HIV-1 Infection and Type 1 Interferon: Navigating Through Uncertain Waters

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Abstract

HIV-1 remains a chronic viral infection of global health importance. Although HIV-1 replication can be controlled by antiretroviral therapy (ART), there is no cure due to persistence of a long-lived latent reservoir. In addition, people living with HIV-1 who are taking ART still bear signatures of persistent immune activation that include continued type 1 interferon (IFN) signaling. Paradoxically, type 1 IFN exerts a limited role on the control of chronic HIV-1. Indeed, recent reports from humanized mice suggest that type 1 IFN may partly maintain the latent reservoir. In this review, we discuss the molecular interactions between HIV-1 and the type 1 IFN signaling pathway, and examine the efficacy of type 1 IFNs *in vivo*. We also explore whether limited type 1 IFN manipulation may have a therapeutic role.

Keywords: HIV-1 pathogenesis, type 1 interferon, immune activation, persistent latent reservoir

Introduction

HIV-1 INFECTS 37 MILLION PEOPLE worldwide. Although people living with HIV-1 (PLWH) are living longer due to antiretroviral therapy (ART),¹ they still suffer from adverse health outcomes. Moreover, PLWH require lifelong therapy to prevent virologic rebound from the long-lived HIV-1 latent reservoir.² Immunotherapies have been considered as a strategy to eradicate the latent HIV-1 reservoir that principally exists in resting CD4⁺ T cells. In that context, therapeutic manipulation of aspects of the type 1 interferon (IFN) system may contribute to HIV-1 eradication. Exogenously administered type 1 IFN inhibits HIV-1 replication potently: several lines of evidence have shown that interferon-stimulated genes (ISGs), the workhorses of the type 1 IFN system, partly drive HIV-1 adaptation³ and render defective many of the proviruses that seed the latent reservoir.⁴ However, exogenous type 1 IFN has many off-target effects that limit its usefulness in people. In addition, the type 1 IFN system may play a role in the persistent immune activation that continues to cause morbidity even among those treated with ART. Notably, recent evidence suggests that HIV-1 may exploit the type 1 IFN system. We have undertaken this review to summarize the key benefits and disadvantages of type 1 IFN and its manipulation on HIV-1 control. In addition, we discuss whether strategies to eradicate the latent HIV-1 reservoir may be bolstered by manipulation of components of the type 1 IFN system.

Molecular Mechanisms of Type 1 IFN

Type 1 IFN signaling can be divided into sensing and effector functions. Classically, pathogen-associated molecular patterns are sensed by cell surface and intracellular pattern recognition receptors (PRRs),^{5,6} triggering a signaling cascade that includes the activation of transcription factors, such as by phosphorylation of IRF3 or activation of NF- κ B. These transcription factors upregulate cytokines including type 1 IFN.^{5,6} PRRs that have been shown to sense HIV-1 include TLR7, cGAS, and IFI16. It was reported that upon entry, HIV-1 triggers TLR7 and TLR9 in plasmacytoid dendritic cells (pDCs), activating IRF5 and IRF7 to secrete type 1 IFN.⁷ In human monocyte-derived macrophages and THP-1 cells, single-stranded HIV-1 DNA that forms stem loops are sensed by IFI16, triggering the STING complex to activate IRF3, thereby resulting in type 1 IFN secretion.⁸ In a separate report of HIV-1 infection of THP-1 cells, type 1 IFN production was shown to be dependent on cGAS sensing of products of HIV-1 reverse transcription, also involving STING and IRF3.⁹ However, it has also been reported that early reverse transcription products are masked by TREX1 in THP-1 cells, thereby preventing type 1 IFN signaling.¹⁰

