Review

Type III Interferons in Viral Infection and Antiviral Immunity

Jian-hua Zhou^a Yi-ning Wang^a Qiu-yan Chang^b Peng Ma^b
Yonghao Hu^a Xin Cao^{a,b}

^aCollege of Veterinary Medicine, Gansu Agricultural University, Lanzhou, ^bCenter for Biomedical Research, College of Life Science and Engineering, Northwest Minzu University, Lanzhou, China

Key Words

Interferon • Immune defense • Viral infection • Innate immune • Adaptive immune • Cytokine

Abstract

Interferons (IFNs) can serve as the first line of immune defense against viral infection. The identification of IFN- λ s 1, 2, 3 & 4 (termed as type III IFNs) has revealed that the antiviral immune response to viruses contains more components than the type I IFNs that have been known for more than 50 years. IFN- λ s are IFN- λ 1 (IL-29), IFN- λ 2 (IL-28a), IFN- λ 3 (IL-28b) and IFN- λ 4, which resembles IFN- λ 3. IFN- λ s have type I-IFN-like immune responses and biological activities, but our knowledge of these novel players in the antiviral response is not well established. In this review, we try to describe the current information on the expression and function of IFN- λ s in the innate antiviral immune defense and IFN- λ 2's role in regulating and shaping the adaptive immune response. We suggest that IFN- λ s are key antiviral cytokines, directly performing an antiviral immune response at epithelial surfaces in the early stages of viral infection, and that these cytokines also skew the balance of Th1 and Th2 cells to Th1 phenotype. In addition, genetic polymorphisms in IFN- λ genes can impair antiviral immune responses in clinical treatment.

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Introduction

The first line defense for resisting pathogen infections generally depends on the innate immune response. During the course of the immune response, the pattern recognition receptors (PRRs), which are limited by the germ line, are used for identifying molecular organizations conserved among classes of pathogens, such as viral double-stranded RNA. Interferons (IFNs), which are host-encoded secreted proteins and are classified into three types (I, II & III), often join in multiple immune interplays and perform both the induction and regulation of innate and adaptive antiviral mechanisms when viruses infect the host. Once viral infections occur, the expression of type I IFN (generally focusing on IFN- α & IFN- β) will function as a pivotal innate antiviral defense response [1]. The antiviral activity performed

by type I IFNs directly inhibits viral replication. In addition, type I IFNs can mediate cellular immune functions of both the innate and adaptive immune system to carry out resistance to viral infections and keep long-term immunity [2]. Due to obvious antiviral functions of type I IFN [3], many studies on the immune activities of type I IFN have been carried out, and a large amount of information has been obtained about the molecular mechanisms of its biological actions, the immune induction of type I IFN and immune evasion performed by viruses [4]. Based on the many studies for type I IFN, it is used as an immune inducer or drug to treat persistent viral infection. Among the three types of IFNs, type III IFNs, termed IFN- λ or IFNLs, also play important roles in antiviral immune activities [5]. Type III IFNs (IFN- λ 1, 2 & 3) were discovered as interleukin (IL)-29, 28a & 28b and have many immune activities in common with type I IFNs [6, 7]. A new member, termed IFN- λ 4, was later discovered and can be expressed only by individuals who carry the gene symbol (IFNL4- Δ G allele [rs368234815]) [8]. Of note, innate antiviral responses to virus particle entry were directly mediated by PRRs and were independent of both TLR and RIG-I pathways, namely, in an IFN-independent manner [9]. This finding illustrates that the early events involved in innate antiviral activities are more complex than previously thought and highlights that researchers still need to evaluate many more cases to understand the early steps of the host-virus struggle. In this review, we try to introduce how the type III IFNs were discovered and discuss what has been learned about their role in the mediation of the innate / adaptive immune systems and their mechanism of antiviral defense. Finally, we suggest future directions for the research on type III IFN biology.

