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Review

Type I Interferons: Distinct Biological Activities and Current Applications for Viral Infection

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Abstract
The interferons (IFNs) are a primary defense against pathogens because of the strong antiviral activities they induce. IFNs can be classified into three groups: type I, type II and type III, according to their genetic, structural, and functional characteristics and their receptors on the cell surface. The type I IFNs are the largest group and include IFN-α, IFN-β, IFN-ε, IFN-ω, IFN-κ, IFN-δ, IFN-τ and IFN-ζ. The use of IFNs for the treatment of viral infectious diseases on their antiviral activity may become an important therapeutic option, for example, IFN-α is well known for the successful treatment of hepatitis B and C virus infections, and interest is increasing in the antiviral efficacy of other novel IFN classes and their potential applications. Therefore, in this review, we summarize the recent progress in the study of the biological activities of all the type I IFN classes and their potential applications in the treatment of infections with immunodeficiency virus, hepatitis viruses, and influenza viruses.

Introduction

Interferons (IFN) were initially described in 1957 as soluble glycoproteins with strong antiviral effects [1, 2]. Three types of IFNs, types I, II and III, have been classified based on of their genetic, structural, and functional characteristics and their cell-surface receptors [3]. IFN biological activities include antiviral, antiproliferative and immunomodulatory effects in the host response to viral or bacterial infection. As a result, IFN induction is a powerful

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tool in the host response to cancer or viral infection [2]. Type I IFNs, specifically IFN-α and IFN-β, are part of the standard treatment for chronic hepatitis B and C virus infections. In addition, interest is increasing in the antiviral efficacy of other novel IFN classes. For example, FeIFN-ω produced by silkworm larvae is approved in several countries for the treatment of canine parvovirus, feline leukemia virus, and feline immunodeficiency virus infections [4]. IFN-ε regulates mucosal immunity against viral and bacterial infections, and can suppress HIV replication [5]. Similarly, research has also shown that IFN-τ is particularly effective in inhibiting HIV infection [6]. Nonetheless, individual antiviral and immunomodulatory properties of type I IFN classes IFN-ε, IFN-ω, IFN-κ, IFN-δ, IFN-τ and IFN-ζ have not been investigated as widely as IFN-α and IFN-β. In this review, we summarize achievements in defining the distinct biological activities of type I IFN classes as well as their potential clinical use in antiviral therapy.

Biological activities of type I IFNs

Several classes of type I IFNs exist and they have some similarities. For example, all type I IFNs display the same characteristic structure of helical cytokines with a bundle of four "up-up-down-down" α helices and an additional α helix [7]. In addition, almost all IFN classes are acid stable to pH 2 and are heat-stable. They lack introns and are are closely conserved in length (from 161 to 167 amino acids) and protein sequence (about 75-99% amino acid sequence similarity) [8-10]. In addition, IFN classes share a common surface receptor of two IFN-α receptor subunits (IFNAR1 and IFNAR2) and have the same mechanism of action of their biological activities [11]. Generally, IFNs induce IFN receptor phosphorylation following binding to IFNAR. Binding leads to activation of the Jak-STAT pathway. Activation gives rise to the activation of ISGs via recognition of upstream sequence elements in promoters and formation of antiviral proteins such as OAS, PKR, ISG and Mx, which exert distinct biological activities (Fig. 1) [2, 12-14]. The differences among type I IFN classes is prominent compared to these common points. Detailed lists of main characteristics and biological activities are in Tables 1 and 2, respectively.

IFN-α/β

The type I IFN family in humans is composed of 12 IFN-α subtypes encoded by 14 nonallelic genes including one pseudogene and two genes that encode the same protein. One IFN-β is encoded by a single IFNB gene in spite of gene duplication [9, 54]. The various IFN-α subtypes have many common points. For example, all are clustered on chromosome 9 [55]. IFN-αs, which are composed of 165 to 166 aa, have 80% amino acid sequence identities. IFN-βs are composed of

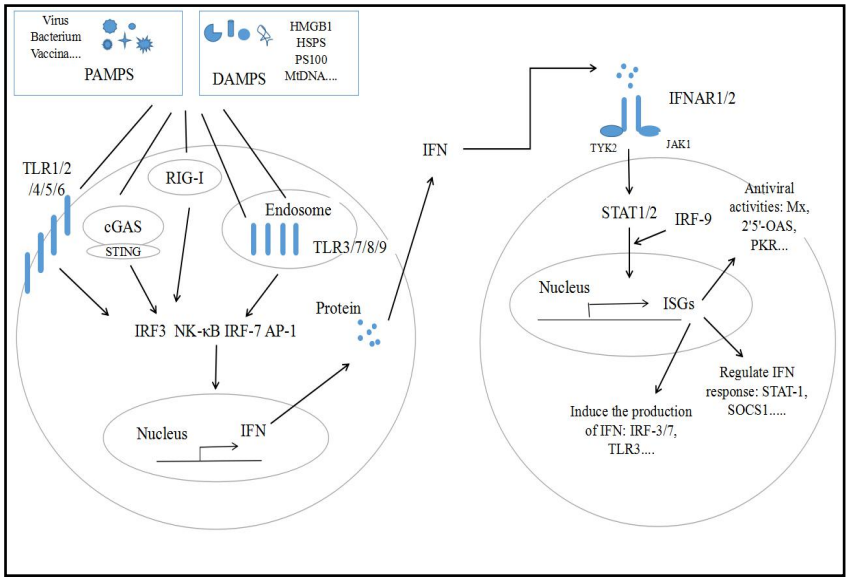

Fig. 1. Type I IFN signaling pathway.