Along the same lines, there is controversy as to whether HIV-1 triggers type 1 IFN upregulation in cells that it infects: three separate groups^{11–15} demonstrated in cell lines that the HIV-1 accessory proteins Vif, Vpu, and Vpr degrade IRF3, while Nasr *et al.* reported that HIV-1 infection prevents nuclear translocation of IRF3 in macrophages.¹⁶ In contrast, Hotter

et al. have shown that in peripheral blood mononuclear cells (PBMCs) infected with a GFP-tagged HIV-1 virus, IRF3 is not depleted by HIV-1 infection.¹⁷ Hotter *et al.* also reported that NF- κ B activation is inhibited by Vpu.¹⁷ Manganaro *et al.* reported similar results to Hotter *et al.* in the cells that HIV-1 infects (primary CD4⁺ T cells and macrophages).¹⁸ Similarly, Harman *et al.* reported that IRF3 is largely intact in HIV-1-infected cells, but that TBK1 phosphorylation was inhibited by Vif and Vpr.¹⁹ In a comprehensive investigation into HIV-1 signaling, Rasaiyaah *et al.* found that HIV-1 contains adaptations in its capsid that permit infection of macrophages without triggering type 1 IFN responses.²⁰ These evasion mechanisms may enhance HIV-1 replication: Tsang *et al.* reported that the infectivity of HIV-1 in macrophages is dependent on the degree of evasion from macrophage sensing of HIV-1 nucleic acids.²¹

Whether or not type 1 IFN signaling is triggered in the cells that HIV-1 infects, it is quite clear that PLWH exhibit an immune activation state that is partly composed of elevated levels of type 1 IFN.^{22–25} Although various types of cells can potentially secrete 1 IFN during HIV-1 chronic infection,^{26–28} type 1 IFN in these people is likely to derive at least partially from professional signaling cells such as pDCs. In support of this, *in vitro* depletion of pDCs from simian immunodeficiency virus (SIV) infected macaques completely abrogated circulating type 1 IFN.²⁹ Several groups have partly reconciled the conflicting data on HIV-1 and type 1 IFN signaling by showing that HIV-1 infected lymphocytes, and not cell-free virus, potentially stimulate pDCs to produce type 1 IFNs in a TLR7-dependent manner.^{30,31} Herein, we conjecture that HIV-1-mediated suppression of type 1 IFN signaling may be important for establishing persistence during the acute stages of infection, whereas it may be less important during the chronic stages of infection, when there is abundant secretion type 1 IFN by cells that need not be permissive for HIV-1 infection.

After extracellular release, type 1 IFN signals in an autocrine or paracrine mode through the interferon alpha/beta receptor (IFNAR1/2) complex. Upon ligation of type 1 IFN with IFNAR1/2, receptor-associated Janus kinases phosphorylate STAT1 and STAT2 proteins that in turn dimerize. After nuclear translocation, the STAT1/2 dimer binds to IRF9 to form the ISGF3 transcription factor complex. ISGF3 binds to hundreds of interferon-sensitive response elements in the genome, leading to the upregulation of a distinct set of genes that are defined collectively as ISGs.^{5,6}

Many of the upregulated ISGs are antiviral molecules that have been well-described elsewhere.⁵ Importantly, HIV-1 replication has been shown to be restricted by several ISGs, including MX2, ISG15, APOBEC3G, BST2, TRIM5 α , SAMHD1, and SFLN11. MX2 inhibits nuclear translocation of HIV-1 cDNA after reverse transcription, preventing proviral DNA integration.³² ISG15 prevents HIV-1 replication by inhibiting ubiquitination of HIV-1 gag, thereby impeding virion release.³³ APOBEC3G induces hypermutation in HIV-1 proviral DNA during reverse transcription, introducing frequent nonsense mutations that render the provirus replication incompetent.³⁴ APOBEC3G has also been reported to inhibit HIV-1 reverse transcription.³⁵ BST2 (also known as tetherin) inhibits budding of new virions.³⁶ BST2 is also known to activate NF- κ B signaling upon the inhibition of budding of the virion.³⁷ TRIM5 α has been reported to inhibit HIV-1

replication by inducing disassembly of capsid proteins.³⁸ SAMHD1 has been described as critical in restricting HIV-1 replication in macrophages by decreasing the intracellular amount of deoxynucleoside triphosphates.³⁹ SFLN11 utilizes a unique mechanism to inhibit HIV replication by changing codon usage to prevent the translation of HIV-1 proteins.⁴⁰