The discovery of type III IFN

Type III IFNs, including IFN- λ 1, IFN- λ 2 & IFN- λ 3, were first described by computational predictions according to genomic data [6, 7]. The discovery of IFN- λ 4 was done by analyzing many single nucleotide polymorphism (SNP) markers located upstream of the IFN- λ 3 chromosomal region, based on the genome-wide related studies of hepatitis C virus infection [8]. To better classify the gene symbol of IFN- λ 4, basic information on the location of the IFN- λ family in the genome is illustrated in Fig. 1. The four members all exist in a region from 19q13.12 to 19q13.13 in the long (q) arm of chromosome 19. The *IFNL1* gene (IL-29) is located downstream of *IFNL2* (IL-28a), and the *IFNL3* gene is located downstream of *IFNL4*. The three proteins (IFN- λ 1, IFN- λ 2 & IFN- λ 3) are transcribed and translated from the genes (*IFNL1*, *IFNL2* & *IFNL3*) and are highly similar to each other. In detail, the similarity extent between IFN- λ 2 and IFN- λ 3 is approximately 96% at the amino acid sequence level, and the amino acid identity between IFN- λ 1 and IFN- λ 2 / IFN- λ 3 is approximately 81% [6, 7]. Although IFN- λ 4 most closely resembles IFN- λ 3, the amino-acid identity between IFN- λ 3 and IFN- λ 4 is approximately 30% [10]. The IFN- λ receptor was investigated by the means of scanning translated human genomic sequences for sequences related to class II cytokine receptors. IFN- λ 1-4 are regarded as type III IFNs because they signal through a receptor complex which is distinct from the receptor used by type I and type II IFNs [11, 12]. Hence, the further description of a new type of innate antiviral cytokine raised a number of questions and urged for an additional understanding of the role of IFN- λ s in antiviral

Fig. 1. Location of the genes of the IFN- λ family in chromosome 19.

defense. Here, we show some new data involved in the roles of IFN- λ s in innate and adaptive immune responses in order to illustrate the biological activities of these IFNs and provide some reference suggestions for the potential clinical application of IFN- λ s to viral infections.

The generation of IFN- λ s during viral infection

A pivotal step of IFN generation is the requirement for detection of microbes by intracellular receptors. The viral genetic materials are the most potent inducers of IFN responses. In the cytoplasm, 5'-triphosphorylated or double-stranded (ds) RNA is recognized by the domain 'DEXD-H box' helicases RIG-I and MDA5 [13, 14]. In the endosomes, ssRNA or dsRNA can be recognized by Toll-like receptors (TLR3, TLR7, TLR8 & TLR9) [15-17]. In some cases, DNA can serve as a potent inducer for IFN generation, but little evidence about receptor systems mediating these events has been reported. It has been reported that DNA-dependent activator of IFN-regulatory factors (DAI), also termed DLM-1 or ZBP1, can recognize Z- / B-DNA and trigger IFN expression [18, 19]. The interaction between IRF3 and DAI can contribute to IFN responses to human cytomegalovirus DNA [20]; however, DAI is likely to increase the levels of HIV-1 replication through the DAI-NF- κ B pathway [21]. Interestingly, due to the cross-talk between DNA- and RNA- sensing systems, RNA polymerase III recognizes some DNAs as templates and performs de novo generation of 5'-triphosphorylated RNAs with double stranded structures, which can trigger IFN systems via the RIG-I pathway [22, 23]. Furthermore, other new pathways involved in DNA-sensor triggering IFN systems have been identified, including the cGAS-STING pathway and the absent in melanoma 2 (AIM2) inflammasome pathway [24-26]. In cGAS-STING pathway, dinucleotide 2',3'-GMP-AMP can serve as an endogenous second messenger in innate immune signaling induced by the non-self DNA associated with bacterial and viral infection and be recognized by the receptor STING to induce the phosphorylation of TANK-binding kinase 1 (TBK1) and IRF3 resulting in IFN generation [27]. For a new receptor for cytoplasmic DNA, AIM2 can shape an inflammasome with the ligand and ASC (apoptosis-associated speck-like protein domain containing a caspase activation and recruitment domain) to activate both caspase-1 and NF- κ B. These signal transductions then trigger the type I IFN system and pyroptotic and apoptotic death pathways [28-30]. Altogether, the intracellular sensing of microbes through different receptor systems of the innate immune system triggers signaling to some transcriptional factors and finally results in IFN generation.

