoir (latent or low-replicating HIV infection) in lymphoid tissues [2, 3]. In addition, some cART-treated patients with effective HIV-1 suppression fail to reverse hyper-inflammatory or hyper-immune activation and achieve full immune recovery [1]. The mechanism underlying those "immune non-responder (INR)" patients remains unclear. Although type 1 interferons (IFN-I) are reduced under ART [4], low levels of IFN-I persist and IFN-stimulated-genes (ISGs) are still upregulated in peripheral blood cells or lymphoid organs [5, 6], which may contribute to increased clinical complications and mortality in cART/HIV-1 patients [1]. Persistent hyper-inflammation has also been associated with pathogenesis in non-human primates (NHP) with SIV infection, but the underlying cellular and molecular effectors remain elusive. Strong correlations have been established between persistently activated IFN signaling with HIV-1 [7] or SIV disease progression [8, 9]. First, IFN and ISG responses persist in HIV-1 infection and pathogenic SIV infections in Asian macaque species, but resolve to baseline in non-pathogenic SIV infections of African monkeys [10, 11]. Second, HIV-infected patients that do not exhibit disease despite high plasma virus have paradoxically low levels of ISG expression [12]. Therefore, there is a strong correlation between HIV-1 pathogenesis and IFN-signaling gene signature. Due to the limitation of human studies, however, the functional role of IFN-I in HIV-1 is not clearly defined. To functionally define the role of IFN-I in HIV-1 persistence and pathogenesis, several recent studies have been reported in HIV-1-infected human patients, and in SIV-infected NHP models. In earlier studies, administration of recombinant IFN-I showed little or no beneficial effects in HIV-1 patients [13–15]. In fact, it may have accelerated HIV-associated

This article is part of the Topical Collection on *HIV Pathogenesis and Treatment*

✉ Lishan Su
lsu@med.unc.edu

[1] Department of Microbiology and Immunology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

immunological diseases in those HIV-1 patients treated with IFN-I [16–18]. Consistently, recent studies with peg-IFN in HIV-1 patients under HAART showed unclear or minimal effect on the persistence of HIV-1 reservoirs during HAART [19–21], but enhanced HIV-1-associated CD4 depletion [19], although lower HIV-1 replication was detected in the IFNα-treated group after stopping HAART [19]. In SIV-infected monkeys under cART, pegylated-IFN has shown no effect on SIV replication or T cell function [22].

Several recent reports have attempted to define the role of IFN-I signaling in SIV-infected NHP models, by modulating IFN-I activities before and during SIV infection. Using a recombinant human IFN-1ant that binds IFNAR2 but not IFNAR1 (thus antagonistic to wild type human IFN-I [23]), blocking IFN-I signaling prior to and during acute SIV infection in monkeys elevated SIV replication and accelerated AIDS progression, confirming an important role of IFN-I in controlling early SIV infection [24]. In contrast, administration of IFN-α2a initially upregulated expression of antiviral genes and prevented systemic infection. However, prolonged IFN-α2a treatment induced IFN-I desensitization, increased SIV infection, and accelerated disease progression. Thus, early IFN-I signaling during acute SIV infection is critical to suppress SIV replication, but its persistence may be detrimental and accelerate SIV disease progression. In a similar study, an antibody (AGS-009) that neutralizes 11/13 of IFN-α subtypes was infused 1 day prior to SIV infection. No obvious effect on ISG expression was detected, but high-dose AGS-009 treatment induced a slight increase in acute-phase viral replication. Early blockade of IFN-α during acute infection, interestingly, decreased the level of activated CD4+ and CD8+ T cells during chronic infection phase, but accelerated progression to AIDS [25]. This study again indicates that IFN-I signaling during acute SIV infection plays a critical role to modulate SIV disease progression. One caveat in this study is that AGS-009 only neutralizes 11 of 13 IFN-α subtypes, not other IFN-I types including two IFNα subtypes and IFNβ.

