

COMMENTARY

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INTERFERONS AND HIV INFECTION: THE GOOD, THE BAD, AND THE UGLY

STANDFIRST

Type I interferons simultaneously control HIV replication and induce systemic immune activation, but whether the net effect is beneficial or detrimental remains controversial.

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ABSTRACT

Whether type I interferons (IFNs) hinder or facilitate HIV disease progression is controversial. Type I IFNs induce the production of restriction factors that protect against mucosal HIV/SIV acquisition and limit virus replication once systemic infection is established. However, type I IFNs also increase systemic immune activation, a predictor of poor CD4⁺ T-cell recovery and progression to AIDS, and facilitate production and recruitment of target CD4⁺ T cells. In addition, type I IFNs induce CD4⁺ T-cell apoptosis and limit antigen-specific CD4⁺ and CD8⁺ T-cell responses. The outcomes of type I IFN signaling may depend on the timing of IFN-stimulated gene upregulation relative to HIV exposure and infection, local versus systemic type I IFN-stimulated gene expression, and the subtype of type I IFN evaluated. To date, most interventional studies have evaluated IFN α 2 administration largely in chronic HIV infection, and few have evaluated the effects on tissues or the HIV reservoir. Thus, whether the effect of type I IFN signaling on HIV disease is good, bad, or so complicated as to be ugly remains a topic of hot debate.

KEYWORDS

HIV, SIV, AIDS, interferon type I, IFN, CD4

Type I interferons (IFNs) include 13 IFN α subtypes, IFN β , IFN ϵ , IFN κ and IFN ω . All type I IFNs bind the cell surface receptor IFNAR, a heterodimer of IFNAR1 and IFNAR2, but with varying affinities for each subunit [1, 2]. Binding and signaling through IFNAR results in the transcription of a multitude of IFN-stimulated genes (ISGs), and while all type I IFNs can activate antiviral pathways, the specific ISGs transcribed may vary widely [2].

Plasma IFN α levels are increased within the first week of HIV infection [3]. Based on data from rhesus macaque studies, ISGs are upregulated in peripheral blood and lymphoid tissues during acute simian immunodeficiency virus (SIV) infection, and despite decreasing, ISG expression remains higher in chronic SIV infection compared to pre-infection levels [4-6]. While continued ISG expression in chronic HIV infection may reflect the host's efforts to control virus replication and delay progression to AIDS, ISG expression has also been proposed to contribute directly to increasing the systemic inflammation that has been implicated in disease progression and mortality. Indeed, the complex system of IFN signaling renders classifying its biological outcome as good, bad or even ugly, somewhat of a challenge.

THE GOOD . . .

Type I IFNs stimulate expression of HIV restriction factors that limit virus replication. These restriction factors act at virtually every stage of the HIV replicative cycle, from reverse transcription (SAMHD1 and APOBEC3) to nuclear entry (MX2) to transcription (Schlafen 11) and budding (tetherin) [7-12]. Endogenous type I IFN production likely contributes some protection against infection, consistent with data that transmitted/founder viruses are relatively resistant to type I IFNs [13, 14]. Intramuscular IFN α 2a administration to rhesus macaques prevented systemic SIV infection following intrarectal inoculation as long as ISGs, including restriction factors, were upregulated [6]. In addition to upregulation in peripheral blood mononuclear cells, restriction factors were upregulated in rectal tissue and lymph nodes, protecting against transmission across the mucosal barrier and against dissemination, respectively. Similarly, vaginal IFN β administration prevented simian/human immunodeficiency virus (SHIV) infection in rhesus macaques following vaginal challenge with concomitant upregulation of ISGs in vaginal suspensions [15], suggesting that expression of antiviral proteins at the site of inoculation is sufficient to protect against systemic infection. Clearly, therefore, type I IFN signaling can prevent retrovirus infection in primates.