Table 1. Main characteristics of type I IFN classes

	IFN-α	IFN-β	IFN-ε	IFN-ω	IFN-τ	IFN-κ	IFN-δ	limitin
species	Most animals	Most animals	Human, mice, Swine, Cattle, Canine, Rhesus macaques, pangolin, Fish, Horse	Human, Cat, Pig, Horse, Rabbit, Cattle, Serotine bat, Sheep	Cattle, Sheep	Human, Horse, Mouse, Porcine, Chicken, Serotine Bat	Pig, Horse, Sheep	Mouse
subtypes	13,6,17,14,9 numbers in human, horse, pig, cattle, dog, respectively	1,4,1 numbers in human, horse, pig, respectively	Only one number has been identified in these species	5,13,7/8,12,8,24,5 numbers in human, cat, pig, horse, rabbit, cattle, sheep, respectively	3 subtypes in cattle	one number in these species	4,11 numbers in sheep, pig, respectively	No data
Human gene locus	9p21+3(T)	9p21+3(T)	9p21+3(C)	9p21+3(T)	None	None	9p21+3(T)	None
Main cellular source	PDCs, Hematopoetic Cells, mainly leukocytes	DCs, Fibroblasts and Epithelial cell types	Cells of CNS, female reproductive organs	PDCs, Hematopoetic Cells, mainly leukocytes	Trophoblasts and Endometrial Cells	Epidermal Cells, Keratinocytes	Blastocyst Cells	Mature T Lymphocytes, Bronchial Epithelial and Salivary Duct Cells
Receptor chain	IFNAR1/IFNAR2							
Acid stability	+							

Table 2. Biological activities of type I IFN classes

IFN classes	Induction	Differential biological effects	Induced ISGs	References
Human IFN-α	By CpG or imiquimod in PBMC; In poly I:C-stimulated DC and CpG-stimulated macrophages; By HSV, NDV and RSV in PBMC	Anti-viral activity against human metapneumovirus, VSV, SFV, influenza A virus, HBV, HCV, HEV, HIV-1; Induces chemokinesis of T cells and T cell migration	Potent inducer of IFIT1, CXCL10, CXCL11, ISG15, CCL8, 2′5′OAS, APOBEC3G, APOBEC3A, PKR and IDO induction	[15-17]
Human IFN-β	Most virus	Anti-viral activity against dengue virus, HSV, HCMV, Ebola virus, HBV, HCV, influenza A viruses and the SARS-CoV, Zika virus, HIV	Induces PKR, 2′5′OAS, Mx, ISG	[18-22]
IFN-ε	Not induced by SIV, pattern recognition receptor pathways, Semliki Forest virus, herpes simplex virus 2 (HSV), mengovirus, and Chlamydia; Up-regulated by TNF-α stimulation, seminal plasma, estrogen	Bovine IFN-ε has anti-VSV activity against in MDBK, EBK, BT and PK-15 cells, but not on MDCK and BHK21 cells; rCaIFN-ε has high antiviral activities against VSV, CDV, H1N1 and low in CPV in MDCK cells; Antiviral activities against Vaccinia virus, HIV, HSV2 and C. muridarum infections; Lower antiviral against vesicular stomatitis virus in aminion-derived WISH cells	Potent inducer of PKR, 2′5′OAS	[4, 23-27]
IFN-ω	By PRV or poly(I).poly(C) in PK15 cells; Not induced by lyssavirus infection	Antiviral activities against CPV, FLV, FIV, BVDV, VSV, FCV, FHV-1,bovine enterovirus, infectious bovine rhinotracheitis virus, pseudorabies virus, European bat lyssavirus, influenza virus, HEV, HBV, HCV, HPV	Induces expression of Mx1, ISG15, ISG56, and Mx2	[3, 28-32]
IFN-δ	By PRV in IBRS-2/PK15, PRRSV in Marc-145/ porcine alveolar macrophages, and by live SV in the equine PBMC, VSV in Marc-145/ PK-15; Not induced by imiquimod-stimulation in pDC	The Porcine IFN-δ8 (PoIFN-δ8) showed a significantly stronger activity than other PoIFN-δ4, PoIFN-δ5; Ovine IFN-δ has an apparent anti-VSV in MDBK cells but no on NBL6 cells; Equine IFN-δ1 (EqIFN-δ1) and EqIFN-δ2 have an apparent anti-VSV in NBL6 cells, while EqIFN-δ2 has higher activities in MDBK cells but EqIFN-δ1 not; IFN-δ showed effective protection against PRRSV in porcine AMs but not in MARC-145 cells	Induces expression of Mx, OAS	[33-36]
IFN-τ	Not induced in response to dsRNA	Anti-viral activity against HIV and FIV, HPV, BKV, Influenza Virus, FMDV,VSV, BVDV, Theiler's virus, bovine leukemia virus; Strong antiviral activity against HIV and FIV than IFN-α, and be >30 times less toxic than human IFN-α	Potent inducer of Mx, ISG15, and OAS	[37-45]
IFN-κ	Downregulated by lyssaviruses; Weak induced by In poly I:C-stimulated normal keratinocytes	Anti-HPV activities by inducing Sp100 Proteins; Anti-VSV, EMCV, HCV; Antiviral activities against avian RNA viruses in ovo; Weak activities against lyssaviruses	Induces ISG15, ISG56, MDA5, IRF1, MX1 and OAS	[46-51]
limitin	Not induced by lipopolysaccharide injection or herpes simplex virus infection	Anti-viral against EMCV, HSV, and MHV; Stronger Antiviral effect than IFN-α; Same activities in the induction of MHC class I, CTL activity, and anti-tumor effect to IFN-α; Lower activities in the inhibition of CFU-GM and BFU-E colony formation, and myelopoiesis and erythropoiesis in vivo than IFN-α	Induces expression of 2′5′OAS, PKR, Mx protein	[52, 53]

166 aa and are N-glycosylated. However, in contrast to IFN-β, only 2 of 13 IFN-α subtypes have glycosylation sites: IFN-α2 and IFN-α14. IFN-α2 is O-glycosylated while IFN-α14 is N-glycosylated [56].

Generally, IFN-α is produced by leukocytes while IFN-β is a fibroblast product. A limited number of IFNs are produced under healthy conditions [57]. IFN-α/β would be considerably upregulated by viral infections or exposure to double-stranded and single-stranded nucleic acids via TLR3 or RIG I, and by some growth factors and cytokines [58]. Many biological activities have been demonstrated such as direct antiviral effects, regulation of immune responses, antiproliferation, and modulation of expression of MHC I and II [11]. However, IFN-α subtypes have distinct biological activities. Differences in receptor-binding affinities among the subtypes are suggested to be responsible for the different activities [59]. For example, IFN-α10 and IFN-α17 have lower bindings affinities to their receptors than IFN-α2a [59]. Distinct receptor affinities can lead to signal differences in the phosphorylation of STAT molecules and mitogen-activated protein [59]. In addition, the quantity of receptors on the surface of specific target cells is associated with different biological activities of IFN subtypes. This finding suggests that abundant IFNAR expression might compensate for the weak

binding affinity of some IFN-α subtypes [60]. Moreover, the tissue-specific pattern of IFN-α subtypes and receptors may be involved in their biological activities [61]. In some studies, the type of IFN produced and the type of virus used may have influenced the expression and action of different IFN-α subtypes [62]. Some studies found that distinct antiviral activities correlate with virus-specific expression levels of ISG subsets. For instance, some ISGs have strong antiviral effects while others promote viral replication *in vitro* [63]. This finding indicates that more studies are needed to define their specific biological activities for use in antiviral therapy.