When administered during chronic SIV infection, IFN-1ant significantly reduced expression of ISGs, but showed no significant effect on SIV replication or SIV-induced inflammatory cytokines [26]. In ART-suppressed chronically SIV-infected animals, IFN-1ant only marginally inhibited the low ISG expression, and showed no effect on SIV infection [26]. In addition, IFN-I blockade showed no effect on T cell activation and exhaustion markers, or any adverse effect on the host. The conclusion from this study is weakened by the fact that the recombinant IFN-1ant, which binds IFNAR2 but not IFNAR1, still has some low IFN-I activity to induce antiviral ISGs in human cells, and is thus only partially antagonistic to wild type IFN-I [23]. Indeed, two doses of IFN-1ant in SIV/ART-treated animals resulted in reduced expression of ISGs, but three doses showed no such effect [26]. Its antagonistic effect is likely only obvious when endogenous IFN-I is high, but not in SIV/ART-treated animals with persistent but low IFN-I signaling. A more complete blockade of all IFN-I signaling with IFNAR-blocking mAb is required to clearly define the role of IFN-I signaling during chronic SIV infection with and without ART.

Role of IFN-I Signaling in HIV-1 Infection, Pathogenesis, and Therapy in Humanized Mice

Humanized mice transplanted with human immune tissues or cells have served as robust models to study HIV-1 infection [27–29]. Humanized mice transplanted with HSC or both HSC and thymus fragments (hu-HSC, hu-HSC/TEC [30], or BLT [31] mice) have enabled investigation of HIV-1 persistence and human immune responses to HIV-1 infection, as well as human immunology and immunopathology [32, 33].

Humanized mice have been used to functionally define the role of Treg [34, 35] and of plasmacytoid dendritic cell (pDC) [36–40] in HIV immuno-pathogenesis; as well as in human vaccine evaluation [41–43]. Importantly, HIV-1 infection results in immune activation, correlating with T cell depletion and functional impairment in lymphoid organs of humanized mice [40]. As in human patients, cART could efficiently inhibit HIV-1 replication, but HIV rebounds rapidly post-cART discontinuation [44••, 45–47]. Furthermore, humanized mice have been used to study HIV-1 latency [46, 47] and HIV-1 therapy by broadly neutralizing antibodies (bnAb) [48, 49], and by IFNAR-blocking mAb [44••, 50, 51••, 52] for HIV-1 reservoir reduction or elimination. Therefore, humanized mice are proven relevant and robust to study HIV-1 persistence, pathogenesis, and therapy [32, 33].

Blockade of IFN-I Signaling Elevates Early HIV-1 Replication During Acute Infection in Humanized Mice The role of pDCs in HIV-1 disease progression is not well defined due to lack of a robust model. We and others have reported that functional human pDCs are developed in lymphoid tissues in humanized mouse models [29, 40]. Human pDCs are rapidly activated by HIV-1 infection and the level of pDC activation is inversely correlated with CD4+ T cell numbers [40], which is consistent with the observation from HIV-1-infected patients [7] and SIV-infected monkeys [8, 9]. To define the role of human pDCs in HIV-1 replication and immunopathogenesis in vivo, a monoclonal antibody that specifically and efficiently depletes human pDCs in all lymphoid organs in humanized mice in vivo was developed [38, 39]. When pDCs were depleted prior to and during early HIV-1 infection in humanized mice, no induction of IFN-I or ISGs was detected, indicating that pDCs are the major source of early IFN-I induction in response to HIV-1 infection. Consistently, HIV-1 replication (viremia determined by HIV-1 genomic RNA in the blood) was elevated to 5×–10× higher than control mice. To define the role of IFN-I in early

HIV-1 infection and pathogenesis in vivo, a monoclonal antibody (mAb) that blocks IFNAR1, thus all IFN-I signaling in humanized mice, was developed. Similarly as pDC depletion, HIV-1 replication was significantly elevated when the anti-IFNAR1 antibody was used to completely block IFN-I signaling in humanized mice [44••, 53•]. Therefore, IFN-I expression from pDCs plays a critical role to suppress acute phase HIV-1 replication in humanized mice.

