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Type I Interferons in NeuroHIV

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Abstract

Infection with Human Immunodeficiency Virus (HIV)-1 continues to cause HIV-associated neurocognitive disorders despite combined antiretroviral therapy. Interferons (IFNs) are important for any antiviral immune response, but the lasting production of IFNα causes exhaustive activation leading eventually to progression to AIDS. Expression of IFNα in the HIV-exposed central nervous system has been linked to cognitive impairment and inflammatory neuropathology. In contrast, IFNβ exerts anti-inflammatory effects, appears to control, at least temporarily, lentiviral infection in the brain and provides neuroprotection. The dichotomy of type I IFN effects on HIV-1 infection and the associated brain injury will be discussed in this review, because the underlying mechanisms require further investigation to allow harnessing these innate immune factors for therapeutic purposes.

Keywords: HIV-1, IFNα/β, type I interferon, NeuroAIDS, neurodegeneration, neuroprotection

Introduction

Infection with Human Immunodeficiency Virus (HIV)-1 continues to cause HIV-associated neurocognitive disorders (HAND) despite combined antiretroviral therapy (cART) (50,108). HIV-associated dementia (HAD) is the most severe manifestation of the disorders, and there is currently no treatment available for any form of HAND. Several lines of evidence strongly suggest that neurodegeneration occurs as a consequence of HIV-1 infection and neurotoxic immune stimulation of microglia and macrophages (MΦ) in the brain (12,37,39,42,60–62,85,86,97) and impairment of neurogenesis (44,66,94,111).

Beyond activation of MΦ and microglia, infection with HIV-1 triggers an innate immune response that includes interferons (IFN) (20,22,76,98). While IFNs are important for an antiviral immune response, the lasting production of IFNα and -γ causes an erroneous and exhaustive activation leading eventually to immune suppression and progression to AIDS (22,76,98,104). Moreover, expression of IFNα in the HIV-exposed central nervous system (CNS) has been linked to cognitive impairment and inflammatory neuropathology (7,9,80,106,107). In contrast, IFNβ exerts anti-inflammatory effects (54,55,73), appears to control, at least temporarily, HIV and SIV infection in the brain (8,9,25,38,64,65,83), and to provide neuroprotection (120). However, in HIV-1 infection, expression of IFNβ appears to be transient in contrast to that of IFNα (9,76,80). Transient expression of IFNβ has been observed in the CNS of SIV-infected macaques in association with extended viral control and delayed progression to disease in the brain (3,9) as well as in transgenic (tg) mice expressing in their CNS the viral envelope protein gp120 of the CXCR4-utilizing HIV-1 isolate LAV (121,123). Moreover, treatment of the gp120tg mouse model of HIV-associated brain injury with exogenous recombinant IFNβ resulted in neuroprotection against toxicity of the viral envelope protein (120). The dichotomy of type I IFN effects on HIV-1 infection and the associated brain injury will be discussed in this review because the underlying mechanisms require further investigation to allow harnessing these innate immune factors for therapeutic purposes.

HIV-1 Infection Associated with Neurotoxicity

HIV-1 infects microglia/MΦ and T cells through the chemokine receptors CCR5 and CXCR4, which, in conjunction with CD4, function as coreceptors for the virus (6,15,23,24,30,32). Interestingly, in the absence of intact virus, the HIV-1 envelope protein gp120 of CCR5-preferring, CXCR4-preferring, and dual-tropic viral strains all can trigger macrophage neurotoxicity and induce injury and apoptosis, *in vitro* and *in vivo*, in both primary human and rodent neurons (17,43,52,61,62,68,69,72,86–88,112,114,121). Moreover, in MΦ, HIV-1 infection and exposure to just the viral proteins gp120 or Tat seems to initiate a similar neurotoxic phenotype (42,43,74,117). Although HIV-1 primarily infects macrophages and microglia in the CNS, the virus and its envelope protein also cause impairment of neurogenesis

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by interfering with the proliferation of neural progenitor cells (44,66,94,111).

Neuropathology of HIV-1 Infection

The neuropathology associated with HIV-1 infection in the CNS is characterized by astrocytosis, myelin pallor, infiltration of MΦ, increased number of resident microglia and multinucleated giant cells, diminished synaptic and dendritic density, and selective neuronal loss (18,78,79,92). However, the increased number of microglia and MΦ, decreased synaptic and dendritic density, evidence of excitotoxins, and selective neuronal loss are the pathological hallmarks most closely associated with the clinical signs of HAND/HAD. Many regions of the brain can be affected, including frontal cortex, hippocampus, substantia nigra, putamen, basal ganglia and cerebellum, and HAND/HAD is associated with evidence of neuronal apoptosis (reviewed in (11,34,60,63,71)).