IFN-ε

IFN-ε was described in 2004 for the first time. It consists of 192 amino acids and shares about 30% homology with IFN-α and IFN-β in humans [8]. Unlike IFN-α/β, IFN-ε is constitutively expressed in the lung, brain, skin, small intestine, rectum, jejunum, and reproductive tissues. It shows substantial expression in the uterus, cervix, vagina, and ovarian tissue [8, 24].

Studies demonstrate that IFN-ε is positively modulated by hormones, seminal plasma, and TNF-α stimulation and expression correlates negatively with progesterone levels [8, 64, 65]. Two stable stem-loop structures (loops 1 and 2) were identified in the 5′-untranslated region of IFN-ε mRNA, and they markedly suppresses IFN-ε mRNA expression. However, only loop 1 is essential for enhancing mRNA expression unless the loop structure is disrupted [66]. The molecular transporter and chaperone Importin9, which binds to the IFN-ε 5′-untranslated region (UTR) stem-loop structures, affects IFN-ε constitutive expression. Expression levels of IFN-ε decrease following IPO9 overexpression and increase in response to IPO9 silencing [66]. These findings suggest that the IPO9, with the participation of stem-loop structure 1, serves as a negative, specific, post-transcriptional modulator of IFN-ε mRNA.

It has been demonstrated that IFN-ε also exerts its biological activity by stimulating immune mediators and activating the JAK-STAT signal pathways *in vitro* and *in vivo* [8]. For example, a recombinant vaccinia virus co-expressing HIV gag or pol genes and murine IFN-ε (VV-HIV-IFN-ε) inhibits growth of VV in L929 murine cell lines and increases upregulation of activation markers (CD69 and CD86) and antiviral protein expression [26]. Between IFNAR1 and IFNAR2, IFN-ε has a higher binding affinity for IFNAR1 [67]. In addition, unlike IFN-α, IFN-β is not induced in response to activation of TLRs 2, 3, 4, 7/8, and 9 [64]. Other differences exist between IFN-ε and other IFNs. First, the antiviral, natural killer cell-cytotoxicity activity and antiproliferative activities of IFN-ε are weaker than IFN-α and IFN-β [27]. Second, some studies showed that IFN-ε exhibits antiviral activity against cells derived from species that have near relatives and are expected to be homologous cells [23, 25]. Third, IFN-ε differs from IFN-α in macrophages by inducing an antiviral state mediated by more different factors [4]. Studies have revealed that numbers of genes or expression levels induced by type I IFN, IL-6, and TNF pathways in response to IFN-α and IFN-ε are not identical, in spite of some overlap among IL-1α, IL-1RA, IL-4, VEFG, and GCSF [4]. IFN-α mediates more genes and upregulates genes more than [The phrasing of this edit should be checked for accuracy.]IFN-ε in the type I IFN signaling pathway, whereas IFN-ε induces more genes in the TNF-α pathway and more ROS generation and phagocyte activation than IFN-α, to block HIV replication [4].

IFN-ω

Since the discovery of IFN-ω genes in humans about 30 years ago, IFN-ω has been identified in other animal groups including feline, porcine, equine, rabbit, cattle, and serotine bat, but not noted in canines or mice [3]. Treatment with IFN-ω is suggested to be effective for patients who are resistant to IFN-α because the antigenic structure of IFN-ω is distantly related to IFN-α, β, λ, with no crossreaction with antibodies against these other IFNs [68]. Recombinant FeIFN-ω is approved for treatment of FLV and FIV infections in some countries. FIFN-ω has 13 subtypes that have high similarity (95% to 99%) at the nucleic acid and amino acid level. All of them contain an N-terminal secretory signal sequence at position 1 to 23. Lengths of mature FeIFN-ω subtype polypeptides are 173 aa (except FeIFN-ω2 and FeIFN-ω4

which have 180 aa). The mature amino acid sequence of FeIFN-ω has six additional amino acids at the carboxyl-end and an N-glycosylation recognition site that differs from other mammalian subtypes [69]. In addition, seven prolines are conserved among these subtypes, four at positions 4, 26, 39, and 117 of mature proteins, similar to other mammalian IFN-ω proteins at positions 4, 26, 39, and 116, respectively [69, 70]. The cysteines at positions 1, 29, 100, and 140 of the mature proteins correspond to IFN-ω at positions 1, 29, 99, and 139.

IFN-ω has antiviral activities similar to other types I IFNs. However, unlike IFN-α, it has cross-species activity to some extent. This activity indicates that cells have a tendency to be insensitive to IFN-ω from distantly related species [23]. IFN-ω is involved in the nonspecific response based on increased expression of several acute phase proteins and MHC I molecules; upregulation of the phagocytic activities of whole blood cells, macrophages and NK cell activities; and decreased concurrent viral excretion [71-74]. Different therapy protocols might also contribute to the distinct expression of innate immunity cytokines following IFN-ω treatment. For example, IL-6 plasma levels decrease and proviral load increase in FIV-cats treated with rFeIFN-ω by a subcutaneous licensed protocol. IL-6 mRNA expression decreases in an oral group. Viremia and other cytokines (IL-1, IL-4, IL-10, IL-12p40, IFN-γ and TNF-α) do not change with therapy [75]. A previous study showed that cytotoxic effects (e.g. apoptosis, necrosis, and early senescence) of human IFNβ gene lipofection showed the same or a superior effect to that of high doses of the exogenously applied recombinant IFNβ protein [76]. Based on these findings, the researchers also found that fIFN-ω lipofection and expression is equal to or more effective than rFIFN-ω protein at suppressing cell growth by inducing ROS generation, mitochondrial potential disruption and calcium uptake [77]. These kinds of approaches may offer equal or superior biological activities with less adverse effects for the treatment of some diseases.

