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Type I interferon and hepatitis B virus

Shi Zou[a], Xiaozhou Yang[b]

Abstract
In addition to its antiviral effect, type I interferon (IFN-I) also functions in the regulation of immune response and involves in the regulation of the activity of immune system that is recognized as pleiotropic cytokine mediating both immunostimulatory and immunosuppressive effects. In acute and chronic infection, IFN-I can induce a various spectrum of immune responses. Although IFN-I has been applied in the treatment of chronic hepatitis B, the treatment efficacy are still not satisfactory and only 30% of certain patients have shown positive effect with IFN-1 treatment. IFN-I is recently reported not to be eligible for the elimination of hepatitis B virus (HBV) in some specific cases. This review summarizes the immunomodulatory functions of IFN-I and the role in HBV.
Keywords: Type I interferon; immune regulation; Hepatitis B virus

Introduction

Type I interferon (IFN-I) has multiple functions both directly and indirectly modulating the natural and adaptive immune response in the presence of a virus infection, It has been demonstrated that IFN-1 involves in both innate and adaptive immune response. However, IFN-I is a negatively regulatory factor that regulates immune response and can be used as an immunosuppressive agent. IFN-I links to its corresponding receptors, triggering the activation and transduction of downstream signaling pathways exhibiting different immunomodulatory functions in different infectious periods and various cell types and cell stages respectively. The global infection rate of chronic hepatitis B (CHB) has climbed up to 5% with 240 million CHB carriers. Although IFN-1 treatment is widely used as a standard treatment approach of CHB, the problems of substantial side effects and low antiviral response rate limit its widespread application for the treatment of HBV.

IFN-I induction and its signal pathway

IFN-I which comprises IFN-α, IFN-β, IFN-ω, IFN-κ and IFN-ε, is primarily generated through a series of biosynthesis such as fibroblasts, lymphocytes and endothelial cells under the stimulation of viruses, bacteria and their products. The invasion of viruses or bacteria is mainly recognized by pattern recognition receptor (PRR) which is expressed on the cell surface, cytoplasm or nucleus, to whose responsibility lie on sensing foreign nucleic acids and their own DNA as well as other non-nucleic acid pathogen related molecular patterns (PAMP). PRR family includes resinous acid-induced gene I-like receptors (RLRs), Toll-like receptors (TLRs), Nucleotide-binding oligomerization domain-like receptors (NLRs) and some DNA receptors that binds to corresponding ligand to activate downstream signaling pathways and triggers IFN-I production [1-4]. On the cell surface, TLRs (such as TLR4) spot on bacterial lipopolysaccharide (LPS) and transfer signals through the beta interferon TTRIF to effectively promote IFN-I production [5]. In the cell, they can recognize double-strand RNA, single-strand RNA and unmethylated CpG DNA, of which RIG-I and melanoma differentiation-related gene 5 (MDA5) are the main cytoplasmic receptors responsible for detecting RNA and specific AT-rich DNA bases [2]. Besides, a bunch of receptors like DNA-dependent interferon regulatory factor activator (DAI), DEAD box and DEAH box helicase in the cytoplasm, and the newly discovered cytoplasmic Cyclic guanylate-adenylate synthase (cGAS) DNA sequence are able to recognize DNA [2, 4]. In addition, NOD1 and NOD2 in cells are capable of recognizing nucleic acids and ligands and inducing IFN-I production [6, 7].

The effect of IFN-I depends on its binding to the IFNα/β receptor (IFNAR) on the cell surface compiled by almost all cells within the inner environment. The conformational change of receptor occurs after engagement of the receptor. In the classic JAK-STAT pathway, Janus kinase 1 (JAK1) interacts with non-receptor tyrosine kinase (TYK2) with cross-phosphorylation and the activated JAK1 and TYK2 activates STAT [8] to homopolymerize or heterodimerize STAT1/2. STAT heterodimer then forms ISGF3 with IRF9 (Figure1). These complexes translocate into the nucleus and bind to interferon stimulus response element (ISRE) under the promoting process of the IFN-I, regulating ISG expression which encodes hundreds of sub-species to initiate the downstream IFN-I reaction [9]. Besides, IFN-I is also an activator of STATs pathways such as STAT3, 4, 5 and 6, activating multiple downstream genes [10, 11] and downstream transcription factors through non-STAT pathway like mitogen-activated protein kinase (MAPK) [12] and phosphatidylinositol 3-kinase (PI3K) pathways [13]. MAPK activation results in production of ISG while activation of PI3K signaling mediates pro-apoptotic and anti-apoptotic effects and also induces the activation of mTOR to regulate mRNA translation [14]. IFN subgroups play different roles in IFN-I expression thus inducing antiviral and antiproliferative effects respectively [15, 16], probably due to variation in IFNAR1 conformational changes

