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REVIEW

Potential role of interferon-lambda in the treatment of inflammation and cancer: an update

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Abstract: The interferon (IFN) family comprises various cytokines with potent responses against RNA and DNA viruses as well as antitumor activities. A recently identified interferon subgroup consists of the so-called lambda interferons with several members, including IFN-λ1, IFN-λ2, and IFN-λ3 (also denoted interleukin [IL]-29, IL28-A, and IL28-B). They represent a newly identified group of the class II cytokine family. While they are functionally related to type I IFNs, they are structurally related to the IL-10 cytokine family. The lambda IFNs signal through a cytokine receptor complex which is unique for IL-28 and IL-29, designated IL-28Rα, and a second chain, the IL-10R2, which is shared with receptors for IL-10 related cytokines such as IL-22 and IL-10. In this review, we summarize recent findings about the relationship between type I and type III IFN signaling as well as their antiviral and antitumor activity. A better understanding of the functional role of IFN-λ in viral infections and immune responses in innate and adaptive immunity opens new therapeutical approaches for the treatment of chronic inflammatory diseases and cancer.

Keywords: interferon, interleukin-28, cancer, viral infections, antiviral, antitumor, immunity

Introduction

Interferon (IFN) was first identified in the late 1950s (1957) by Isaacs and Lindemann.[1] They found that IFN production was induced by virus-infected chicken embryo cells and that IFN functions as inhibitor of viral replication. For a long time IFNs were thought to have an impact only in virus infection but later on it was shown that they have also proinflammatory effects and this is especially true for the IFNγ cytokine. IFNs such as IFN-α, IFN-β, and IFN-γ may act on innate immune cells as well as on the adaptive immune system. Innate immunity relates to the first barrier defense against invading pathogens, and one of the first responses of virally infected organisms consists of the secretion of IFNs. Studies in mice have shown that insensitivity towards IFNs results in impaired capacity to sustain viral defense and to control viral infections.[2–4] The relevance of these findings is highlighted by studies in patients showing that dysfunctions in IFN expression and/or signaling cause a high prevalence of viral infections. Additionally, the IFN pathways are also activated in multiple diseases like systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis,[5] underscoring the potential relevance of treating inflammatory diseases by modulating IFN function. Indeed, the clinical use of IFNs was started in the 1980s for the treatment of viral diseases, multiple sclerosis, and cancer.[6]

In addition to the known groups of IFNs, a novel group of IFNs was recently discovered independently by two groups: Kotenko and Gallagher[7] and a group

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around Klucher and coworkers.[8] They identified from human genomic sequences a family of three cytokines, designated interleukin-28A (IL-28A), IL-28B, and IL-29, also called IFN-λ2, IFN-λ3, and IFN-λ1. Based on these findings, IFNs can now be classified into three different types, which share similar properties, amino acid sequences, and structural motifs (Table 1). Functionally, IFN-λs are related to type I IFNs. Structurally, they are related to the IL-10 superfamily and are now referred to as type III IFNs.[7] Whereas IL-29 is present in humans, in mice it is encoded by a pseudogene and therefore not functionally active.

The IFN family and their signaling pathways

Type I IFNs are a homologous cytokine family whose genes are located on chromosome 9. They are mostly nonglycosylated proteins of 165 to 200 amino acids that share 30% to 85% homology within a species. Type I IFNs binds on cell-surface receptors composed of two ubiquitously expressed transmembrane proteins, IFN receptor 1 (IFNAR1) and IFNAR2. The signaling is dependent on the association of two cytoplasmic tyrosine kinases, TYK2 and the Janus tyrosine kinase (JAK) 1 (Figure 1). After ligand binding the signal transducers and activators of transcription (STATs) become phosphorylated, form heterodimers together with IFN regulatory factor 9 (IRF9) to build the heterotrimeric complex IFN-stimulated gene factor (ISGF3), and translocate to the nucleus to activate the transcription of antiviral genes.[9–11] Type I IFNs can be expressed by almost every cell type. However, it should be noted that humans have 13 functionally active IFN-α molecules expressed predominantly by leucocytes and one IFN-β molecule produced by fibroblasts and plasmocytoid dendritic cells, and to a lesser extent IFN-ω, IFN-ε, and IFN-κ. There is only one type II IFN, namely IFN-γ. This type of IFN is mainly produced by natural killer (NK) and T cells and signals through a distinct heterodimer of two membrane spanning receptors, IFN-γR1 and IFN-γR2. The former receptor is constitutively expressed on all cell types, whereas the latter receptor is tightly regulated and expressed on few cell types only (eg, T lymphocytes). In T cells, the receptor is capable of recruiting STAT1 on activation, leading to STAT1 phosphorylation and translocation in the nucleus.[12–16] Finally, the key transcription factor T-bet becomes activated, leading to IL-12Rbeta2 chain expression and subsequent Th1 T cell differentiation.

