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Interferon α subtypes in HIV infection

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ABSTRACT

Type I interferons (IFN), which are immediately induced after most virus infections, are central for direct antiviral immunity and link innate and adaptive immune responses. However, several viruses have evolved strategies to evade the IFN response by preventing IFN induction or blocking IFN signaling pathways. Thus, therapeutic application of exogenous type I IFN or agonists inducing type I IFN responses are a considerable option for future immunotherapies against chronic viral infections. An important part of the type I IFN family are 12 IFNα subtypes, which all bind the same receptor, but significantly differ in their biological activities. Up to date only one IFNα subtype (IFNα2) is being used in clinical treatment against chronic virus infections, however its therapeutic success rate is rather limited, especially during Human Immunodeficiency Virus (HIV) infection. Recent studies addressed the important question if other IFNα subtypes would be more potent against retroviral infections in *in vitro* and *in vivo* experiments. Indeed, very potent IFNα subtypes were defined and their antiviral and immunomodulatory properties were characterized. In this review we summarize the recent findings on the role of individual IFNα subtypes during HIV and Simian Immunodeficiency Virus infection. This includes their induction during HIV/SIV infection, their antiretroviral activity and the regulation of immune response against HIV by different IFNα subtypes. The findings might facilitate novel strategies for HIV cure or functional cure studies.

1. Introduction

The type I interferon (IFN) family is a pleiotropic cytokine family, which members are immediately induced during many viral infections. Once produced, mainly by plasmacytoid dendritic cells (pDCs) but also by other immune cells, they bind to their ubiquitously expressed IFNα/β receptor (IFNAR) consisting of the two subunits IFNAR1 and IFNAR2. The affinity of type I IFNs to IFNAR2 is much higher than to IFNAR1 [1,2], leading to an initial IFN-IFNAR2 binding followed by recruitment of IFNAR1 to form the ternary complex at the cell surface. Subsequently, phosphorylation of the cytoplasmic receptor unit and associated Janus family tyrosine kinases (Tyk2 and Jak1) occurs, resulting in recruitment and phosphorylation of signal transducers and activators of transcription proteins (STAT1, STAT2) by the activated kinases. Phosphorylated STAT1 and STAT2 associate with IFN regulatory factor 9 (IRF9) to form the trimeric IFN-stimulated gene factor 3 (ISGF3) complex, which translocates to the nucleus. This complex binds to the IFN-stimulated response element (ISRE), which leads to the transcription of numerous IFN-stimulated genes (ISGs). During individual viral infections specific patterns of ISGs are expressed resulting in distinct antiviral activities that depend on the infecting virus [3]. These activities include directly acting ISGs like apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G (APOBEC3G), Tripartite Motif 22 (Trim22), Tetherin, SAM domain and HD domain-containing protein 1 (SAMHD1), myxovirus resistance 2 (Mx2) and IFN-induced transmembrane proteins 1-3 (IFITM1-3) [4–11]. In addition to these direct effects on virus replication type I IFNs also indirectly modulate virus-specific immune cell functions and cell proliferation.

Type I IFNs belong to a multigene family consisting of numerous IFNα subtypes but only one IFNβ, IFNε, IFNκ, and IFNω (human) or limitin (mouse) [12]. All 13 human IFNα subtype genes are located on chromosome 9, whereas the murine genome encodes for 14 different subtypes on chromosome 4 [13]. IFNα subtype genes exist in all kinds of vertebrates [14,15] and they likely developed from an ancestor *IFNA-*

Abbreviations: AIDS, acquired immune deficiency syndrome; APOBEC3G, apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G; ART, antiretroviral therapy; BLT, bone marrow-liver-thymus; Dpi, days post infection; HIV, human immunodeficiency virus; IDO, indoleamine-2,3-dioxygenase; IFITM, IFN-induced transmembrane proteins; IFN, interferon; IFNAR, IFNα/β receptor; IRF, IFN regulatory factor; ISG, IFN-stimulated genes; ISGF3, IFN-stimulated gene factor 3; ISRE, IFN-stimulated response element; LPMC, lamina propria mononuclear cells; MAP, mitogen-activated protein; MHC, major histocompatibility complex; Mx2, myxovirus resistance 2; NK cells, natural killer cells; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cells; PKR, protein kinase R; rh, rhesus; SAMHD1, SAM domain and HD domain-containing protein 1; SIV, simian immunodeficiency virus; STAT, signal transducers and activators of transcription proteins; TRAIL, tumor necrosis factor related apoptosis inducing ligand; Trim, tripartite motif