[a] Department of Infectious Diseases, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, 430022, China
[b] Department of Infectious Diseases,The Second Affifiliated Hospital of Dalian Medical University, Dalian, Liaoning 116023, China
Corresponding author: Dr. Xiaozhou Yang, No. 467 Zhongshan Road, Shahekou Region, Dalian, Liaoning 116023, China; E-mail: wowodou8@163.com.

triggered by ligand binding of IFNAR1 and IFNAR2 receptor subunits [16]. Therefore, the signal transduction of IFN-I exhibits antiviral and immune response at the level of cell, concentration and IFN subgroup. Here, we plan to provide all aspects of IFN-1 transduction and cellular responses through certain key signal pathways during viral infection.

Impact of IFN-I on Inflammatory Response

PAMP binds to PRR and induces the production of IFN-I. IFN-I up-regulated MHC-I in various cells [17] as MHC-I is a cluster molecules necessary for T cell differentiation, proliferation, and eliminating infected cells during inflammatory cytokines such as IP-10, iNOS, IL-12, TNFα [20]. For immature DCs, IFN-I induces cell maturation and amplifies the expression of MHC molecules and modulate certain molecules (such as CD80 and CD86) on surface of DCs, thereby increase the potential of T cell function [21]. IFN-I also promotes the migration of DC to lymph nodes by up-regulating the expression of chemokine receptors to enable T cell activation [22]. Analogous to DCs, macrophages/monocytes are stimulated by IFN-α to operate chemokines such as CxCL9 and CxCL10 [23]. In respiratory syncytium virus infection, downregulation of IFN-I related signaling pathway could weaken inflammatory response [24].

As a recent study reveals that IFNβ signaling can directly inhibit NLRP1 and NLRP3 inflammations in a STAT1 dependent manner, which also induces the production of IL-10 to activate the IL-10 transcription factor STAT3, reducing the levels of pro-IL-1α and pro-IL-1β9. Physiologically, high levels of IFN-I strongly engender a reduction in IL-12 level during mouse cytomegalovirus (MCMV) and LCMV infections [26], weakening the pathological response of IL-12. In virus infection, the direct or indirect impact of activated IFN-I and function of NK cells promotes NK cells to secrete IFN-γ and strengthens their cytotoxicity [18], which is essential for virus purging. In case of MCMV infection, IFN-I promotes NK cell aggregation and cytolytic function through STAT1-mediated signal transduction pathway without switching on the production of IFN-γ, probably due to the indirect effect of IL-15 [19]. Besides, IFN-I can also stimulate mature dendritic cells (DCs) to secrete chemokines. In LPS-stimulated DCs [27] or macrophages [28], IFN-I can mediate the secretion of IL-10 in these cells. Clinically anti-inflammatory effect of IFN-I is also illustrated by its application to the treatment for multiple sclerosis [29]. The mechanism may be that IFN upgrades IL-10 secretion and downgrades the antigen delivering function of glial cells [30] mainly through activating STAT3 and IRF1 signaling pathways [31] or PI3K pathways [32].

Regulation of IFN-I on adaptive immune response

IFN-I is closely associated with the differentiation of $CD4^+$ and $CD8^+$ T cells, promoting the differentiation of $CD4^+$ T cells into Th cells [33], increasing the synthesis of cytokines such as IL-18 and IL-21, potentiation the effect of Th1 cells [34, 35]. Yet on the contrary, IFN-I also interferes with the expression of Th2 transcription factors and even impedes the differentiated Th2 cells [36]. $CD4^+$ T cell depletion in STAT1-deficient mice decreases the lethality of LCMV infection and alleviates the tissue development. For suppressor cells, Srivastava et al. [37] has revealed that the IFNAR1 signal on $FoxP3^+$ Tregs limits the inhibitory function of Treg cells in acute LCMV, hence facilitating virus control. Knocking out the IFNAR1 weakens the virus-specific T cell response and allows virus replication. IFN-I effect in $CD8^+$ T cells is to upregulate the expression of MHC-I in various antigen-presenting cells (APC), promoting the proliferation of $CD8^+$ T cells and enhancing cell killing ability [38]. It also modulates toxicity of NK cells to protect specific anti-virus $CD8^+$ T cells [39] when directly promoting the differentiation of $CD8^+$ T cells [40]. Besides, IFN-I is seemed to affect the differentiation and function of memory $CD8^+$ T cells. In viral infection, IFN-I promotes the function and transferable ability of memory T cells through various ways. During the respiratory tract infection induced by Sendai virus, memory T cells may also be chemotactic under the influence of IFN-I, swimming to lung [41]. During the re-infection of LCMV, IFN-I promotes the production of chemokines to enable central memory T cells to transfer correctly; in MCMV infection, chemotactic inflammatory monocytes produce cytokines such as IL-15 and IL-18, prolonging the survival and enhancing the function of memory $CD8^+$ T cells. Similar to T cells, IFN-I also has bilateral effect on the B cells. For mature B cells, IFN-I could promote the activation of B cells, increase the production of antibodies, leading to the switch of subtype antibodies after influenza virus, VSV and WNV infection [42, 43].