IFN-κ

Similar to IFN-ε, which is constitutively expressed in specific tissues, IFN-κ is also mainly expressed in the uterus [78]. It is also detected in other tissues such as the Peyer's patch, ovary, liver, and peritoneal macrophages although at low levels. It is not detected in brain, kidney, spleen, tonsil, heart, small intestine, colon, placenta, or testis [51, 78]. The IFN-κ gene has classic characteristics including a 5'-UTR, 3'-UTR, and open reading frame. The gene contains two exons (although it is intronless in the serotine bat), separated by an intron. The second exon cannot be translated into an amino acid sequence [78]. Bovine IFN-κ does not have an N-linked glycosylation site but contains four O-linked glycosylation sites and a signal peptide of 27 amino acids, which is longer than other type I IFNs such as IFN-α, IFN-β, IFN-ε, or IFN-ω. Both human IFN-κ and BoIFN-κ contain three putative VRE elements at the same position. Studies found that the length of the CD loop region is responsible for the structural differences between IFN-κ and other type I IFNs [51]. For example, BoIFN-κ has an insertion of 20 amino acids while human IFN-κ contains only 13 amino acids.

Similar to the expression pattern of IFN-ε, the expression of HuIFN-κ has been observed only in keratinocytes and certain lymphoid cell populations. such as monocytes, and monocyte-derived dendritic cells [79]. HuIFN-κ has demonstrated antiviral activity against VSV and EMCV [79]. Habiger and others revealed that IFN-κ reduces human papillomavirus transcription and replication in CIN612-9E cells by inducing Sp100 proteins, which are restriction factors for HPV18 infection [50]. However, these biological activities of IFN-κ are lower than IFN-α/ω. In a study, BoIFN-κ had a protective effect against VSV or BVDV infection of MDBK and BT cells even though the effects were less than the effects of BoIFN-αA [51]. In another study [48], recombinant esIFN-κ suppressed EBLV-1, EBLV-2, and RABV replication in an *Eptesicus serotinus* brain cell line. However, the effect was weaker than esIFN-ω. The authors suggested that IFN-κ may be important for antiviral activity by inducing production of IFN-β in reproductive organs such as the uterus and ovary as well as being a possible skin defense against cellular challenges and skin-infecting pathogens [47, 79].

IFN-δ

IFN-δ was identified by Lefevre and Boulay in 1993 [6]. It is expressed in porcine blastocysts during implantation, suggesting unique functions during pregnancy [6]. IFN-δ seems more closely related to the IFN-α, IFN-τ, and IFN-ω cluster than to IFN-β. Of note, the IFN-δ family comprises a large number of members with diversity that is greater than other multigene porcine or horse IFN families such as IFN-α and IFN-ω [36]. In the porcine family, 11 PoIFN-δ-related genes and 7 pseudogenes have been identified within a 600-kb region on porcine chromosome 1 [36]. The number of cysteines in porcine IFN-δ has no equivalent among other type I IFNs: the preprotein contains 9 and the mature protein 7 Cys residues. Five of the seven cysteine residues of the mature protein (positions 9, 56. 58, 107 and 145) are atypical among type I IFNs. Mature Porcine IFN-δ, with 149 residues, possesses the shortest sequence of all known type I IFNs, while ovine IFN-δ (139 aa) appears to be the smallest known natural mammalian type I IFN [33, 34]. Some IFN-δs are probably highly glycosylated, as they display one or two potential N-glycosylation sites in OvIFN-δ and the porcine IFN. All IFN-δs have two other cysteine residues, Cys77 and Cys128, except for IFN-δ2 and IFN-δ7, which have an additional COOH-terminal cysteine residue, Cys166.

IFN-δs exhibit antiviral and immunomodulatory activity through typical type I IFN signaling, with lower antiviral activities than IFN-α [35]. However, the differential affinity of IFN-δ for certain hosts could influence their biological activities. For example, an OvIFN-δ supernatant has apparent antiviral activity with MDBK cells but no antiviral activity is detected with NBL6 cells. EqIFN-δ1 and EqIFN-δ2 supernatants have an apparent titer with the NBL6 cell line, but the EqIFN-δ1 gene product has a very narrow species specificity compared to EqIFN-δ2 [34]. In addition, this activity is distinct among cell subtypes, in challenges with different viral species. For example, PoIFN-δ8 showed a significantly stronger activity against PRV in IBRS-1/PK-15 cells than PoIFN-δ4, PoIFN-δ5 [36]. However, in another study, IFN-δ8 showed the lowest activity of among PolFN-δs in a high anti-VSV-activity group with MARC-145 cells [35].

IFN-τ

IFN-τ was first discovered as an antiluteolytic protein during ovine pregnancy. It is constitutively secreted by trophoblasts and endometrial cells beginning on about day 10, increasing between days 13 and 16, when it reaches a peak, with secretion stopping after day 21 of pregnancy. IFN-τ is pivotal for maintaining levels of progesterone from the corpus luteum during the initial stages of postconception [80]. IFN-τ shares about 75% identity with IFN-ω and has 172 aa with two disulfide bridges (1-99, 29-139) and an amino terminal proline. Not every IFN-τ is glycosylated. For instance, ovine IFN-τ lacks glycosylation, while bovine IFN-τ is N-glycosylated at ASN78 and caprine IFN-τ is a mixture of nonglycosylated and glycosylated forms. Although secretion is specific to ruminant mammals (e.g., sheep, cows, oxen, goats, gazelle, giraffe and deer), all have several variants of IFN-τ, except for giraffes, and 7 putative analogs of IFN-τ are identified in humans [80-83]. Studies show that human trophoblast IFN in placental trophoblast cells has 85% sequence identity to IFN-τ in ruminants [79].