Type I IFN signaling may also be beneficial during acute retrovirus infection. Decreasing or delaying type I IFN signaling by *in vivo* blockade of IFNAR during acute SIV infection increased the SIV RNA setpoint [6], suggesting that the precise timing of ISG expression determines host control of virus production. Administration of IFN α 2 during chronic HIV infection tends to decrease HIV RNA and p24 antigen levels but is by no means a panacea as it has yet to be shown that it improves clinical outcomes beyond antiretroviral therapy (ART) alone [7, 16-27]. However, recent data from *in vitro* and humanized mice studies suggest that IFN α 8 and IFN α 14 suppress HIV replication to a much larger extent than IFN α 2 [28, 29], likely reflecting their higher affinities for IFNAR and subsequent increased MX2 and tetherin expression and APOBEC3 activity. Thus, type I IFN signaling can both prevent retrovirus infection and suppress retrovirus replication after infection.

THE BAD . . .

Clearly the elaboration of type I IFNs constitutes a proinflammatory response. In HIV infection, increased systemic immune activation predicts poor CD4⁺ T-cell recovery on ART and increased morbidity and mortality [30, 31]. Many have postulated that natural hosts of SIV such as sooty mangabeys and African green monkeys do not progress to AIDS because they downregulate ISGs and systemic immune activation just weeks after SIV infection [4, 5]. Notably, these species suffer less immunologic and structural damage to the gut during acute infection, which may explain the decreased inflammation in chronic infection [32]. Thus, once chronic SIV infection is established, these natural hosts have reverted to pre-infection levels of immune activation.

Several mechanisms have been proposed to explain this association of immune activation with disease progression. Increased ISG expression in CD4⁺ T cells is associated with CD4⁺ T-cell depletion [33], possibly via apoptosis mediated by tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) [34]. Type I IFNs also upregulate the HIV coreceptor CCR5 and induce pDC production of CCR5 ligands, creating and recruiting more target cells and further facilitating CD4⁺ T-cell depletion [35, 36]. In addition, type I IFNs suppress thymic output, further limiting CD4⁺ T-cell recovery [37]. Indeed, higher circulating IFN α levels are associated with lower CD4⁺ T cell counts [38], and IFN α 2a administration decreases CD4⁺ T cell counts in HIV-infected people [39]. Thus, while type I IFNs can suppress virus replication, they are also associated with increased CD4⁺ T-cell depletion.

In addition, chronic type I IFN signaling suppresses adaptive immunity. In the LCMV mouse model, blockade of type I IFN signaling improved antigen-specific CD4⁺ T-cell responses [40, 41], so type I IFNs not only suppress CD4⁺ T-cell recovery but also functionality. Type I IFNs do stimulate CD8⁺ T-cell activation and proliferation [27, 38, 42]. However, if type I IFN signaling precedes antigen exposure, proliferation of antigen-specific CD8⁺ T cells is suppressed [43]. Thus, HIV-infected people exposed to new antigens, including in the context of vaccination, may have suboptimal T-cell responses. Together, these findings suggest that chronic type I IFN signaling can increase susceptibility of HIV-infected persons to other infections.

THE UGLY . . .

Whether HIV clinical outcomes can be improved by increasing or decreasing type I IFN signaling remains hotly debated. The effect of type I IFN signaling on HIV disease pathogenesis varies based on whether acquisition, acute infection, chronic untreated infection, or chronic infection with virologic suppression is considered.