As for the roles of transcription factors in the expression of the two types IFNs, the transcriptional strategies rely on nuclear factor (NF) κ B and IFN regulatory factors (IRFs). Despite the generally similar transcription model for the expression of the two types, there are important differences in the transcription mechanisms mediating expression of the two types [31]. Taking IFN- α for example, a cluster of IRF-binding sites exist in IFN- α promoters, but there are different affinities for the binding of IRF3 and IRF7 to the corresponding sites, and IRF7 has a strong trend to bind the IFN- α promoter to induce gene expression [32, 33]. For IFN- β expression, both IRF3 and IRF7 can bind well to the correct site in the promoter. Due to the expression being constitutive, while IRF7 expression is IFN-specific, IFN- β expression is an early innate immune response, while IFN- α expression is a delayed response but is at high levels [33, 34]. Turning to the expression of IFN- λ s, the promoters of all IFN- λ genes have binding sites for NF- κ B and IRFs [35, 36]. Of note, the promoter in the IFN- λ 1 gene has a high affinity for IRF3, while that of IFN- λ 2/3 has a high affinity for IRF7. Therefore, IFN- λ 2/3 responses represent a delayed kinetics compared with that of IFN- λ 1 [36]. Compared with the human IFN- β promoter, a cluster of distal NF- κ B sites play an important role in the full induction of IFN- λ 1 and these sites activate the IFN- λ 1 promoter without IRF-3/7 [37]. When the NF- κ B pathway was inhibited in dendritic cells (DCs), IFN- λ generation was seriously blocked, but this inhibition had a minor effect on type I IFN generation [38]. Despite the same transcriptional factors joining in the activation of generation of type I and III IFNs, the NF- κ B pathway is a pivotal regulator in IFN- λ generation, whereas the IRFs pathway

dominates type I IFNs expression. Furthermore, due to the independent action of NF- κ B and IRF-3/7, IFN- λ promoters seem to be more flexible than the IFN- β promoter in receiving distinct signals for activating IFN- λ generation independently.

IFN- λ s induction and signal pathways

All biological activities of cytokines are performed by engagement with specific receptors which receive stimuli and then trigger intracellular events via signal transduction pathways. The stimuli which trigger the expression of *IFNL* genes, including viruses, are similar to those translations of type I IFNs [6, 7, 39-41]. Nonetheless, there are differences in receptor and transcription factor requirements between type I IFNs and type III IFNs. The signal transduction of type I IFNs depends on the IFNAR complex, which is composed of IFNAR 1 & IFNAR2, while the signal transduction of type III IFNs relies on the IFN- λ -specific IL-28Ra chain and IL-10R2 chain, which includes IL-10 and other members of the IL-10 super-family [6, 7]. When the host detects pathogen-associated molecular patterns by PRRs, type I & III IFNs can be synthesized. For signal transduction induced by type I IFNs, the interactions between IFN- α/β and IFNAR trigger the activation of the specific receptor interacting tyrosine kinases Jak1 and Tyk2, which can phosphorylate members of the signal transducer and activator of transcription family (STAT) to trigger STAT dimerization and activation of the related transcription factor activities [42]. STAT1 & 2 are regarded as the main IFN-activated transcription factors, which, together with IRF9, form a trimeric complex,

Fig. 2. A model of the similarities in signal transduction triggered by receptors of types I and III IFNs. Types I and III IFNs rely on IFNAR1 / IFNAR2 and IL-28R α / IL-10R2 receptor complexes, respectively. To some degree, the intracellular signaling transductions induced by the two different receptor complexes are similar, particularly with the IFN-activated transcription factor ISGF3 consisting of SAT1-SAT2-IRF9. ISGF3 can binding to interferon-stimulated response elements (ISRE) in the promoters of numerous IFN-stimulated genes (ISGs) to trigger the expression of ISGs.

