Journal of Clinical Infectious Diseases & Practice

Mini Review Open Access

Antagonism of Type I Interferon Early Response and the Increased Risk by HIV and AIDS-Associated Viruses

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Abstract

Type I interferon (IFN) response initially limits HIV-1 spread and may delay disease progression by stimulating several immune system components. Nonetheless, persistent exposure to type I IFN in the chronic phase of HIV-1 infection is associated with desensitization and/or detrimental immune activation, thereby hindering immune recovery and fostering viral persistence. This review provides a basis for understanding the complexity and function of IFN pleiotropic activity in HIV-1 infection. In particular, the dichotomous role of the IFN response in HIV-1 immunopathogenesis will be discussed, highlighting recent advances in the dynamic modulation of IFN production in acute versus chronic infection, expression signatures of IFN subtypes, and viral and host factors affecting the magnitude of IFN response during HIV-1 infection. Lastly, the review gives a forward-looking perspective on the interplay between microbiome compositions and IFN response.

Introduction

Type I interferons (IFN-I) are cytokines abundantly produced during various immunological conditions and are known to play a pivotal role in the control of several viral infections. All type I IFNs bind with various affinities to their common receptor IFNAR, engagement of which triggers downstream transcription of a vast array of IFN-simulated genes (ISGs). Complete absence of IFN-I signaling by deletion of IFNAR in mice has been shown to enhance mortality from vesicular somatic virus, West Nile virus and lymphocytic choriomeningitis virus (LCMV). With repercussions for both innate and adaptive immune responses, the overall immunological consequence of IFN-I signaling is highly contextual and may vary across viral infections, bacterial infections, auto-immune disorders, and so on. Here, we focus on viral infections, specifically human immunodeficiency virus (HIV) infection during which IFN-I signaling via ISG expression in immune cells can lead to an antiviral state that interferes with several aspects of virus replication [1].

IFN and Clinical HIV Infection The most effective regimen to treat against HIV is highly active antiretroviral treatment (HAART) with physicians prescribing these combination antiretroviral therapies (cART) to limit the replication of HIV down to undetectable levels. IFN itself is a potent antiviral treatment that can activate the antiviral state in the host during HIV infection. Never the less, there had been many controversies on whether IFN is an effective treatment for HIV due to its positive effect on acute viral infection and negative effect on chronic infec- tion. Sustained IFN is believed to be partially responsible for immunological exhaustion that could lead to diminished T-cell function in chronic HIV infection. An additional finding focused on the fact that if these anti-IFNAR mAbs are administered during cART therapy, HIV-1 rebound after cART was delayed in the anti-IFNAR mAb-treated animals. This strategy can provide a novel therapeutic approach to treat patients living with HIV-1 infection with a sustained IFN-I level during cART [2]. In another study, elevated IFN-I signaling during chronic HIV infection was shown to be the main cause for underlying chronic inflammation, immune activation, and CD8+ T-cell exhaustion. Here, they showed that the combination of ART and IFNAR blockade during chronic HIV infection increased viral inhibition and ultimately led to a reduction in the reactivatable HIV reservoir. The study highlights the importance of IFN during viral infection and supports the ideas that IFN may act on both sides of the table during chronic HIV infection, fueling persistent immune activation and viral dissemination [3].

Detrimental effects of IFN-I signaling

Aside from restriction factors, other ISGs enhance pathogen associated molecular pattern (PAMP) detection and IFN signaling. For example, in response to viral PAMPs, IFN-I produced by plasmacytoid dendritic cells (pDCs) induces expression of the transcription factor IRF7 in neighboring cells which results in systemic expansion of IFN-I signaling [4]. Similarly, other ISGs such as cGAMP and IFI16 all contribute to a persistent production of IFN-I. The constant engagement of IFN-I signaling is thought to be at least in part responsible for the detrimental effects of IFN-I. Several studies have reported an association between IFN-I signaling and enhanced CD4 T cell depletion, potentially mediated through increased apoptosis [5], increase of CCR5-expressing HIV target cells or suppression of thymic output. Moreover, studies on LCMV have shown that chronic IFN-I signaling is associated with immune suppression characterized by reduced antigen-specific T cell responses, reduced T cell proliferation and increased CD8 T cell exhaustion. In HIV disease, type I interferon signaling is a major driver of immune activation, one of the strongest predictors of HIV disease progression to AIDS and non-AIDS morbidity and mortality. Collectively, these findings raised considerable interest in the potential therapeutic benefits of blocking IFN-I during HIV infection [6].