Similar to IFN-α and IFN-β, IFN-τ possesses antiviral activity and antiproliferative effects. IFN-τ has a receptor binding domain at the C-terminus and a biologically active site at the N-terminus [84]. IFN-τ is suggested to have comparable antiviral activity effects as IFN-α from the same species. It has high species specificity and some biological activities are remarkably decreased when administered to another species [85, 86]. IFN-τ also stimulates some interleukin expression and secretion such as IL-6 and IL-8. However, the mechanism involved in inducing cytokine secretion is dependent on STAT3 rather than STAT1 signaling [87]. IFN-τ displays >30 times less toxicity than IFN-α [45, 88]. This difference in cytotoxicity is illustrated by the differential selectivity of individual N-termini towards receptors and the differential degree of receptor avidity [84]. Overall, these unique properties will be useful in the treatment of viral diseases, including HIV infection and hepatitis.

IFN-ζ

Based on growth inhibition of a myelomonocytic leukemia cell line, IFN-ζ was initially cloned in 2000 [89]. A seemingly secreted glycoprotein, IFN-ζ is composed of 182 aa residues with a signal peptide of 21 amino acids at the N-terminal end and an N-linked glycosylation site at amino acid residue 68. IFN-ζ lacks an internal transmembrane domain. It appears to have an IFN-like globular structure of five long α-helices and one short helix in the middle of a loop connecting helices B and C, with possible disulfide bonds between residues 52 and 157 and between residues 80 and 130 [90]. IFN-ζ shares high nucleotide homology with IFN-α and IFN-β at residues 45-60, 105-115, and 135-165, corresponding to the N-terminal half of the AB loop, the C helix, and the DE loop, together with helices D and E [90].

IFN-ζ shares activities with other type I IFNs such as IFN-α: It induces the surface expression of MHC class I, enhances CTL activities, and inhibits growth of lymphohematopoietic cell lines as strongly as IFN-α. This kind of IFN has relatively higher antiviral activity than IFN-α [52]. Apart from their antiviral effects, other differences exist among them: (I) Signals induced by IFN-ζ are similar but distinct in contrasted to signals of other type I IFNs. Studies revealed that IFN regulatory factor-1 (IRF-1) dependency for antiviral activities is distinct between IFN-ζ and IFN-α. A higher concentration of IFN-ζ is needed compared to IFN-α for antiviral activity and transcription of proteins in IRF-1-deficient fibroblasts [53] (II) Some common adverse effects such as myelosuppression and fever are not observed in mice treated with IFN-ζ compared to IFN-α [52] (III) IFN-ζ does not inhibit colony production of myeloid and erythroid progenitors while IFN-α is known to suppress lymphohematopoiesis [52]. In addition, IFN-ζ suppresses the proliferation of megakaryocyte progenitors without influencing megakaryocyte differentiation, although higher concentrations are required. A possible explanation is that IFN-ζ induces lower expression of Daxx and weaker phosphorylation of Tyk2 and Crk than IFN-α [91] (IV) Formation of IFN-ζ is distinct from other known IFNs. IFN-ζ is constitutively produced by mature T lymphocytes in the spleen and thymus and by bronchial epithelial and salivary duct cells in healthy mice [92] (V) Unlike IFN-α/β, IFN-ζ gene expression in lymph nodes is unchanged with lipopolysaccharide injection or herpes simplex virus infection [92]. Overall, the narrow biological activities of limitin may indicate that it is important in homeostasis of lymphoid organs and their response to pathogens.

Current potential applications of type I IFN classes

Immunodeficiency virus

IFN-α and HIV in humans. Some clinical trials on HIV infection show that treatment with IFN-α has significant therapeutic potential, alone or in combination with long-term ART. It has been demonstrated that IFN-α is well tolerated and decreases HIV viral loads and proviral DNA levels in $CD4^+$ T cells, induces tumor regression and suppresses HIV p24 core antigen levels [93-96]. Distinct anti-HIV effects of IFN-α subtypes are seen. For example, although IFN-α2 has been used in human clinical trials for HIV-1 patients, it as less potent anti-viral activity than IFN-α14 when used in postexposure prophylaxis or treatment of acute viral infection, with better regulation of immune hyperactivation [97]. In addition, IFN-α14 therapy correlates with increasing patterns of host innate immunity, including significantly higher induction of tetherin and MX2, increasing APOBEC3G signature mutations in HIV-1 proviral DNA, and higher frequencies of TRAIL+NK cells. Unlike other antiretroviral drugs, IFN-α14 decreases both viremia and proviral loads [97]. However, HIV seems to become resistant to IFN-α following infection, especially in chronic viral infections with $CD4^+$ T-cell depletion and inhibition of memory B-cell reconstitution, involving evasion mechanisms to avoid antiviral responses to IFN-α during IFN-α therapy [98, 99]. Clinical trials of chronically infected patients found that IFN-α therapy fails to suppress HIV-1 replication and causes severe side-effects, including toxicity, ART failure and progression to AIDS [100]. Some novel methods and therapeutic strategies that can overcome viral latency have been developed

such as HDAC, disulfiram, galectin-9, ingenol-3-angelate, prostratin, 5-azadC, bryostatin-1, and Runx1 [100, 101]. TLR7/8 agonists induce production of IFN-α that effectively inhibits HIV-1 replication in activated lymphocytes, macrophages or latently infected monocytic cell lines [102, 103]. Because HIV eradication is not achieved by highly active antiretroviral therapy, a strong rationale to investigate the curative potential of IFN-α is needed. Recently, IFN-λ, a type III IFN, was identified and shown to have similar biological characteristics as IFN-α and IFN-β [104, 105]. However, it has a more restricted receptor complex and restricted tissue expression than IFN-α, and these features makes it an ideal therapeutic antiviral agent against HCV [106]. Preclinical studies showed that treatment with IFN-λ effectively inhibited HCV replication in human hepatocytes [107, 108]. Furthermore, it reduced the incidence of IFN-α-induced adverse events, and the IFN-λ-based treatment showed no significant hematological toxicity. Therefore, the application of IFN-λ in the treatment of chronic hepatitis C warrants investigation.