Interferons

IFNs were identified over 50 years ago and were characterized for their ability to ''interfere'' with viral replication (57). These cytokines are produced and secreted in response to pathogenic host invasion and inflammation by a variety of nucleated cells both in the CNS and the periphery, including astrocytes, microglia, neurons, macrophages, and T lymphocytes (29). These cytokines play critical roles in immunomodulatory activities that affect both the innate and adaptive immune responses (51). IFNs are separated into three different families based on the receptor type used. The type I IFN family encodes 13 IFNα subtypes in humans (14 in mice), a single IFNβ gene, IFNω, IFNκ, and IFNε, which together signal through the IFN-α/β receptor (IFNAR) that is composed of IFNAR1 and IFNAR2 subunits (110). In contrast, the type II IFN family consists solely of IFNγ, which is produced primarily by T cells and natural killer cells, whereas the type III group is composed of IFNλ1, IFNλ2, IFNλ3, and the recently discovered IFNλ4 (21,100).

HIV-1 Infection and IFNs

HIV appears to invade the CNS soon after peripheral infection, but severe neurological symptoms do often not present until later stages of disease progression (82). This delay in clinical manifestations can be explained by the host's ability to mount an antiviral immune response, which results in viral control during the acute stages of infection (3). In the periphery, HIV triggers a rapid nonspecific activation of the innate immune system, followed by a slower, but antigen-specific, adaptive immune response (84). In the brain, the blood–brain barrier restricts access of T and B cells, and therefore shifts the burden of HIV control to local innate immune defense mechanisms (115). IFNs are a major component of the first line of host defense against HIV and critical mediators of the immune response in the brain (47). Important for the periphery and the brain, IFNα, -β and -γ all can inhibit HIV-1 infection of MΦ and $CD4^+$ T cells (45,75,89,113).

During HIV infection, Type I IFN induction and secretion can be activated by several different mechanisms and the extent of induction depends on cell type and viral structure available for recognition by cellular Pattern Recognition Receptors (2). Intracellular sensing of HIV infection includes the Toll-like receptors (TLRs), of which TLR-7 is responsible for recognition of viral single-stranded (ss) RNA in endosomes. Cytosolic DNA sensors include the enzyme cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) synthase (c-GAS) and IFNγ-inducible protein 16 (IFI16), which detects HIV reverse-transcribed DNA products, and retinoic acid-inducible gene-1 (RIG-1), which senses viral RNA (31).

Plasmacytoid dendritic cells (pDC) are major producers of type I IFN/IFNα in the periphery and can be activated by free HIV particles as well as virus-infected $CD4^+$ T cells (70). When HIV is taken up by pDC through endocytosis, TLR7 detects endosomally delivered ssRNA and activates the myeloid differentiation primary response gene 88 (MYD88) signaling pathway. This signaling cascade leads to activation of IFN Regulatory Factor 7 (IRF7) and activation of the nuclear factor-κB (NF-κB) transcription factor to promote robust production of IFNs, specifically IFNα (10,14,70). In conventional Dendritic Cells (cDCs) and macrophages, HIV cDNA can be detected by c-GAS or IFI16 that can activate stimulator of IFN genes (STING) in the endoplasmic reticulum and induce IFN production through IRF3 and NF-κB. Finally, cytosolic RIG-1 can detect genomic viral RNA and trigger a STING-dependent immune response and the activation of IRF3 (2,31).

Because of its pronounced antiviral activity, IFNα has been investigated for HIV-1 treatment in several settings: before the introduction of cART, as part of a structured treatment interruption strategy, in acute HIV infection, as a component of salvage therapy and most recently, in attempts of eradication of viral reservoirs (102,122). Early attempts of treating established HIV infection had been disappointing or inconclusive, perhaps in part because under chronic conditions, IFNα eventually suppresses the function of the immune system, which then facilitates viral persistence and progression to AIDS (122). Therefore, it may not be surprising that one recent study suggested that blocking type I IFN signaling during chronic HIV infection–in this case with an antibody against IFNAR2–facilitates the restoration of immune function (127). However, other recent investigations related to HIV eradication suggest that IFNα in combination with cART and viral reactivation agents may support the elimination of HIV-1 reservoirs (41,56,93,105,116). The CNS is a HIV-1 reservoir and as such presents a major challenge for viral eradication (35,46,91). Given that IFNα clearly has a temporary antiviral effect on HIV-1, timing of IFNα treatment, time of onset and length of application, may be critical factors for successful eradication.