However, recent evidence hinted that IFN-I obstructed adaptive immune response. The experiment of Vandenbark et al. [44] confirmed that IFNβ treatment boosted the number of Treg and the expression of Foxp3 mRNA in the PBMC of multiple sclerosis patients. The negative regulatory effect of IFN-I on the proliferation of $CD8^+$ T cells may hinge on the specific stages of IFN-I production if before the stimulation of antigen [45]. In vivo studies have shown that certain procedures with poly(I:C) in mice have a quite probability of inducing IFNα/β-dependent apoptosis, thereby consuming out CD8+ T cells [46]. Once the mouse gets infected with influenza, IFN-I catalyzes CD8+ T cells to secrete IL-10[47], and increase the expression of PDL-1 in epithelial cells [48]. In the LCMV mouse model, IFN-I was depicted to encumbrance the production of IFN-γ on CD8+ T cells through the STAT1 pathway [49]. For immature B cells, the IFN-I mainly hinders the maturation and decreases survival of B cells [50]. Studies have shown that the absence of IFNAR1 is accompanied with a higher level of influenza virus-specific antibodies in mice after virus infection [51]. During acute LCMV infection, knocking down the IFN-I enhances the differentiation of TFH, germinal center B cells, and catalyzes anti-LCMV antibody responses in STAT3-deficient mice [52]. IFN-I can also participate in the role of controlling neonatal inflammatory response through IL-10 induced by $CD5^+$ B cells [53].

Roles of IFN-I in HBV

1. IFN-I entangles with the clearance of HBV: The natural cause of HBV increases the risk of liver

failure, cirrhosis and primary hepatocellular carcinoma, as one of the most endangered pathogens affecting the health and increasing the mortality rate. IFN-I is widely used in the treatment of CHB. Mechanistically, IFN-I suppresses HBV transcription, degrades HBV RNA, inhibits reverse transcription of pgRNA, shows a great influence of the formation of nucleocapsid or aggravating its degradation, the specific antiviral mechanism is complicated, controversial and still remain enigmatic. Here we systematically traced back three elementary pathogenesis in IFN-1 regulation in HBV. (1) IFN-I resists HBV through antiviral protein. It induces the production of ISG and certain proteins including oligo adenylic acid synthase (OAS), ISG15, protein kinase (PKR), and Mx, with direct or indirect antiviral effect. ISG is mainly revolutionized for initially antiviral effect of IFNα/β. These genes are either continuous expressed in the microenvironment as a result of decreased IFNα/β. Further, their reaction to the IFNα/β production during infection when IFNα/β motivate adjacent cells to effectively obstructed the replication of the fusion genome of virus [54]. ISG20 is implicated to inhibit HBV replication by selectively degrading HBV RNA [55]. (2) The study of Shen X et al. [56] demonstrated that treatment with peginterferon α-2b increased the number of associated NKp30+ cells in the serum and strengthened cytotoxic action. (3) IFN-I directly couples with viral gene promoter to regulate the viral transcription and translation process. The cytokines involved within IRFs signaling pathway participate in the regulation of the HBV enhancer I and X promoter (Ehn I/Xp) to exert direct antiviral effects [57]. However, interferon treatment is not compatibility for all patients with chronic hepatitis B, considering that antiviral ratio is only 20%-40%.