IFN-ε and HIV in humans. Previous studies suggest that the upregulated expression of IFNε in the cervical epithelium is associated with decreased levels of genes related to HIV-1 DNA integration and replication. In addition, susceptibility to HIV infection has a negative relationship with IFNε levels during the menstrual cycle [109-111]. These results indicate that the IFNε cytokine may contribute to anti-HIV responses. Several studies demonstrated that human IFN-ε suppresses HIV replication at stage(s). One study [4] found that IFN-ε blocks HIV infection in the early stages of the HIV cycle, from viral entry to nuclear import, by inducing CC-chemokines, downregulating CCR5, and inhibiting reverse transcription and nuclear import. While this activity reached a high point after 24 hours of treatment and then decreased, a potential mechanism is that IFN-ε induces significant phagocytosis and ROS, which contribute to blocking HIV replication. However, protection does not appear to operate through known type I IFN-induced HIV host restriction factors such as APOBEC3A and SAMHD1. In a study conducted by Garcia-Minambres et al. [112], IFN-ε mediated its antiviral activity at different steps of the HIV replication cycle by inducing expression of HIV restriction factors including TRIM5α, MX2, HERC5, BST2, IFITM3, and APOBEC3G. The levels induced were comparable to IFN-α and IFN-β. In addition, IFN-ε also decreased the infectivity of progeny virion particles at that stage of infection by upregulating expression of HIV restriction factors such as IFITM3. Future studies are needed to learn the exact mechanism of IFN-ε–mediated HIV inhibition, to develop safer new strategies to prevent HIV transmission.

IFN-τ and HIV in humans. IFN-τ has more potency than human IFN-α2a in suppressing HIV replication in monocyte-derived macrophages, which are a reservoir of HIV during the early stages of infection, in spite of its lower affinity for IFNAR [113]. Several potential mechanisms are involved in this action. (I) IFN-τ upregulates expression of cellular antiviral factors such as MxA protein and 2′,5′-oligoadenylate synthetase/RNase L, MIP-1α, MIP-1β, RANTES, IL-4, IL-10, and IL-6, but not IL-1ß or TNF-α. These effectors further contribute to degrading integration of intracellular viral RNA. In particular, β-chemokines suppress HIV replication by competitively binding to CCR5 a co-receptor for HIV [91, 113-115]. (II) It suppresses reverse transcription by preventing formation of the reverse transcription complex [114]. IFN-τ seems to have the highest antiviral activity when administered orally, and it shows no evidence of toxicity compared to IFN-α2 even at concentrations of 1000 U/mL [43, 45]. Overall, efficiently preventing HIV infection and production of viral particles may be an alternative HIV treatment to IFN-α. However, some studies indicate that IL-6 may promote viral replication at later stages of infection. Nonetheless, IFN-τ resulted in greater decreased viral RNA than direct treatment with IL-6 [113]. Some conflicting results about whether IFN-τ elicits production of IFN-γ associated with a predominately Th1 response have been reported [116, 117]. Thus, additional research is needed to investigate the exact functions of these cytokines in the mechanism of IFN-τ antiviral effects.

IFN-ω, -ζ and FIV in cats. rFeIFN-ω was the first licensed interferon compound for use in cats for treatment of FIV and FeLV infection [118]. The first study supporting its clinical application was conducted in 2004 and found that cats infected with FeLV or co-infected FIV displayed a significant clinical improvement and a prolonged survival with rFeIFN-ω treatment [73, 116]. Other studies showed that treatment with rFeIFN-ω improved clinical signs, decreased concurrent viral excretion and hematologic parameters, and increased levels of acute phase proteins, a key component of the innate immune system [71, 119]. However, rFeIFN-ω did not change hypergammaglobulinemia, proviral load, or viremia. These results suggest that a main innate immune reaction rather than acquired immunity is induced by rFeIFN-ω [72, 119]. rFeIFN-ω therapy seems to be cost-limiting so an alternative oral protocol for FIV-infected cats has been suggested. Similar to the licensed protocol, clinical improvement was observed in cats treated with oral rFeIFN-ω [72]. However, hematology, biochemistry profiles and APP profiles did not significantly change in cats following this protocol [72]. Other studies showed that an rFeIFN-ω licensed protocol decreases concurrent viral infections, even if no true changes are observed in FIV viral load. However, a significant clinical improvement in cats treated with oral rFeIFN-ω was observed, although no changes were seen for viral load or concurrent viral infection [120]. These results indicate that the two protocols are probably acting distinctly. Th-1 and Th-2 responses do not significantly change with either protocol, and only levels of IL-6, a pro-inflammatory cytokine involved in different immune pathways, particularly the innate immune response, significantly change in both groups [75]. In cats treated with the licensed protocol, IL-6 plasma levels are significantly reduced. Treatment with oral rFeIFN-ω did not change IL-6 plasma levels, but concurrent mRNA expression significantly decreased [75]. These results indicate that rFeIFN-ω has anti-inflammatory properties and higher pulsate therapy is more available than continuous low dose therapy for decreasing pro-inflammatory stimuli [75].

Strong immunomodulatory, antitumor, and antiviral effects with weak myelosuppressive and low acute toxic effects of limitin indicate that it is superior than IFN-α [53]. It is demonstrated to have antiviral activities against mouse hepatitis virus. Therefore, a human homolog of limitin or an engineered cytokine with some features of limitin may be useful for treatment of diseases such as HBV or HCV infection. High-dose and/or long-duration limitin therapy could improve viral status [52].

Hepatitis

IFN and viral hepatitis B & C in humans. The combination of pegylated IFN-α plus ribavirin (PegIFNα-RBV), including PegIFNα-2b, and PegIFNα-2a, is not only a treatment option for HBV and HCV but is still the standard treatment for these infection in most countries because the new DAAs are not yet approved, too expensive, or not subsidized. Interestingly, PegIFNα-RBV has acquired the maximum quality-adjusted life-years compared to other antiviral treatments in our country [121]. PegIFNα-2b and PegIFNα-2a have similar clinical efficacy for HCV therapy although they have different pharmacokinetic properties [122]. Similar to responses to other viruses, IFN-α subtypes have different anti-hepatitis virus activities. IFN-α2a and IFN-α2b are superior to IFN-α1, IFN-α16 and IFN-α21 against HCV replication [123]. However, studies show that IFN-α8 is the most effective at suppressing intracellular HCV replication among human IFN-α1, α2, α5, α8, α10, and IFN-αcon1 [124]. IFN-α17 has three times more anti-HCV activity than IFN-α2a against HCV in Huh7 cells. These different efficiencies may be caused by different affinities for IFNAR2, and as a result, different stimulation of the Jak-Stat pathway [125]. Although the use of PegIFN-α to replace non-PegIFN-α significantly increased therapy efficacy, it was not tolerated or safe. Studies found that the absence of KIR2DS2 is associated with a larger and faster decline in platelet count during HCV treatment with PegIFN-α [126]. A weak response rate to high doses and long durations of IFNα-2b therapy was observed in patients coinfected with HBV [127]. For these reasons, new, more effective therapies for hepatitis virus patients are awaited.