Persistent IFN-I Signaling Contributes to HIV-1 Disease and Persistence In Vivo With depletion of pDCs during persistent HIV-1 infection in humanized mice, HIV-1 replication was also elevated in blood and lymphoid tissues. Consistent with higher viral loads, human T cells expressed higher levels of activation markers such as CD38 and HLA-DR. Surprisingly, depletion of pDCs could rescue human immune cells from HIV-induced depletion in the presence of increased HIV-1 replication [38, 39]. When tested with the IFNAR1-blocking mAb during persistent HIV-1 infection, the HIV-1 replication level in the IFNAR1-blocked group was also enhanced, associated with complete suppression of ISG expression. Phenocopying the pDC depletion study, human T cells were rescued in number and functions in anti-IFNAR1 mAb-treated mice. Hence, blocking IFNAR1, like pDC depletion, also reverses HIV-1 disease progression during persistent HIV-1 infection in humanized mice [44••, 50, 51••, 52, 53•]. Besides human T cells, pDC depletion or IFNAR blockade also reversed HIV-induced immunopathology in other cell types and organs including innate lymphoid cell type 3 (ILC3) and hematopoietic progenitor cells (HPCs) in the bone marrow [37, 38]. In an independent study, an IFNAR2-blocking mAb also achieved similar ISG inhibition or rescue of human T cells was observed in humanized mice [51••]. Distinct from the IFNAR1-blocking mAb, however, the IFNAR2-blocking mAb reduced HIV-1 replication in humanized mice without ART. It is not clear if the difference on HIV-1 replication is due to the different antibodies that target IFNAR1 or IFNAR2. Other factors such as different HIV-1 isolates may also have contributed to the difference. Nonetheless, these two studies have independently concluded that persistent IFN-I signaling during chronic HIV-1 infection contributes critically to the depletion and impairment of human T cells in humanized mice. This is consistent with recent findings reporting that IFN-I plays a detrimental role during chronic LCMV infection and blocking IFN-I signaling by an IFNAR1 antibody could enhance antiviral immune response and lead to early clearance of LCMV infection [54, 55].

Blocking IFNAR in Humanized Mice with HIV-1/cART Reverses T Cell Immune Exhaustion, Rescues Anti-HIV T Cell Activity, and Reduces HIV-1 Reservoirs HIV-1 infection in humanized mice can be effectively suppressed by combination ART with two RT inhibitors and one integrase inhibitor as in human patients. As in HIV-1 patients, cART fails to fully suppress HIV-induced inflammation such as ISG expression. In addition, HIV-1 reservoirs are detected by cell-associated HIV-1 DNA or by virus outgrowth assays (VOA). When cART is stopped, HIV-1 rebounds rapidly to pre-cART levels in all animals [44••, 46, 47, 52]. Therefore, humanized mice provide a highly relevant and robust model to study HIV-1 reservoir persistence, immunopathogenesis, and therapy. In humanized mice infected with HIV-1 and treated with cART drugs, IFNAR blockade fully reversed inflammation, rescued human T cells, and reduced exhaustion markers such as PD1/TIM3 induction on CD8 T cells. Importantly, 3 weeks of IFNAR mAb treatment rescued anti-HIV T cell functions. Thus, effective cART led to recovery of human T cells but failed to reverse aberrant immune hyper-activation and T cell exhaustion, and inhibition of IFN-I signaling in combination with cART rescued human T cell functions [44••, 50, 51••, 52, 53•]. Consistently, both levels of cell-associated HIV DNA and cells with infectious HIV-1 were reduced in mice treated with IFNAR-blocking antibodies [44••, 51••, 52]. When cART was stopped, a significant delay of HIV-1 rebound was observed and the virus rebounded to a lower level [44••]. Therefore, IFNAR blockade provides a new promising HIV-1 cure strategy to reduce or control HIV-1 reservoirs (Fig. 1).