ISGF3, which drives the transcription of IFN-stimulated genes (ISGs) (PMID: 7959489). Following studies for functions of the STAT family, STATs 3, 4 & 5 can be activated by type I IFNs as well [43]. Despite the differences between the receptor systems used by types I & III IFNs, the intracellular signaling programs activated by IFN- λ s are similar to some degree. The combination of IFN- λ and IL-28R α induces a conformational change, which efficiently carries out the recruitment of IL-10R2 to the IFN- λ -IL-28R α -IL-10R2 complex. The receptor-associated tyrosine kinases (TYK2 and JAK1) are then activated to control the tyrosine phosphorylation of the intracellular domain of the IL-28R α chain [44, 45]. STAT proteins track and bind to the motifs with phosphotyrosine in this domain and shape ISGF3, such as that of type I IFN. ISGF3 moves from the cytosol into the nucleus and binds to interferon-stimulated response elements (ISRE) in the promoters of ISGs (Fig. 2), which can produce many proteins with antiviral functions [10, 46, 47]. Despite the similar models of signal transduction mediated by types I & III IFNs, type I IFNs can induce ISGs expression with a higher kinetics than that of type III IFNs and type III IFNs can prolong a steadier high level of ISGs expression than that of type I IFNs [46]. It remains unclear as to whether type III IFN has immune activities not shared with that of type I IFNs and whether the two types of IFNs perform antiviral activities with different kinetics.

Roles of IFN- λ s in antiviral responses

IFNs are commonly regarded as antiviral cytokines in innate immune responses. In the type III IFN family, IFN- λ 1, IFN- λ 2 & IFN- λ 3 represent antiviral activities against a range of viruses *in vitro* [6, 7]. This rapidly raised questions about the functions of IFN- λ s in limiting the replication of major human pathogenic viruses. The first report about the antiviral response of IFN- λ s is that IFN- λ s can block the replications of hepatitis C virus and hepatitis B virus *in vitro* [48]. However, IFN- λ 4, which is generated only by individuals who carry the IFNL4- Δ G allele as the major variant in Africans and the minor variant of Asians, is linked with the failure to resist an HCV infection either spontaneously or in response to treatment [10]. According to the current data about the functions of IFN- λ s, numerous studies have focused on their contribution to antiviral immune responses. Recombinant IFN- λ 1 & - λ 2 restrict the replication levels and cytotoxic activity of herpes simplex virus (HSV) in HepG2 cells [40]. Following this, IFN- λ 1 & - λ 2 can induce the expression of CC chemokines, which are able to bind to the HIV-1 entry co-receptor CCR5 and restrict the HIV-1 infection of macrophages [49]. Depending on a mouse model of viral infection, IFN- λ can induce the antiviral factor Mx1 to restrict the influenza A virus in the lung; however, IFN- λ fails to induce Mx1 to restrict the replication of hepatotropic virus in the liver [50], suggesting that IFN- λ plays an important role in the innate immune response in mucosal tissues. When mice with types I & III IFN receptors knocked out were challenged by yellow fever virus (YFV), these mice exhibited distinct changes in the frequencies of multiple immune cell lineages, impaired T-cell activation and severe perturbation of the proinflammatory cytokine balance [51]. Furthermore, a broad spectrum of the antiviral immune activities of IFN- λ have been identified in the liver, lung, brain and intestinal tract [52-55]. Collectively, the replication of functionally and structurally diverse human viruses is impaired by IFN- λ in various organs and tissues.

Despite the similar antiviral responses between type III and type I IFNs mentioned above, the two types of IFNs differ substantially with respect to which cells they aim for. The receptors (IFNARs) of type I IFNs exist ubiquitously, however, the receptor (IL-28R α) only exists in a few cell types, including some classes of leucocytes like macrophages, peripheral blood lymphocytes, conventional DCs, epithelial cells and plasmacytoid DCs, and therefore, the cellular response to IFN- λ is limited to a narrow spectrum of cell types and tissues [6, 7, 41, 56-60]. These data also indicate that the differential expression of type I versus type III IFN receptors has obvious effects on the biological activities of these functionally related cytokines in the antiviral response of living organisms. Following investigations into

the antiviral immune responses of IFN- λ *in vitro*, recombinant IFN- λ added exogenously or expressed from a recombinant virus was able to restrict viral replications in mice, including Zika virus (ZIKV), vaccinia virus, influenza A virus, influenza B virus, severe acute respiratory syndrome coronavirus, human metapneumovirus, respiratory syncytial virus, HSV-2, and others [40, 50, 61-64]. These studies reported that IFN- λ plays a pivotal role in antiviral immune responses *in vivo* and that epithelial surfaces are the main battlefield for the performance of IFN- λ in the innate immune responses which occur in respiratory and gastrointestinal tracts. The profound outcomes mentioned above were mainly dependent upon the infection model (IL-28RA-/- mice and IFNAR-/-mice). The literature reports that STAT1-/-mice display a more profound phenotype when compared with IFNAR-/-mice after a viral challenge. This suggests that the STAT pathway plays an important role in the innate immune responses of IFN- λ and IFN- γ [64-66].