The mechanisms of type 1 IFN-induced HIV-1 restriction factors have largely been worked out *in vitro*, whereas their relevance can be observed *in vivo* by measuring their effect on HIV-1 adaptation. For example, HIV-1 capsid mutations have been found that appear to confer progressive resistance to the activity of MX2.³ Similarly *in vitro*, the HIV-1 Vif protein antagonizes APOBEC3G, leading to its ubiquitination and degradation.⁴¹ Furthermore, Vpu displaces BST2 from binding to new virions.⁴² HIV-1 evolution, therefore, has been partly constrained by ongoing type 1 IFN responses, highlighting their importance. Research on whether HIV-1 affects the post-IFNAR signaling cascade (i.e., effector function) is relatively sparse: Ranganath *et al.* demonstrated that the U1 and OM10.1 cell line that contains integrated HIV-1 proviruses induced lesser amounts of ISGs upon type 1 IFN stimulation compared with uninfected cell lines (U937 and HL60 cells).⁴³

In addition to the direct restriction of HIV-1 replication, type 1 IFN plays a crucial role in modulating adaptive immune responses. For instance, in the presence of type 1 IFN, CD8⁺ T cells exhibit greater expansion, proliferation, and killing of target cells than in the absence of type 1 IFN.^{44,45} Although the role of type 1 IFN on adaptive responses to HIV-1 has not been studied extensively, one may cautiously extrapolate from the experience with other chronic viral infections. IFNAR^{-/-} mice with acute Friend murine retrovirus infection demonstrated more spleen damage, which is indicative of more viral replication, than wild-type mice. Interestingly, knockout of IFNAR resulted in a decrease in the percentages of CD4⁺ and CD8⁺ T cells, while the number of B cells and natural killer (NK) cells was not affected.⁴⁶ In lymphocytic choriomeningitis virus (LCMV) infection, an often-used model system of chronic viral infection, type 1 IFN has been shown to be required for early CD8⁺ T cell effector function.⁴⁷ Moreover, mice that were administered type 1 IFN showed more germinal center formation and secreted greater amounts of antibodies, and this phenotype was reversed in IFNAR knockout mice.^{44,48} These results suggest that type 1 IFN is also involved in B cell responses. Conversely, type 1 IFN has not been shown to be wholly beneficial for the host in priming adaptive responses. Type 1 IFN inhibited virus-specific B cell responses to LCMV.⁴⁷ Indeed, several investigators have reported that IFNAR blockade in a model of LCMV persistence led to improved viral clearance,^{49,50} and later investigations have demonstrated that this phenomenon is associated with improved anti-LCMV T cell responses.⁵¹ Importantly, there has not been an exhaustive study on the role of type 1 IFN on adaptive immune responses to HIV-1.

In Vivo Studies

The type 1 IFN/immune activation phenotype in SIV/HIV-1

A number of observational studies have been conducted in animal models and in humans to survey how SIV or HIV-1 affects endogenous type 1 IFN responses (Table 1). Notably,

TABLE 1. SUMMARY DATA ON TYPE 1 INTERFERON TREATMENT AND BLOCKADE
IN *IN VIVO* HIV-1 AND SIMIAN IMMUNODEFICIENCY VIRUS INFECTION