Blocking IFN-I signaling

Blocking IFNAR during acute SIV infection in vivo increased

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Received: 03-Mar-2023, Manuscript No: jcidp-23-90990, **Editor assigned:** 06-Mar-2023, PreQC No: jcidp-23-90990(PQ), **Reviewed:** 20-Mar-2023, QC No: jcidp-23-90990, **Revised:** 25-Mar-2023, Manuscript No: jcidp-23-90990 (R) **Published:** 31-Mar-2023, DOI: 10.4172/2476-213X.1000173

Citation: Roff S (2023) Antagonism of Type I Interferon Early Response and the Increased Risk by HIV and AIDS-Associated Viruses. J Clin Infect Dis Pract, 8: 173.

SIV plasma viremia, supporting the importance of IFN-I signaling for control of the infection during acute stage. In contrast, reduced inflammation and improved viral clearance was observed after blockade of IFN-I signaling with an anti-IFNAR antibody in murine LCMV infection. Recently, two independent studies showed that administration of anti-IFNAR antibodies to ART-suppressed, HIV-infected humanized mice resulted in reduced immune activation and lowered reservoir size. The results of these mouse studies encouraged the idea that blocking IFN-I signaling during chronic HIV infection may help improve clinical outcome [7]. In chronically SIV-infected rhesus macaques, systemic administration of a long half-life IFN-I antagonist significantly decreased ISGs with no impact on plasma virus load, immune activation or virus reservoir, irrespective of ART. With no obvious adverse effects, it remains to be determined what benefits will be gained from blocking IFN-I signaling during chronic HIV infection. Reduced T cell activation and virus reservoir achieved in humanized mice treated with anti-IFNAR blocking antibodies was not observed in non-human primates treated with an IFNα antagonist. Recent studies demonstrated that virus control is mediated by IFNβ and T cell exhaustion by IFNα in murine LCMV infection; and that in humanized HIV-infected mice, IFNβ or IFNα14 but not the commonly used IFNαa2 significantly suppressed HIV replication. Therefore, it is tempting to speculate that different members of the IFN-I family play different roles and manipulating specific type I IFNs might be needed to selectively target detrimental activities while maintaining beneficial ones [8].

Overall outcome and implication for HIV infection

All HIV/SIV studies on type I IFNs undoubtedly concur that the effects of enhancing or suppressing IFN-I signaling are strongly influenced by the timing of treatment. During acute infection, the antiviral effects of IFN-I outweigh the deleterious effects. IFN-I treatment has so far not been shown to match the efficacy reached with ART and would not be useful as monotherapy [9]. However, ART alone does not resolve chronic immune activation and is not sufficient to completely purge the HIV reservoir, potentially because antiretroviral drugs do not reach sufficient levels in lymphoid tissues where HIV predominantly resides. Because IFN-I readily penetrates tissues, a legitimate question to address would be whether ART and IFN-I combination in acute HIV infection may impact the establishment or size of the virus reservoir. During chronic HIV, limiting IFN-I's contribution to ongoing immune activation is thought to be a major target for clinical improvement. To date, this concept remains to be proven in experimental settings. Importantly, no study in non-human primate or humanized mice has so far shown a detrimental effect of blocking IFN-I signaling during chronic HIV/SIV infection; suggesting that type I IFNs may not be as critical for the control of the infection as they are in the acute phase [10].

Conclusion

While IFN was discovered for its powerful antiviral impact on innate immunity, the large numbers of anti-IFN strategies that are encoded in so many viruses underscore the coevolution that viruses have undertaken with humans and other hosts. With our understanding of viral pathogenesis constantly growing, it is now an opportune time to focus on developing strategies to open up the antiviral potential of IFN by targeting the many ways that viruses have developed to avoid IFN.

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