Despite IFNs serving as the first line immune defense for invading viral infections, viruses can adopt various strategies to inhibit the antiviral immune responses of IFNs. Like viruses inhibiting type I IFNs responses by a variety of methods, both DNA and RNA viruses use various evasion strategies to block the molecules essential for type III IFN expression (e.g., IRF3) and to inhibit necessary biological functions (e.g., STAT1/2), leading to the impairment of type III IFNs responses [67]. The cytoplasmic protein (E3L) of the vaccinia virus can impair a PKR-dependent pathway to prevent an antiviral immune response mediated by IFN- λ [68]. Ebola viruses (EBoV) can generate a viral protein (VP24) that inhibits downstream from IRF3 activation, blocking IFN- λ expression [69]. The viral protease (2A^{pro}) of coxsackie virus can block both the TLR3 pathway and RIG-I / MDA5 pathways to further generate signal transduction proteins (TRIF and IPS1) and therefore reduce IFN- λ expression [70]. Despite IFN- λ performing an important antiviral immune response to norovirus infection of intestinal epithelial cells, a viral protein (NS1) acts through direct antagonism of IFN- λ system and dominates viral cell tropism [71]. The two HIV-1 accessory proteins (Vpr & Vif) can bind to TANK-binding kinase 1 (TBK1) and block the expression of types I & III IFNs in human DCs and macrophages [72]. Although IFN- λ plays a pivotal role in antiviral immune responses at epithelial surfaces, viruses try their best to evade antiviral immune responses for the establishment of infection.

Effects of IFN- λ on adaptive immune responses

Due to some similar functions and signal pathways between type I and type III IFNs, the IFN- λ system is suspected to possess some new aspects of the innate immune system regulating the adaptive immune response. IFN- λ regulates the differentiation of DCs from monocytes through shaping the IFN- λ receptor complex and the stimulation through this receptor specifically induces the proliferation of tolerogenic CD4⁺CD25⁺Foxp3⁺ regulatory T (Treg) cells, resulting in the generation of tolerogenic DCs which can suppress IFNs functions [73]. Following similar study results, a recombinant adenovirus expressing human IFN- λ 1 can reduce serum IgE secretion and enhance the number of splenic CD4⁺CD25⁺Foxp3⁺ Treg cells, attenuating allergic airway inflammation [74]. Subsequent studies also noted that IFN- λ decreases Treg activity during the development of an adaptive immune response in more physiological systems [75]. Thus, an immunostimulator (aged garlic extract) can enhance the level of IFN- λ and IL-4 cytokines in splenocytes stimulated by specific tumor antigen and reduce the scale of Treg cells in the spleen [76]. It seems that IFN- λ enables the adaptive immune system to diminish immunosuppression regulated by Treg cells. However, most recently, when compared with the activities of immunosuppression regulated by live Treg cells, dead Treg cells sustain and amplify the suppressor capacity of immune responses [77]. Based on these findings, we speculate that further investigations into the role of IFN- λ in reducing activities induced by Treg cells may shed light on how to control Treg cell behavior and improve the efficacy of therapeutics targeting cancer checkpoints.

Individual IFN subtypes have different efficiencies in selectively activating immune cell subsets to trigger antiviral immune activities resulting in the production of sustained B and T cell memory [78]. Early after the initial discovery of IFN- λ , some reports suggested that IFN- λ could regulate helper T cells and down-regulate IL-4 and IL-13 expression in the absence of an IFN- γ response [79, 80]. Despite skewing the Th1/Th2 profile towards a Th1 phenotype, common single nucleotide polymorphisms in IFN- λ and its receptor α -subunit genes affect IFN- λ signaling and thereby modulate the Th1/Th2 balance and impair the therapy effect of IFN treatment during infections [81-83]. Together with a recent report of IFN- λ blocking the conversion of central memory T cells into effector memory T cells, these results suggest that IFN- λ may regulate the most beneficial T cell environment by the prevention of Th2 differentiation and therefore sustain the optimal adaptive antiviral immune response to combat viral infections.