	Result	Model tested
Type 1 IFN signaling status	Upregulated ^{22–25,52–54,70,71}	<i>In vivo</i> SIV infection, ^{52–54} humanized mice, ^{70,71} humans ^{22–25}
Administration of type 1 IFN		
Plasma HIV-1 RNA	No effect, ⁶⁷ decreased, ⁶⁹ modest decline ^{74–77,79,80}	<i>In vivo</i> SIV infection, ⁶⁷ humanized mice, ⁶⁹ humans ^{74–77,79,80}
Immune activation	Increased ^{73,74,78}	Humanized mice, ⁷³ humans ^{74,78}
Disease progression	ND	ND
HIV-1, SIV reservoir	No effect, ^{81–83} decreased ^{75,84}	<i>In vivo</i> SIV infection, ⁸¹ humans ^{75,81–84}
Blockade of type 1 IFN (acute)		
Plasma HIV-1 RNA	Increased ^{56,57}	<i>In vivo</i> SIV infection ^{56,57}
Immune activation	Decreased ⁵⁷	<i>In vivo</i> SIV infection ⁵⁷
Disease progression	Faster ^{56,57}	<i>In vivo</i> SIV infection ^{56,57}
HIV-1, SIV reservoir	ND	ND
Blockade of type 1 IFN (chronic)		
Plasma HIV-1 RNA	Decreased, ^{70,71} increased ⁷²	Humanized mice ^{70–72}
Immune activation	Decreased ^{70,71}	Humanized mice ^{70,71}
Disease progression	ND	ND
HIV-1, SIV reservoir	Decreased ^{70,71}	Humanized mice ^{70,71}

This table summarizes the signature of type 1 IFN signaling and the effect of type 1 IFN administration or blockade (acute and chronic infection) on plasma HIV-1/SIV RNA level, overall immune activation, disease progression, and the size of HIV-1/SIV latent reservoir *in vivo*.

IFN, interferon; ND, no data; SIV, simian immunodeficiency virus.

there appear to be differences in the kinetics of ISG expression between sooty mangabeys and African green monkeys, natural hosts of SIV that do not experience AIDS, and rhesus macaques, in which SIV is pathogenic and leads to AIDS.⁵² All macaques upregulate MxA (the simian ortholog of human Mx1) expression 7 days after infection, whereas only rhesus macaques have durably high MxA expression for up to 29 days after infection when sooty mangabeys and African green monkeys exhibited attenuated MxA expression.⁵² Further research in nonhuman primates has confirmed that during acute SIV infection, ISGs are strongly upregulated in African green monkeys, rhesus macaques, and sooty mangabeys^{53,54}; however, ISG expression decreased to preinfection levels only in African green monkeys.⁵⁴ This was not thought to be due to differential sensing of SIV by pDCs,⁵⁵ although it may be related to altered sensing in other cell types.²⁹ Because SIV causes AIDS in rhesus macaques, but not in African green monkeys, the authors concluded that pathogenic SIV infection may be associated with abnormally persistent ISG upregulation. In fact, Sandler *et al.* demonstrated that type 1 IFN treatment before infection significantly decreased CD4⁺ T cells and the CD4⁺/CD8⁺ T cell ratio.⁵⁶ In a separate study, type 1 IFN blockade appeared to lessen the activation of CD4⁺ and CD8⁺ T cells in SIV-infected rhesus macaques,⁵⁷ further supporting that type 1 IFN responses may be pathologic and contribute to AIDS.

Data from humans reinforce the notion that type 1 IFN responses are persistently upregulated after the acute phase of HIV-1 infection. Hardy *et al.* reported a correlation between plasma type 1 IFN levels and plasma HIV-1 RNA levels.²² Catalfamo *et al.* showed that CD4⁺ T cells from HIV-1 infected persons with uncontrolled infection had higher levels of phosphorylated STAT1 with type 1 IFN stimulation compared with CD4⁺ T cells from HIV-1 infected persons with suppressed

viremia.²³ A hallmark signature of HIV-1-related immune activation is CD4⁺ T cell activation, defined by upregulation of various surface markers such as CD38, CD25, and HLA-DR. Activated CD4⁺ T cells in HIV-1-infected individuals were found to have upregulated ISGs compared with activated CD4⁺ T cells in HIV-1 uninfected individuals.²⁴ Our group recently reported ISG elevation in activated CD4⁺ T cells in chronic HIV-1 infection that is at least partly controlled by ART.²⁵