Since the discovery of the antiviral activities of IFN-ω against HEV, recombinant human IFN-ω has been shown to be well tolerated in humans. It induces a SVR in patients infected with hepatitis C virus genotypes 1, 2 and 3 in clinical trials [128]. IFN-ω considerably reduces the production of HBsAg, comparable to the reduction obtained by treatment with IFN-α [29]. In a series of safety pharmacology experiments or in local tolerance studies, IFN-ω did not correlate with any biologically relevant adverse effects including acute, subacute, subchronic and reproductive toxicity in monkeys, rabbits, and rats [30]. Several strategies are suggested to improve IFN-ω effects. Nonglycosylated recombinant IFN-ω has similar antiviral potency to IFN-α, while glycosylated recombinant IFN-ω is more potent in decreasing HCV RNA replicons than either IFN-α or non-glycosylated IFN-ω [129]. Eight additional TFs that are not induced by IFN-α are activated by glycosylated IFN-ω and may contribute to its high potency. These TFs are sterol regulatory element binding transcription factor, activating enhancer binding protein 2-like YY1 site, interferon conserved sequence-binding protein, erythroid Kruppel-like factor gene, homeotic gene forkhead of Drosophila 8/hepatocyte nuclear factor 3/mouse forkhead lung protein, HNF-1A, interferon consensus sequence binding protein, and lymphocyte-enriched DNA binding protein LyF [129]. When expressed in yeast, recombinant human IFN-ω-Fc fusion protein (rhIFN-ω-Fc) has more specific activity than when expressed in a Chinese hamster ovary cell line; its terminal half-life is 35 times higher than rhIFN-ω [130]. However, an obvious drawback of IFN-ω is that it requires daily subcutaneous administration, which might influence patients' compliance and impair its effectiveness. A proprietary delivery system (Omega DUROS® device) that is implanted subcutaneously and provides continuous drug delivery for 48 weeks is suggested to overcome this drawback [131]. In addition to the anti-HCV activities of IFN-α and IFN-ω, a limited study showed that IFN-κ has cell-associated antiviral effects against the HCV replicon [49]. Further research is needed to explore the antiviral activities of IFN-κ in cell culture and in animal models.

IFN and HEV in humans. HEV, a non-enveloped positive-sense single-stranded RNA virus, is classified in the family *Hepeviridae* within the genus *Orthohepevirus* [132]. Until now, seven genotypes (gt) have been described, and gt 1 and 3 are found most frequently in humans [133]. Generally, HEV infections lead to arthralgia, vomiting, weakness, reduced appetite, abdominal pain, and hepatitis with accompanying symptoms, including jaundice and itching [134]. However, the antiviral treatment options for HEV infection is still limited. RVB has also been reported that have a broad spectrum antiviral activity against both RNA and DNA viruses. The treatment of RVB has also been demonstrated to efficiently inhibit HEV replication [135]. In addition, RBV cause SVRs in approximate seventy-five percent of the patients and it remains to be considered as first-choice therapy for most patients [136, 137]. Expect RVB, IFN-α is also proposed to be available compounds for treatments of HEV infections. It has been demonstrated that IFN-α2a and IFN-α2b have the strongest antiviral activity against HEV of the 13 IFN-α subtypes [135]. Furthermore, IFN-α has a moderate and delayed anti-HEV effect *in vitro* and in patients, in contrast to its effect against HCV. Recently, researcher found that HEV is highly sensitive to pegIFN-αtreatment *in vivo*. Although PegIFN-α resulted in SVRs in five patients with liver transplants who were infected with HEV, therapy with IFN-α2a correlated with some side effects in organ transplant patients [139, 140]. As a result, this treatment is suitable only for well-selected patients with chronic HEV infections. No significant outcomes were observed after any IFN-α subtype was combined with ribavirin at a constant ribavirin dose of 25 μM, in one study [135]. Future studies are necessary for enhancing of the efficiencies and decreased side effects of antiviral agents and their combination.

Influenza Virus

IFN-α and influenza virus. The epithelial cells of the upper respiratory tract are the primary sites of influenza infection. IAV infection induces expression of proinflammatory cytokines IL-1, IL-6, chemokines RANTES, monocyte chemotactic protein, tumor necrosis factor alpha, and IL-8 and limited amounts of type I IFNs IFN-α/ß [141, 142]. Macrophages produce significant levels of IFN-α/ß, IL-1ß, TNF-α, chemokines, and IL-18 [143]. IAV-infected DCs, especially plasmacytoid DCs, respond to influenza virus infection dose dependently, inducing high expression of IFN-α/ß in spite of low-titer H1N1 influenza virus infection [144, 145]. High-titer H1N1 influenza virus infection stimulates rapid pDC apoptosis [146]. IFN-α suppresses acute influenza A virus replication and alleviates the excessive immunopathology caused by IAV [147]. IFN-α downregulates some effector mechanisms including IFN-γ production by NK and $CD8^+$ T cells through IL-10 production, and promotes rapid induction of an adaptive immune response [148]. The antiviral activities of IFN-α have been evaluated *in vitro*. Matzinger et al. [149] demonstrated induction of ISGs following systemic and mucosal administration of a recombinant PegIFN-α to Rhesus macaques. Induction was associated with reduced tracheal viral titers and systemic responses (fever, body weight) following infection with H1N1. Intranasal administration of ferret IFN-α reduced morbidity from H1N1 infection. In chickens, IFN-α treatment induced more rapid seroconversion than natural infection by low-pathogenicity influenza virus [150]. In addition, low-dose natural human IFN-α protects cynomolgus macaques from pulmonary tissue damage following administration to the buccal mucosa and decreases the alveolar inflammatory response when used at high oral dose [151]. IFN-α also promotes rapid induction of the antibody response and protective efficacy of influenza vaccine [152], these results indicates this kind of IFN can be a potent adjuvant for influenza vaccines.