Future trends of application for clinical treatment

Based on the literature about IFN- λ , it is now well established that IFN- λ plays a key role in innate / adaptive immune responses and a future drug against chronic viral infections. This field urgently requires further investigation into both the basic biology and therapeutic antiviral activity of IFN- λ . For example, so many studies have improved our understanding of the effects of different IFN- λ subtypes on the clearance of HCV infection [84-89]. However, confusion remains about the effect of IFN- λ subtypes on the immune response to viral infections. Even though HCV-infected patients with the IFNL4- Δ G allele generally fail to clear HCV infections and IFN- λ 4 is only slightly secreted, these patients have lower HCV viral loads without treatment [10]. Most recently, it has been reported that genetic variants in IFNL4 have different efficiencies of clearing HCV infection in the Chinese Han population [90]. Specifically, it remains unclear as to whether there is a relationship between the antiviral immune responses of mouse models with an invading HCV infection and the absence of cytokines (IFN- λ 1 or IFN- λ 4) [91]. Such knowledge might highlight new pathways for the improvement of IFN- λ subtypes in the development of HCV vaccines. Due to the partially overlapping signaling pathways (RIG-I, MDA5 and MAVS) mediated by type I and type III IFNs, the paradoxical immune activities might be performed by the two types of IFN. Regardless of IFN subtypes, RIG-I activates two distinct categories of ISGs, one JAK-STAT-dependent and the other JAK-STAT-independent, which coordinately contribute to the antiviral immune response to HEV infection [92]. However, persistent activation of the JAK-STAT-dependent signaling pathway enables HEV-infected cells to resist exogenous IFN treatment, while the depletion of IFN- λ receptors or MAVS (mitochondria antiviral signaling protein) resorts to the antiviral immune response induced by IFN, suggesting that the persistent presence of IFN- λ benefits the establishment of HEV infection [93]. Together with a recent report of antiviral immune activities mediated by IFN- λ , we still lack important pieces of information on basic IFN- λ functions. What is the molecular nature of the interactions between the cytokine and the receptor? Most recently, a crystallized ternary complex (IFN- λ -IL28Ra-IL-10R2 complex) highlights the plasticity of IFN- λ signaling and its therapeutic potential [94]. A better understanding of the interplay between IFN- λ and its receptors can shed light on what activates signaling and could also allow for the development of cytokines with altered function. Turning to signal transduction mediated by IFN- λ , the current knowledge is that type I and III IFNs induce similar signaling pathways. Even though JAK-STAT-dependent signal transduction is performed by both type I and III IFNs, we still have very limited knowledge on other IFN- λ -activated pathways that could potentially affect the immune activities of IFN- λ s.

For the link between the innate immune response and IFN- λ , further investigation is needed into the relative contribution of IFNL polymorphisms in the immune defense of the host. For instance, it was recently reported that IFNL3 and IRF7 polymorphisms can modulate the immune response against HSV-1 in Alzheimer's disease [95] and that IFNL3

polymorphisms also play a role in the immune response to IFN therapy in chronic HBV and HCV infected patients [96, 97], suggesting that genetic polymorphisms of IFNL3 could play an obvious role in innate defense. With respect to the role of IFN- λ in the adaptive immune response, we need to identify which cells of the adaptive immune system responding to IFN- λ and the role of endogenous IFN- λ in the maintenance and development of optimal adaptive immune responses to resist viral infection. The related studies could contribute to the development of therapeutic IFN- λ drugs and vaccine adjuvants related to IFN- λ .

Conclusion

In conclusion, type III IFNs have been identified as a new class of cytokines that are specialized virus-induced IFNs with immune and biological functions both overlapping with and distinct from type I IFNs. A better understanding of the related functions and interactions between the different antiviral systems in the immune system can benefit researchers in the development of therapeutic methods or immune regulators involving IFN- λ to invade viral pathogens in the host and to establish long-term immunity without excessive activation of inflammation.

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Disclosure Statement

All authors declare that they have no competing interests.

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