Constitutive type 1 IFN signaling is likely to be the result of continued PRR triggering by HIV-1. In addition, Hardy *et al.* investigated type 1 IFN signaling in HIV-1 chronically infected patients and reported that monocytes and some classes of dendritic cells, but not T cells, have less surface expression of IFNAR.⁵⁸ Despite the ubiquity of type 1 IFN signaling in HIV-1 infection, it is possible that this signaling is dysregulated, and not properly targeted: for example, Kamga *et al.* found that PBMCs from HIV-1 infected persons did not produce as much type 1 IFN as those from healthy donors upon *in vitro* stimulation by HSV-1, and that this may be explained by a decline in pDC numbers in HIV-1 infection.⁵⁹

The differences between acute and chronic exposure to type 1 IFN can also be observed in the resistance of HIV-1 to type 1 IFN. In a series of articles, it was revealed that viruses that are transmitted and that result in acute HIV-1 infection in new hosts are resistant to the effects of type 1 IFN.^{60–63} In contrast, HIV-1 appears to revert to a more type 1 IFN-sensitive state later during infection, presumably when adaptation to other selective forces dominate. Contradictory findings were reported by Deymier *et al.*, who demonstrated that there is no difference in IFN sensitivity between nontransmitted and transmitted virions during heterosexual transmission between epidemiologically linked couples.⁶⁴ Possibly, whether transmitted virus can gain IFN resistance is dependent on the duration of the infection, HIV-1 subtypes, and difference in host immune response.

The effect of exogenous type 1 IFN on SIV/HIV-1 replication

Multiple studies have been performed to investigate whether type 1 IFN treatment, exogenously administered, can inhibit SIV infection and disease progression. Veazey *et al.* reported that IFN- β administration before SHIV infection prevented vaginal transmission of SHIV in rhesus macaques.⁶⁵ Importantly, type 1 IFN antagonism using a reversible IFNAR inhibitor was shown to enhance SIV disease progression and mortality when administered before or during acute infection.⁶⁶ Vanderford *et al.* developed a recombinant type 1 IFN agonist that transiently upregulates ISGs and induced approximately a 1 log₁₀ SIV RNA cp/ml decline in treated sooty mangabeys.⁶⁶ These findings support the canonical role of type 1 IFN as inducing anti-SIV activity in the host. However, an intriguing report of type 1 IFN administration to SIV-infected rhesus macaques failed to detect an effect on SIV RNA decline.⁶⁷

Humanized mice are an exciting model in which many questions of HIV-1 replication can be addressed. Using the humanized mouse model, Li *et al.* found that pDCs were principally responsible for elevated plasma type 1 IFN levels during acute HIV-1 infection.⁶⁸ In addition, they found that pDC depletion and the resulting loss of type 1 IFN production facilitated HIV-1 replication.⁶⁸ An intriguing development in the field has been the discovery that HIV-1-infected humanized mice treated with IFN- α 14 demonstrated suppression of HIV-1 replication that was more potent than with other IFN- α subtypes.⁶⁹

In the setting of clear evidence of the antiviral effects of type 1 IFN on HIV-1, two separate groups recently reported that constitutive type 1 IFN signaling is present in a model of chronic HIV-1 in humanized mice, and that this phenotype was associated with CD8⁺ T cell exhaustion.^{70,71} After infection, the mice were treated with ART and were virologically suppressed. Both teams administered an antibody that blocked the IFNAR complex to the mice and found improvements in T cell activation and exhaustion. More impressively, IFNAR blockade led to improved control of HIV-1 replication. In contrast, IFNAR blockade increased plasma HIV-1 RNA level in chronically infected humanized mice without ART treatment, although the plasma IFN levels were also higher in mice with IFNAR blockade.⁷² Taken together, these data imply that type 1 IFN signaling may play a role in suppressing immune responses in HIV-1 infected humanized mice. Furthermore, Long and Stoddart treated humanized mice with recombinant IFN α 2b and found that treatment increased activated CD4⁺ and CD8⁺ T cell proportions, suggesting that type 1 IFN signaling in humanized mice may worsen the T cell activation phenotype that drives disease progression.⁷³ The data from animal models, therefore, are compelling but conflicting. Human or macaque studies using type 1 IFN antagonism during chronic infection (after viremia is suppressed by ART) would be of interest to test whether the humanized mouse studies are generalizable.