Finally, an IFN family distinct from type I IFNs are the type III IFNs. They are also called lambda IFNs and consist of three subtypes: IFN-λ1, IFN-λ2, and IFN-λ3. They activate the same signaling pathway as do type I IFNs but act by binding to a different receptor complex. Together with IRF9, STAT1 and STAT2 form then a trimeric complex, ISGF3, that drives transcription of IFN-stimulated genes for antiviral activity.[17] The IFN-λ receptor is composed of two membrane spanning proteins, IFNLR1 and IL-10R2.[18] Whereas IFNARs are expressed ubiquitiously, IFNLR1 (IL-28Rα) is expressed on only few cell types, especially on epithelial cells.[7,8,19] The different expression of type I versus type III receptors is a key difference between these types of IFNs. This appears to be the main reason for the different biological activities of these functionally related cytokines with antiviral response in vivo. The major parts of the interferon signaling cascade are mediated via STATs and JAKs. All three receptor types of the IFN signaling pathways are associated with the binding of JAK family members. After ligand binding they become activated and then phosphorylated. After that dimers are formed that transduce signals to the nucleus where target structures like ISRE (IFN stimulated response element) and GAS (IFN-λ activated sequence) are activated.

Regulation of IFN-λ gene expression and cellular targets

The production of IFNs is induced by stimulation with various viruses including RNA and DNA viruses, protozoa, and microbial products or by chemical inducers.[20] Similarly to

Table 1 The interferons and their subclasses

Class	Subclass	Genes	Receptor	Cell types	Function
I	α	17 but 13 only	IFNAR1	NK/CD8+	Cytotoxicity, TH1, survival, antiviral, antitumor,
	β	functional in human	IFNAR2	DC	proapoptotic, antiproliferative effects
	ε, κ, ω			B-cells	
II	γ	IFN-γ	IFNGR1	NK/T cells	TH1, immune responses, antitumor effects
			IFNGR2	Macrophages	
III	λ	IL-28A	IFNLR1	Epithelial cells	Antiviral, antitumor, pro- and antiapoptotic,
		IL-28B	IL-10R2	Hepatocytes	antiproliferative effects, immune regulation
		IL-29 (mouse: pseudogene)		pDC/keratinocytes	

Abbreviations: DC, dendritic cells; pDC, plasmacytoid DC; IFN, interferon; IL, interleukin; NK, natural killer; TH, T helper.