The sensitivity of recognition of infect-targeted cells differs among influenza virus types. For instance, influenza B virus, which triggers early IFN responses directly via incoming viral particles before viral replication, transcription or protein synthesis are initiated, induces a faster IFN response than influenza A virus in human cells. Some studies, however, show that hosts affected with seasonal influenza A and B viruses have similar disease severities and localized immune responses [153-156]. In addition, the novel H7N9 virus shows a weak ability to induce host innate immune responses, while responses induced by the H5N1 virus are extremely strong in human primary moDCs [155]. A possible explanation for these differences is that early viral entry mechanisms lead to different activation of biological activities that contribute to viral clearance and clinical outcomes [157].

IFN-ω, -τ and Influenza Virus. Human IFN-ω reduces levels of influenza viral load dose dependently *in vivo*, and daily intranasal treatment inhibits viral replication in lung tissues of guinea pigs [158]. The different antiviral effects of IFN-ω have been investigated with other IFNs. IFN-β and IFN-ω show similar inhibitory activity against influenza virus at all IFN concentrations and both IFNs are significantly more potent at suppressing Ca/04 influenza virus infection than IFN-α at certain concentrations [158]. Another study suggested that IFN-ω activity was two times lower than IFN-β1a activity and somewhat lower than IFN-λ1 and IFN-λ2 activities [159]. However, IFN-ω has the most apparent antiviral activity on IFN-stimulated A549 cells following infection with avian influenza virus. Although with less activity than IFN-β1a, IFN-λ1, or IFN-λ2, IFN-ω appears to be more efficient at reducing viral titers than IFN-α2 [159]. A study from Lachova et al. [160] showed that treatment of influenza-infected A549 cells with IFN-α and IFN-ω induces a similar amount of IFN-α, IFN-β and IFN-λ mRNA but differs in induction of CXCL10 and RIG-1 mRNA. In addition to IFN-ω, IFN-τ has biological effects against influenza virus. Studies show that single-dose intranasal administration of recombinant Ad5-IFN-τ effectively protects mice from mortality and disease from the highly virulent hv-PR8 influenza virus. The mechanism of protection is inducing specific and time-dependent phosphorylation of STAT1, increasing mRNA for ISG15, MX1, and OAS1 and preventing viral replication [44].

Conclusion

Since their discovery about 60 years ago, IFNs have been used in available protocols for clinical treatment of viral diseases. IFN-α, IFN-β are currently used to treat hepatitis B and C viral infections, and have effects against HEV infection and for chronic delta hepatitis. The first licensed interferon compound for use in cats for the treatment of FIV and FeLV infection, rFeIFN-ω has comparable efficacy when used for other diseases such as FCV and FHV-1. In addition, OIE suggests a combination of vaccines plus immunomodulatory or antiviral agents to trigger both innate and adaptive immune responses against some viral diseases such as foot and mouth disease. However, IFNs are not approved for preventing these or other viral infections. An important question is that the biological activities of these IFNs have so far not been evaluated in detail. In spite of combination therapy of IFN with ribavirin, especially pegylated IFN, a consensus IFN or albumin-IFN that showed more potency in improving efficacy and reducing side effects than IFN monotherapy, several issues such toxicity, refractory signalling and viral immune evasion still exist. The existence of large type I IFN classes in hosts may indicate they have a special function. Further future studies are urgently needed to determine these exact functions and the molecular mechanisms of their functional differences. In addition, in-depth investigations such as on the efficacy of doses and delivery modes of type I IFN subtypes are required to efficiently prevent some diseases.

Abbreviations

IFNs (Interferons); FeIFN-ω (feline IFN-ω); HIV (human immunodeficiency virus); ISGs (IFN-stimulated genes); aa (amino acids); VV (vaccinia virus); TLRs (toll-like receptor); VEFG (vascular endothelial growth factor); GCSF (granulocyte colony-stimulating factor); ROS (reactive oxygen species); esIFN-κ (Eptesicus serotinus interferon kappa); EBLV (European bat lyssavirus type 1); ART (antiretroviral therapy); AIDS (acquired immune deficiency syndrome); HDAC (histone deacetylation inhibitors); MIP-1α (monocyte chemoattractant protein-1 α); RANTES (normal T-cell expressed and secreted); DAA (direct-acting agents); TFs (transcription factors); RBV (Ribavirin); SVRs (sustained virological responses); IAV (Influenza A virus); PoIFN-δ8 (Porcine IFN-δ8); EqIFN-δ (Equine IFN-δ); JAK-STAT (Janus kinase-Signal transducer and activator of transcription); pDC (plasmacytoid dendritic cells); CNC (Central nervous system); PBMC (peripheral blood mononuclear cell); HSV (herpes simplex virus); NDV (Newcastle disease virus); RSV (respiratory syncytial virus); VSV (vesicular stomatitis virus); SFV (swine fever virus); IDO (indoleamine 2, 3-dioxygenase); HCMV (human cytomegalovirus); SARS-CoV (SARS coronavirus); SIV (Simian Immunodeficiency Virus); MDBK (Madin-Darby bovine kidney(cells)); BHK-21 (baby hamster syrian kidney cells); BT (primary bovine testicular cells); PK-15 (porcine kidney cells); CDV (Canine distemper virus); CPV (canine parvovirus); FLV (Feline leukaemia virus); FIV (Feline Immunodeficiency virus); BVDV (bovine viral diarrhea virus); FCV (Feline Calicivirus); FHV-1 (Feline Herpesvirus-1); PRV (pseudorabies virus); PRRSV (Porcine reproductive and respiratory syndrome virus); HPV (Human Papillomavirus); DAXX (death-domain associated protein-6); DAMPs (Damage Associated Molecular Pattern Molecules); PAMPs (Pathogen-associated molecular patterns); KIR2DS2 (killer immunoglobulin-like receptor 2DS2); FMDV (foot and mouth disease virus); EMCV (encephalomyocarditis virus); MHV (murine hepatitis virus); CTL (cytotoxic lymphocyte); MHC (major histocompatibility complex); OIE (World Organization for Animal Health).

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Disclosure Statement

The authors declare no conflicts of interest.

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