Although systemic IFN α 2a prevented SIV acquisition after rectal challenge [6], the findings may be different with vaginal challenge. The rectum is rich in CCR5⁺ CD4⁺ T cells, which may be readily infected with SIV [44]. In contrast, in the endocervix, pDCs are recruited to the site of infection where type I IFNs induce pDC production of CCR5 ligands that recruit CD4⁺ T cells. As a result, HIV-infected clusters form that serve as a nidus for dissemination [36]. While these pDCs may produce type I IFNs and induce antiviral protein expression, infection also spreads along the path of these infiltrating inflammatory cells [36]. Topical glycerol monolaureate was shown to suppress chemokines that recruit pDCs and prevent dissemination [36]. Paradoxically, topical IFN β also prevented infection despite increasing the frequency of CCR5⁺ CD4⁺ T cells, likely due to simultaneous upregulation of antiviral mediators [15]. By accessing visceral tissues and lymphatic tis-

sues, systemic type I IFN administration may facilitate proliferation, recruitment, and activation of pDCs and CD4⁺ T cells and thereby facilitate dissemination or, alternatively, prevent spread with widespread induction of antiviral genes. The specific restriction factors critical for HIV control are also unknown, and an approach focused specifically on increasing the host's ability to limit HIV replication rather than upregulating all IFN signaling may result in an intervention with greater tolerability and fewer adverse consequences.

The precise timing of type I IFN signaling in acute retrovirus infection is critical for determining clinical outcomes. Insufficient IFN signaling in the first week of infection can result in rapid progression to AIDS [6]. However, whether boosting type I IFN signaling during acute infection can limit the reservoir has yet to be determined. Data from African green monkeys suggest no adverse consequences from IFN α 2 administration starting 9 days post-infection, although ISGs were not further upregulated [45]. Rhesus macaques treated with type I IFN chimeras during the first 3 months of SIV infection had a similar disease course to untreated animals, but the impact on IFN signaling was not evaluated [46]. Thus, whether IFN signaling can be further induced in acute retrovirus infection remains unknown. Certainly it is tempting to speculate that increased and prolonged restriction factor expression may limit the HIV reservoir and even result in long-term control.

In chronic untreated infection, the data are fairly consistent that IFN α 2a can suppress HIV [7]. However, with the efficacy and tolerability of current antiviral regimens, the most clinically relevant question is whether type I IFNs can impact residual virus that persists despite ART. One potential limitation of antiretroviral medications is their ability to achieve sufficiently high levels in tissues such as lymph nodes [47]. Type I IFNs readily penetrate lymph nodes, the gastrointestinal tract, central nervous system, and other tissues [48]. Nonetheless, in people with chronic HIV infection taking suppressive ART, IFN α 2 treatment has not had a dramatic impact on CD4 T-cell recovery to date, nor has it had a clear detrimental impact [7]. However, these studies have not comprehensively evaluated the impact of type I IFNs on HIV levels in tissues. All studies published to date in chronic infection in non-human primates and humans have used IFN α 2, so whether IFN α 8 and IFN α 14 would have a more pronounced effect is unknown. In addition, repetitive IFN α 2a inoculation can eventually cause an IFN-tolerant state, which increased the virus burden in our rhesus macaque study [6], but type I IFNs with stronger IFNAR affinity that induce different ISGs may not carry the same risk.

The interaction of HIV and type I IFNs is complicated. Factors such as the anatomical site of HIV exposure or stage of HIV disease may determine whether type I IFN signaling is beneficial or detrimental. The 17 different type I IFNs each bind to their receptor differently and induce different signaling cascades, yet most studies in humans have only evaluated one of these type I IFNs. Several questions remain:

1. Can boosting type I IFN signaling during acute HIV/SIV infection result in a smaller reservoir and slower disease progression?
2. Does systemic type I IFN administration protect against or predispose to vaginal acquisition of HIV/SIV?

3. Are type I IFNs other than IFN α 2 more effective *in vivo* at suppressing HIV/SIV replication during acute and chronic infection? Are they more pro-inflammatory or immunosuppressive?
4. Can IFN-induced restriction factors be upregulated in a focused way without risking the potential detrimental consequences of boosting systemic type I IFN signaling?
5. Would blocking IFN signaling in chronic infection contribute to a reduction in systemic immune activation and thus ameliorate clinical outcome?

Ultimately, much remains to be explored to determine whether the functionality of type I IFNs can be harnessed to prevent or cure HIV infection, and we would encourage further clinical studies in humans.

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