Numerous clinical trials spanning the HIV-1 epidemic have involved type 1 IFN administration to PLWH and have shown partial, although transient, control of viral replication.^{74–80} Many of those trials have also shown that exogenous type 1 IFN administration increases T cell activation. It should be noted that several of these trials occurred in persons

who were co-infected with hepatitis C virus (HCV). Importantly, the magnitude of upregulation of ISGs with known HIV-1 restrictive ability was closely associated with the subsequent decline in plasma HIV-1 RNA level, strongly suggesting that exogenously administered type 1 IFN resulted in upregulation of intracellular antiviral molecules that subsequently control HIV-1 replication.⁷⁹ However, it should be noted that the decline in plasma HIV-1 RNA level with exogenous type 1 IFN administration is only ~ 1 log₁₀ cp/ml,⁷⁹ despite weeks of administration. Therefore, the potency of type 1 IFN against HIV-1 may be modest at best.

The effect of type 1 IFN on the SIV/HIV-1 latent reservoir

An intriguing result emerged from the experiments using IFNAR blockade in HIV-1-infected humanized mice that were virologically suppressed with ART^{70,71}: both groups reported that type 1 IFN blockade resulted in significant decreases in measures of the latent HIV-1 reservoir, strongly suggesting that type 1 IFN is at least partly responsible for maintaining the size of the latent reservoir.^{70,71} Although no mechanism was confirmed by these groups, it is tempting to consider that type 1 IFN manipulation may alter the size of the latent reservoir. However, a trial of type 1 IFN treatment in SIV-infected macaques that had ART-suppressed viremia failed to show differences in the size of the latent reservoir as measured by quantitative viral outgrowth, although it did show a small decrease in cell-associated SIV DNA in CD4⁺ T cells from PBMCs.⁸¹

In humans, several clinical trials have evaluated whether exogenous type 1 IFN administration diminished the size of the HIV-1 reservoir: in one, the authors found a small but significant reduction in integrated HIV-1 DNA in total CD4⁺ T cells.⁷⁵ However, the team did not measure whether this translated to an effect on the latent HIV-1 reservoir of replication-competent proviruses in resting CD4⁺ T cells. Morón-López *et al.* showed that short-term type 1 IFN treatment did not alter the size of the HIV-1 reservoir in HIV-1/HCV co-infected patients when cell-associated HIV-1 RNA and infectious virions in the supernatant were quantified.⁸² More recently, HIV-1 DNA kinetics were studied in ART-treated and untreated HIV-1/HCV co-infected persons who received PEG-IFN between 20 and 68 weeks: there were no appreciable changes in HIV-1 DNA levels in any of the participants during PEG-IFN treatment.⁸³ In contrast, a separate trial of PEG-IFN in ART-suppressed HIV-1/HCV co-infected persons showed significant declines in cell-associated and cell-free HIV-1 DNA that was associated with NK cell numbers.⁸⁴

Whether or not the size of the latent reservoir is affected, there is definitive evidence in the latent reservoir of the impact of type 1 IFN on HIV-1: in a series of articles, investigators reported that the majority of HIV-1 proviruses contain major defects that result from APOBEC3G-regulated hypermutation and that render the proviruses replication incompetent.^{4,85} However, as reviewed earlier, hypermutations that are evident in proviruses are likely vestiges of APOBEC3G effects during active HIV-1 replication, rather than during ART treatment when the proviruses are latent. As immunomodulatory treatments are being developed for HIV-

1 cure strategies, it would be important to determine their role on the replication competent latent reservoir.