Type I IFN Signaling and IFN-Stimulated Genes

Both IFNα and IFNβ exert their effects by signaling in an autocrine and paracrine manner through the JAK/STAT pathway to activate transcription of antiviral genes that are known collectively as IFN-stimulated genes (ISGs) (31,109). IFN signaling induces dimerization of its cell surface receptors, IFNAR1 and IFNAR2, and activates the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2). These signaling events lead to phosphorylation, dimerization, and nuclear translocation of cytoplasmic signal transducer and activator of transcription

(STAT) molecules. The IFN-stimulated factor 3 (ISGF3) complex, which consists of a STAT1-STAT2 heterodimer and the cytoplasmic protein IFN-regulatory factor 9 (IRF9), binds to IFN-stimulated response elements (ISRE) in the promoters of most ISGs and activates a classical antiviral response. On the other hand, STAT1 homodimers bind gamma-activated sequences (118) and induce proinflammatory ISGs (58).

Altogether, these pathways result in an induction of numerous antiviral factors that restrict or interfere with HIV/SIV replication at different stages of the viral life cycle. HIV restriction and resistance factors include: tripartite motif-containing protein 5α (TRIM5α), sterile α motif domain and histidine aspartic acid (HD) domain 1 (SAMHD1), apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3), tetherin, IFN-induced transmembrane (IFITM) proteins, schlafen 11 (SLFN11), and MX2. Furthermore, some of these restriction factors can enhance the expression of an antiviral response by sensing viral particles (31,109).

Type I IFNs in the Normal and HIV-Infected CNS

A mouse model with genetic depletion of endogenous IFNβ signaling develops a Parkinson's Disease-like phenotype with motor and cognitive learning deficiencies, a significant reduction in dopaminergic neurons, impaired neuronal autophagy, and presence of α-synuclein-containing Lewy bodies in the brain (33). Interestingly, when these animals were treated with IFNβ, neuronal growth, branching, autophagy flux, and α-synuclein degradation in neurons were restored (33). This study revealed the critical role of physiological IFNβ signaling for normal brain homeostasis and function. Similarly, we detected impairment of spatial learning and memory in the absence of IFNAR1 (Hina Singh, Amanda Roberts, and Marcus Kaul, unpublished results). These findings are also in line with the observation in the normal brain of low-level baseline expression of IFNα and–β, which seems to be required for an effective type I IFN response in case of a viral infection (1,120).

Several studies have been published on the antiviral and neuromodulatory activities of type I IFNs in the CNS, yet the question of whether these cytokines hinder or facilitate HIV disease and HAND progression over time remains controversial (122). Of note, whereas IFNAR1-signaling of type I IFNs is critical for antiviral immunity, IFNα and IFNβ promote different additional biological responses in the CNS (47) in that IFNβ expression is associated with an anti-inflammatory response in the brain and IFNα is linked to increased neurocognitive dysfunction and inflammatory neuropathology (47).

Mice lacking functional IFNAR1 show increased susceptibility to fatal disease in most experimental RNA-virus infections of the CNS (19,36,47,90,103). For example, one study investigating the role of IFNAR1-mediated responses in antiviral control involved chimeric HIV-1 (EcoHIV), wherein gp80 of the ecotropic murine leukemia virus replaces HIV-1 gp120 to permit productive infection of mice (99). In this model, IFNAR1 knockout (KO) mice infected with EcoHIV presented with enhanced virus infiltration into the brain and inflammatory pathology, thus implicating type I IFN responses in control of HIV neuropathogenesis (49). However, since this model lacks expression of HIV gp120 in the brain, which is a critical component associated with HIV neurotoxicity, the role of IFNAR1 responses is not yet known in the context of gp120-induced neuronal injury.

Increased production of IFNα in the brain is a double-edged sword that provides antiviral protection, but also promotes inflammatory neuropathology and cognitive impairment. Transgenic mice that chronically produce IFNα in astrocytes show decreased susceptibility to neurotropic viral infection, but develop progressive inflammatory encephalopathy, gliosis, and neurodegeneration (4).