2. IFN-I obstruct the clearance of HBV: During viral infection, the process of infection is determined by the activation of chronic immune response, also the expression of inhibitory immune regulatory factors, increased interferon signals and lymphatic tissue destruction. Recent evidence showed a diverse opposite conclusion that IFN-I is not positive for virus elimination under certain circumstances. In a mouse model of persistent LCMV infection, IFNAR1-related suppression of the IFN-I signaling pathway neutralized antibodies disturbs the immune system, decreases IL-10 and PD-L1, which significantly accelerates virus clearance [58, 59]. A similar phenomenon has also been observed in the infected mouse model of HBV. A study by Tian Y et al. [60] demonstrates that IFN-I inhibits HBV replication with an increased viruses duplication, but with low viruses duplication of HBC, IFN-I directly promotes HBV gene replication and expression by inducing the transcription factor HNF3γ and activating STAT3. Huang MT et al. [61] found that the continuous expression of HBV-related gene in young mice is closely related to the increased IFN-I affinity in early stage of infection, and suppressed IFN-α/β could be detrimental to HBV persistence in young mice. In addition, in terms of IFNAR-1 gene polymorphism, He et al. [62] elucidates that IFNAR-1 not only participates in determining whether the infection is cleared or chronicized in the early stage of HBV, but also affects the pathogenesis of HBV infection in the long term. Clinically, IFN-α as immunoregulation and antiviral drug, has already been applied to treat HBV and the virus tolerance has been observed. The long-term course of HBV caused by IFN-I often emerge in the early stage of HBV infection [61]. Given the limited resources of human liver samples, it is still unclear whether IFN-I increases HBV in the early stages of liver and whether it will affect the clinical outcome of HBV, which will be our future study.

Disclosure of conflict of interest

None.

Conclusion

The immune regulation of IFN-I is not entirely invariable. Interferon stimulates a variety of cells to produce cytokines to initiate inflammation and confine the proliferation of infected organs and tissues. Meanwhile, IL-10 also has a negative role in inflammation. Immune regulation of IFN-I is determined by the type of pathogenic microorganisms, the stage of infection, the occurence spot of inflammation, and state of cells. The efficacy of interferon for treating CHB patients is determined by the interaction between the host and the virus, IFN-induced antiviral protein, host genetics, cellular immune status and viral factors. At present, interferon is mainly localized to patients with liver dysfunction. A previous study [63] showed that interferon treatment accelerated the clearance of HBsAg and seroconversion in HBV carriers in the inactive carrier state. Therefore, the strategy of interferon for HBV treatment urgently requires improvement. Whether interferon can be applied to some patients with normal liver function, and whether the suppression of interferon production in the early stage of infection can prevent the HBV chronicity remains to be further studied in the future.

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Figure legends

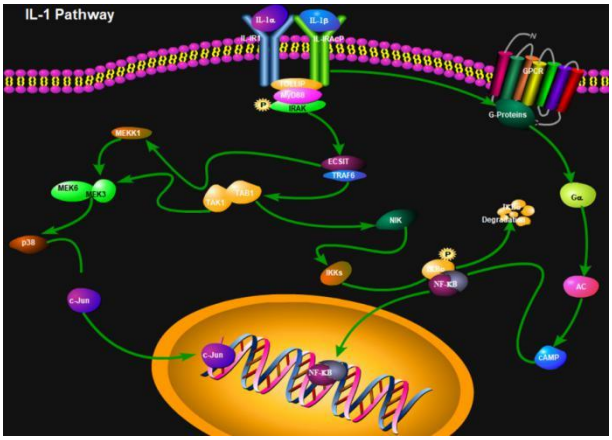

Figure 1. **JAK-STAT pathway**

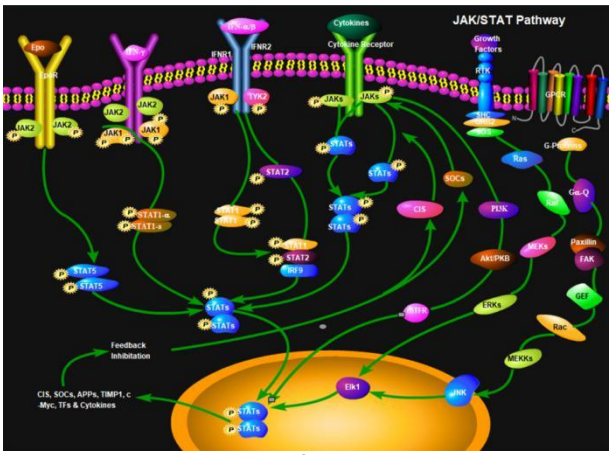

Figure 2. **IFN-1 signaling feedback mechanism**