Potential Challenges

Despite its broad activity as an antiviral, exogenously administered type 1 IFN has limited potency and significant person-to-person variability. The best experience for type 1 IFN use in humans comes from the treatment of other viruses, such as HCV. In chronic HCV infection, pegylated IFN- α given with ribavirin for 48 weeks leads to sustained virologic responses in 40%–60% of patients,⁸⁶ whereas clinical trials of type 1 IFN in HIV-1 over a similar duration have yielded only modest declines in plasma HIV-1 RNA levels of between 0.1 and 1.7 log₁₀ cp/ml.⁷⁹ The broad person-to-person variability in the response of HIV-1 to type 1 IFN treatment is mirrored in the wide range of induction in ISGs that are observed in treated patients.⁷⁴

In the setting of limited efficacy, type 1 IFN treatment is associated with numerous adverse effects and problems with tolerability. Type 1 IFN treated SIV infected macaques experienced gastrointestinal side effects.⁶⁷ Asmuth *et al.* observed that majority of subjects tolerated exogenous pegylated type 1 IFN, whereas a number of patients complained of fatigue, depression, and absolute neutrophil loss.⁷⁴ A longer list of side effects emerges from clinical trials of type 1 IFN in chronic HCV infection, and includes but are not limited to thyroid dysfunction, fevers, chills, headaches, myalgias and arthralgias, gastrointestinal disturbances, suicidality, worsening of autoimmune conditions, and cytopenias.⁸⁷ Many patients report feeling a “flu-like syndrome” that can persist for the duration of therapy. The reported adverse effects are compounded with prolonged duration therapy: typical courses of exogenously administered type 1 IFN are from 12 to 48 weeks. Therefore, any HIV-1 cure strategy that involves type 1 IFN will have to balance the likelihood of success with the potential risks. Because of the profound, unpredictable, and broad toxicities of exogenous type 1 IFN, and in parallel because of the dramatic reduction in the toxicities of ARVs, it may be more tolerable to PLWH to endure manipulations of individual components of the type 1 IFN system, such as by enhancing APOBEC3G activity, rather than to undergo exogenous administration of type 1 IFN.

The Future of Type 1 IFN

A key question to be answered before type 1 IFN manipulation is attempted is whether the latent reservoir in humans is maintained by type 1 IFN, as suggested by the experiments of IFNAR antagonism in humanized mice.^{70,71} Although counterintuitive, other viruses have been identified that are sustained in part by components of the type 1 IFN system. For example, HCV upregulates protein kinase R (PKR), which is also an ISG, to block the translation of other ISGs while its viral protein production is not affected.⁸⁸ Indeed, if type 1 IFN sustains the latent reservoir, then a cure strategy may be bolstered by the administration of small molecules that block constitutive type 1 IFN signaling in patients. Importantly, the benefits of this approach will need to be balanced by considering its inherent risk of immunosuppression. Moreover, given the many profound adverse effects of exogenously administered type 1 IFN, it may be more beneficial to modulate specific ISGs that are associated with HIV-1 than to

broadly target the type 1 IFN system. Perhaps a more tractable approach is to recapitulate the function of potent HIV-1 restriction factors using small molecules. The converse approach, to target and inhibit HIV-1 adaptor proteins that degrade potent type 1 IFN-induced restriction factors, may be one route to control HIV-1. Perhaps most importantly, clinical trials that include type 1 IFN manipulation should include measurements of the effect on replication competent proviruses in resting CD4⁺ T cells, that is, the latent reservoir.

Conclusion

Type 1 IFN is a potent antiviral that suppresses HIV-1 replication. Because of high toxicities and limited effectiveness, more research is required to understand the interrelationship between HIV-1 and type 1 IFN. Future studies should focus on how HIV-1 perpetuates type 1 IFN signaling, whether this sustains the latent reservoir, and which specific ISGs are most critical in controlling or maintaining HIV-1 *in vivo*.

Author Disclosure Statement

No competing financial interests exist.

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