In humans, elevated IFNα expression in the CNS is associated with neurodegenerative disorders, such as Aicardi–Goutieres syndrome and Cree encephalitis (26,125). Moreover, antiviral therapy with IFNα in patients infected with hepatitis C and herpes virus is known to have side effects such as cognitive slowing, amnesia, and impaired executive functions (28,106,124). In the context of HIV infection, three separate studies showed that HIV patients with dementia have significantly higher levels of IFNα in the CSF compared with those without dementia (67,96,101). Moreover, elevated IFNα levels in the CNS correlate with increased atrophy in the frontal cortex of HAD patients and severity of dementia (80,96,101). In addition, a recent study found that IFNα in the CSF also correlates with milder forms of neurocognitive impairment and soluble neurofilament light chain (NFL), a marker of neuronal injury (7). These observations suggest that IFNα is involved in the pathogenesis of HAND before the development of dementia and in the presence of cART. Finally, under certain chronic conditions, IFNα can suppress the function of the immune system, which then promotes viral persistence and progression to AIDS (122).

The role of IFNα in the CNS has also been characterized in a SCID mouse model. Experiments where HIV-infected human macrophages were injected into the SCID mouse brains demonstrated that HIV infection causes significant increases in IFNα expression in the brain, which strongly correlated with cognitive deficits (107). Furthermore, blocking IFNα with neutralizing antibodies significantly improved cognitive impairment and decreased microgliosis in these animals (106).

In contrast to IFNα, IFNβ exerts anti-inflammatory effects and appears to be able to control HIV and SIV infection in the brain. Studies of SIV-infected macaques show that IFNβ is the main type I IFN that is produced by the brain during acute infection and its expression is associated with viral control in the brain (9). Previous studies showed that obstruction of endogenous IFNβ signaling in an experimental autoimmune encephalomyelitis mouse model produced more severe and chronic neurological symptoms, as well as increased microglial activation that can contribute to extensive tissue damage in the brain (119).

In the classical model of type I IFN signaling, IFNβ production leads to induction of IFNα (53). However, during SIV infection brains induce protective antiviral responses through the production of IFNβ, without production of IFNα (5). Meanwhile, in the periphery acute infection with SIV results in significant IFNα increases (5). This differential regulation during SIV infection in the brain depends on CCL2, which is predominantly produced by astrocytes upon viral infection (126). CCL2 binds to the CCR2 receptor on macrophages to selectively suppress IFNα expression