Conclusion and Perspectives

Recent findings in humanized mice have revealed the dual roles of IFN-I signaling in HIV-1 infection and pathogenesis:

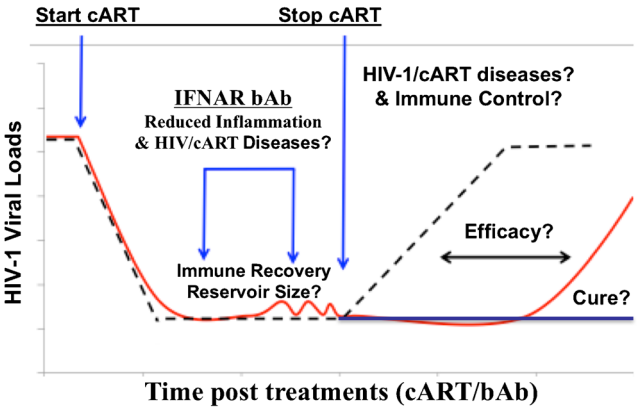

Fig. 1 Targeting IFN-I signaling in HIV-1 persistence, pathogenesis, and therapy. The chronic IFN-I signaling during HIV-1 infection ± cART contributes to HIV-1 disease progression, including hyper-immune activation, immune impairment, and HIV-1 reservoir maintenance. Therefore, inhibiting IFN-I signaling will likely reverse HIV/cART-associated inflammatory diseases, rescue anti-HIV T cells, and reduce HIV-1 reservoirs. cART, combination anti-retroviral therapy; IFNAR, IFN-I receptor; bAb, blocking antibody. Dashed line: HIV-1 rebound after stopping cART; red line: delayed HIV-1 rebound after immune therapy; and blue line: stable control (functional cure) of HIV-1 rebound after immune therapy

it plays a critical role to suppress acute HIV-1 infection and to set the anti-viral program. During chronic infection, however, persistent IFN-I signaling contributes to HIV-associated hyper-inflammation, immune exhaustion, and HIV-1 persistence. Intriguingly, blocking IFNAR in cART-treated humanized mice rescued anti-HIV immunity and reduced HIV-1 reservoirs [44••, 50, 51••].

In ART-suppressed chronically SIV-infected animals, IFN-1ant showed no effect on SIV replication or on T cell activation and exhaustion [26]. The pitfall of that study is that the recombinant IFN-1ant, which binds IFNAR2 but not IFNAR1, still possesses some IFN-I activity to induce antiviral ISGs in human cells [23]. Its antagonistic effect is likely only obvious when endogenous IFN-I is high, but not in SIV/ART-treated animals with persistent but low IFN-I signaling. A more complete blockade of IFN-I signaling with IFNAR-blocking mAb, which blocks signaling of all type I interferons, is required to clearly define the role of IFN-I during chronic SIV infection with and without ART.

It is important to point out the limitations of the humanized mouse models, including limited life span, incomplete human immune functions, and lymphoid organs. The relatively short life span of humanized mice will prohibit prolonged HIV-1 infection and cART; thus, the model may be limited to investigation of HIV-1 reservoirs during short-term cART in vivo. The defects in human immune functions such as lymphoid structure and B cell IgG response, and low reconstitution in gut-associated lymphoid tissues, should be carefully considered when interpreting experimental results for specific questions. The findings in humanized mice with IFNAR-blocking mAb thus should be confirmed in the SIV/NHP models with and without cART. If verified, blocking IFN-I under cART will provide a novel strategy to treat HIV/cART-associated inflammatory diseases in HIV-1 patients, as well as to rescue anti-HIV T cells to control HIV-1 reservoirs (Fig. 1). Regarding the safety of transiently blocking IFN-I signaling in humans, clinical trials in lupus patients have shown that treatment with an IFNAR1 antibody in healthy people for 84 days or in lupus patients for 48 weeks is clinically safe in human subjects [56, 57].

Acknowledgements The author acknowledges the contributions of the current and former Su laboratory members.

Funding Information The author's relevant research has been supported by grants from NIH (AI127346 and AI134631) and by the Lineberger Comprehensive Cancer Center at UNC-Chapel Hill.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Su reports grants from NIH (AI127346 and AI134631). In addition, UNC/Dr. Su has filed a patent (Modulation of Type I Interferons to Reactivate HIV-1 Reservoir and Enhance HIV-1 Treatment, pending).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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