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like gene by gene conversion and duplication [14,15]. All IFNα subtypes have similarities in structure, like the lack of introns or the length of the protein (161–167 amino acids), and their protein sequences are highly conserved (75–99% amino acid sequence identity) [16,17]. They all bind to the same IFNα/β receptor, however the binding affinity to both receptor subunits differs between the subtypes [2]. For example, the affinity of human IFNα1 to IFNAR2 is much lower compared to all other subtypes (40–550 fold lower). Furthermore, it was demonstrated that activation of different downstream signaling cascades, including phosphorylation of distinct STAT molecules and mitogen-activated protein (MAP) kinases, can occur in a subtype-specific manner [18]. Thus, there is growing evidence that different binding affinities, cell type specificities, the microenvironment, receptor avidity, timing and fine tuning of the downstream signaling events may all modulate the response to the individual IFNα subtypes [19,20]. Various *in vitro* and *in vivo* studies already revealed their distinct antiviral and immunomodulatory properties in different viral infections [21–26]. However, the biological role of individual IFNα subtypes during HIV and SIV infection, their induction, antiretroviral capacity and their impact on the immune response against HIV infection has not been studied untilvery recently and will be summarized in this review.

2. Induction of IFNα subtypes during HIV and SIV infection

All human *IFNA* genes cluster on the short arm of chromosome 9 [27] and their expression is mainly triggered by IRF3 and IRF7, however also other IRFs can participate in the expression of *IFNA* genes (e.g. IRF1, or IRF5). IRF3 and IRF7 are both activated by various RIG-I-like helicases and Toll like receptor-mediated signaling pathways resulting in the expression of type I IFNs. The promoter regions of the *IFNA* genes contain positive regulatory domain (PRD) I and III-like elements (PRDLEs) [28], which are binding sites for IRF family members. It was shown that *IFNB* and *IFNA1* (human) or *IFNA4* (mouse) are exclusively induced early in infections dependent on IRF3 [29,30]. This leads also to the expression of IRF7, which is required for the transcription of all other *IFNA* subtypes. However, the regulation of the transcription of *IFNA* genes also depends on the relative expression and ratio of IRF3 and IRF7 in different cell types, which can change during a virus infection. Also the specificity of IRF3 and IRF7 for the promoter region of the different *IFNA* genes might be important for their individual transcription [30].

Previous studies analyzed the *IFNA* subtype gene expression pattern in HIV-infected individuals at the mRNA level [31,32]. A comparison between healthy individuals and HIV-patients (CDC stage A or C) demonstrated an increase in *IFNA6* and *IFNA2* expression in HIV-infected patients compared to healthy controls [26] (Fig. 1). Furthermore, *IFNA1/13, IFNA8, IFNA14, IFNA16, IFNA17* and *IFNA21* were significantly higher expressed in patients with acquired immune deficiency syndrome (AIDS) (stage C) than in HIV$^+$ patients without AIDS symptoms (stage A). The expression of *IFNA4, IFNA5, IFNA7* and *IFNA10* did not change during the course of HIV infection. Remarkably, *IFNA2*, which was strongly elevated during HIV infection, inversely correlated with CD4$^+$ T cells counts. No other *IFNA* subtype correlated with any monitored clinical parameter in this study. Similar results were shown in a study investigating the differences in the gene expression profile of *IFNA* subtypes in chronic HIV-infected patients under antiretroviral therapy (ART) or treatment-naïve individuals [32]. In peripheral blood mononuclear cells (PBMCs) of healthy patients, only a few subtypes were detectable. However, during chronic HIV infection, *IFNA2* and *IFNA16* were significantly enhanced in both groups (ART and treatment-naïve) compared to healthy controls [32] (Fig. 1). In all chronic HIV-positive individuals only seven *IFNA* subtypes (*IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA14* and *IFNA16*) accounted for more than 95% of the total IFNα response. Surprisingly, the expression patterns were very similar between individual patients, suggesting that a common signature of *IFNA* subtypes exists in humans.