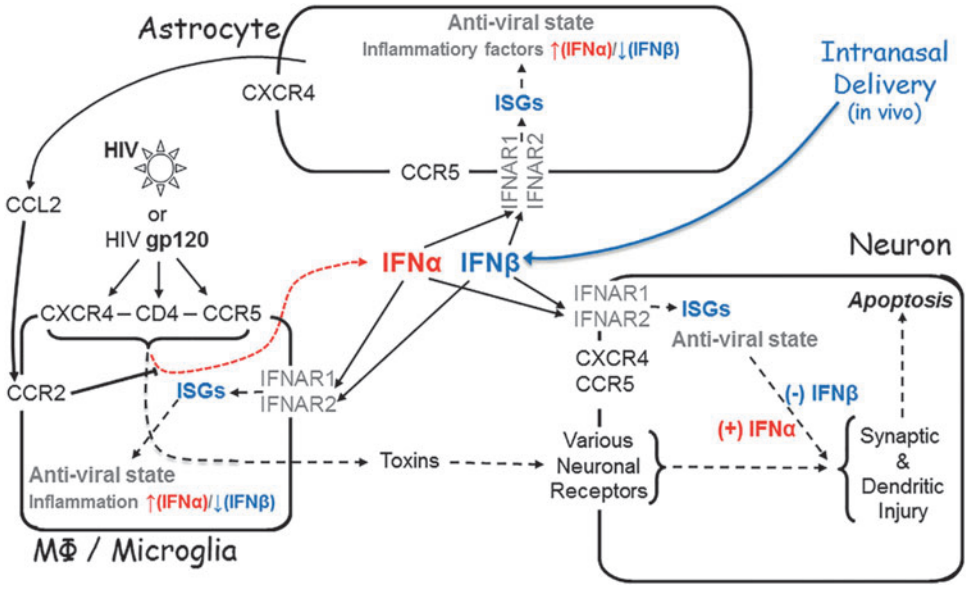

FIG. 1. Schematic model of the effects of IFNα and IFNβ in the HIV-infected brain and HAND. HIV-1 reaches the brain apparently soon after peripheral infection and resides in perivascular MΦ and microglia. These cell types are the primary sites of productive viral infection in the CNS, although all neural cell types can express the HIV coreceptors, CCR5 and CXCR4. HIV-infected and uninfected stimulated MΦ and microglia produce neurotoxins that damage neurons presumably engaging various receptors and mechanisms, all culminating in synaptic and dendritic injury and eventually neuronal apoptosis. HIV-infected MΦ and microglia may, at least temporarily, produce IFNα and IFNβ. CCL2 released by astrocytes, however, can suppress IFNα production by MΦ and microglia. IFNα and IFNβ can interact with all cells in the CNS since all express the two IFNAR subunits. Stimulation with IFNα and IFNβ generally induces ISGs and an antiviral state in all cell types. However, the spectrum of ISGs induced may be different for each type I IFN. IFNα seems to promote inflammatory processes and directly and/or indirectly compromise neuronal function and thus may contribute to the development of HAND. In contrast, IFNβ seems to overall limit inflammatory processes and contribute to neuroprotection by counteracting injurious mechanisms. *In vivo*, exogenous IFNβ can be delivered to the brain through intranasal application. CNS, central nervous system; HAND, HIV-associated neurocognitive disorder; IFN, interferon; IFNAR, IFN-α/β receptor; ISG, IFN-stimulated gene; MΦ, macrophages.

without altering expression of IFNβ and antiviral ISGs, such as MX1 (128). Several SIV studies strongly suggested that tight temporal regulation of the type I IFN response, in particular of IFNα expression, is critical to the avoidance of pathogenic lentiviral infection (16,48,59).

Similar to the observation in the SIV-infected macaques, we detected transiently increased IFNβ mRNA expression in the brains of HIVgp120tg mice at 1.5, but not 3 or 6 months of age (120). These tg mice express the viral gp120 of the HIV-1 isolate LAV under the control of a modified GFAP promotor in astrocytes in their CNS and recapitulate key features of brain damage seen in HIV/AIDS patients (121). As such, HIVgp120tg mice display a decrease of synaptic and dendritic density, an increased number of activated microglia, and pronounced astrocytosis (121). HIVgp120tg mice also develop significant behavioral changes, such as impaired spatial learning and memory at 8–9 months (81) and reduced swimming velocity at 12 months of age (27). Moreover, HIVgp120tg mouse brains share a significant number for differentially expressed genes with human HIV and HIV encephalitis (HIVE) patients, including evidence of an endogenous IFN response (40,81). However, while CCL2 expression was significantly elevated, IFNα remained at baseline level in HIVgp120tg mouse brains. Similar to the SIV model, the absence of an increase in IFNα in association with significantly elevated IFNβ in the brains of HIVgp120tg mice at 1.5 months might be due to upregulated CCL2.

As an antiviral therapeutic tool, IFNβ seems to cause less adverse side effects than IFNα (95). Moreover, due to its immunomodulatory effect, IFNβ is FDA approved for the treatment of multiple sclerosis, which is an inflammatory neurodegenerative autoimmune disease (77,95). IFNβ can also induce expression of factors that have neuroprotective activities, such as nerve growth factor (13), and the CCR5 ligands, CCL4 and CCL5 (65,121). In fact, using mixed neuronal–glial cerebrocortical cell cultures, we recently showed that IFNβ confers neuronal protection against the toxicity of HIVgp120. Moreover, treatment of HIV gp120tg mice with exogenous recombinant IFNβ through intranasal delivery resulted in neuroprotection, including neuronal dendrites and presynaptic terminals in cortex and hippocampus (120). Figure 1 summarizes in a schematic model the effects of IFNα and IFNβ in the HIV-infected brain and HAND.

In summary, based on the available data, it seems highly reasonable to further investigate whether IFNβ as part of the innate antiviral immune response, or if therapeutically administered, can provide a beneficial effect in controlling chronic HIV-1 infection and delay or prevent the development of HAND and its most severe manifestation, HAD.

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Author Disclosure Statement

No competing financial interests exist.

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