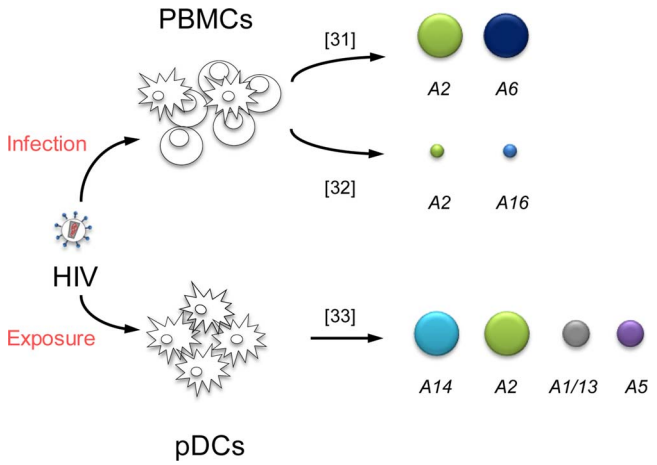

Fig. 1. *IFNA* subtype expression after infection or exposure to HIV.
PBMCs of HIV-infected patients [31,32] and pDCs isolated from healthy patients [33] were analyzed for the expression pattern of individual *IFNA* subtypes. Normalized expression levels are indicated by the size of the circles. For HIV infection of PBMCs *IFNA* subtypes with a significant increase are shown. In HIV exposure experiments *IFNA* subtypes which were strongly induced (> 500 fold) and predominantly expressed are shown.

Another study by Harper and colleagues analyzed the *IFNA* subtype expression in isolated pDCs exposed to HIV-1_{BaL} using next-generation sequencing [33]. They found a predominant expression of five *IFNA* subtypes (*IFNA1/13, IFNA2, IFNA5, IFNA8* and *IFNA14*) in stimulated pDCs but three out of these five subtypes (*IFNA1/13*, *IFNA5* and *IFNA8*) were already expressed in mock-stimulated pDCs [33] (Fig. 1). Comparing these two studies, which either analyzed mixed PBMCs of HIV-infected patients or isolated pDCs exposed but not productively infected with HIV-1, revealed that three of the induced subtypes were identical, whereas at least two were rather different. From these data one can infer, that the cell type as well as the stimulating virus and the sensing pathway may regulate the expression of the individual IFNα subtypes in HIV infection.

Some studies also analyzed the induction of *IFNA* genes during acute SIV infection either in rhesus or pigtailed macaques [34–36]. In rhesus macaques, tissue-specific expression of *IFNA* subtype transcripts was observed in lung, brain, thymus, spleen and various lymph nodes. In the thymus of uninfected rhesus macaques the basal expression of rhesus *IFNA* subtype genes was low and only five out of 13 rhesus (rh) *IFNA* transcripts were detectable (rh*IFNA1, IFNA2, IFNA7, IFNA8* and *IFNA14*) [34]. During acute SIV infection, when the thymus becomes dysfunctional and contributes to pathology, the expression pattern of *IFNA* genes rapidly changed starting as early as day 3 post infection. In particular, rh*IFNA1, IFNA2* and *IFNA3* were expressed in the thymus of seven out of nine rhesus macaques after infection. *IFNA7*, *IFNA8, IFNA13* and *IFNA14* were detected in up to six out of nine acutely SIV-infected animals, whereas all other *IFNA* genes were only sporadically observed indicating that the thymic *IFNA* subtype expression during acute SIV infection was very similar in the out-bread monkeys. Furthermore, no significant differences in *IFNA* expression levels were observed at different time points post SIV infection (3, 7, 10, and 14 days post infection (dpi)). In orally SIV-infected infant rhesus macaques, *IFNA* transcription differed between lymphoid tissues (tonsils; retropharyngeal, mesenteric and axial lymph nodes) and mucosal tissues (colon and gingiva), and the overall magnitude of *IFNA* gene expression correlated with viral loads in the different tissues [35]. The authors of this study detected all *IFNA* subtypes in the rhesus macaques; however the highest increase after infection was reported for *IFNA1/13, IFNA2, IFNA4, IFNA6* and *IFNA8*. In mucosal tissue, these subtypes only slightly increased in expression, most likely because of low numbers of IFN-producing lymphocytes. In lymphoid tissue also *IFNA14, IFNA17* and *IFNA21* were increased by SIV infection, albeit to a lesser extent