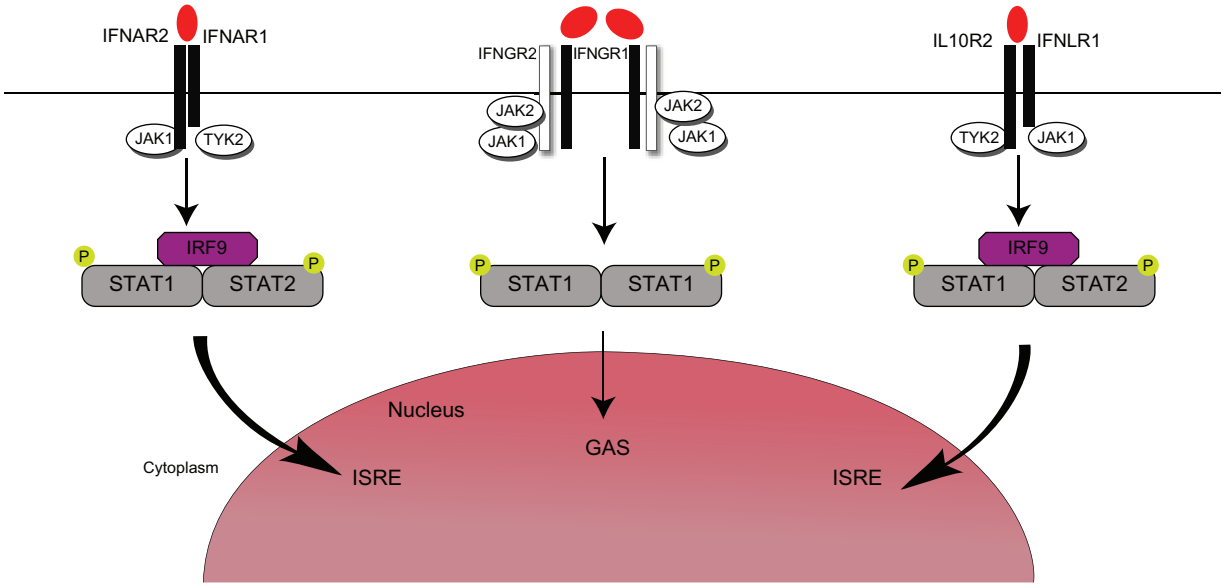

Figure 1 Interferon signaling. Schematic presentation of receptor complexes, intracellular JAK/STAT signaling, and antiviral gene activation for all three types of interferons.
Abbreviations: JAK, Janus tyrosine kinase; STAT, signal transducer and activator of transcription; IRF, IFN regulatory factor; ISRE, IFN stimulated response element; GAS, IFN-λ activated sequence.

type I IFNs, lambda IFNs are induced by viral infections and exhibit antiviral activity in cell culture.[7,8] They demonstrate similarities in the expression pattern to type I IFNs.[21] Furthermore, the IFN-λ gene promoter shares sequence similarities with IFN promoters and is activated by the virus-activated transcription factors IRF3 and IRF7.[22,23] Lauterbach et al recently showed that mouse CD8α$^+$ dendritic cells (DCs) and their human counterparts BDCA3+ DCs are the major producers of IFN-λ on stimulation with double-stranded RNA and TLR3 ligand.[24] This observation correlates with the findings from Kotenko et al[7] and Sheppard et al[8] as these authors showed that peripheral blood mononuclear cells produce high amounts of IFN-λ on TLR3 activation and stimulation with double stranded RNA. Thus, poly I:C appears to be an important adjuvant which induces the systemic production of IFN-λ. Additionally, IFN-λ3 was shown to be an adjuvant of T cell responses in mice.[24,25] Using a systematic screen Ank et al found that only few hematopoetic cells respond to IFN-λ. In particular, however, plasmacytoid dendritic cells were susceptible to stimulation with IFN-λ.[26] Furthermore, in contrast to hematopoetic compartments, epithelial cells and keratinocytes were highly responsive to IFN-λ treatment.[26] Another group investigated the tissue specificity of IFN-λ responsiveness. They showed that the expression of the IL-28Rα and therefore the responsivness to type III cytokines is predominantly seen in stomach, intestine, lung, and skin cells. In particular, epithelial cells were highly responsive to type III IFNs.[27] Within the liver, the receptor was found to be predominantly expressed on hepatocytes.[28] Recently, our group showed that IL-28A emerges as a key regulatory cytokine with pathogenic function in T cell-mediated liver injury.[29] In addition, IFN-λ has been shown to be expressed predominantly by dendritic cells on viral infection and may act directly on epithelial cells or hepatocytes.

Genetics and biological effects of IFN-λ: single-nucleotide polymorphisms of IFNs and their influence in diseases

Three independent groups, namely Suppiah et al,[30] Kotenko et al[7] and Ge et al[31] identified several single-nucleotide polymorphisms (SNPs) near the IL-28B gene region on human chromosome 19 by using genome-wide association studies (GWAS). They additionally showed that the presence of certain SNPs is associated with the response to pegylated IFN-α and ribavirin treatment in hepatitis C virus (HCV) -infected patients in Europe,[30,31] Africa,[31] and Asia.[32] There is striking evidence that the frequency of the CC allele is associated with a higher rate of sustained virological response in HCV-infected patients as compared to patients with the TT genotype. The C allele is quite common throughout eastern parts of Asia, but is less frequent in Africa.[33] Thus, the IL-28B gene encoding for IFN-λ3 has been identified as a key regulator of the immune response in HCV infection. The exact mechanisms of how SNPs in this gene affect the gene function is not well

established, however. Another question is how these SNPs may affect the outcome of other chronic viral infections. On this question, Martin et al showed that the C/C genotype of a specific IL-28B polymorphism (rs12979860) does not influence the outcome of hepatitis B virus or HIV infection.[34] On the other hand IL-28A (IFN-λ2) and IL-29 (IFN-λ1) were considered to inhibit HIV-1 infection in macrophages.[35] However, coinfection of HCV and HIV increases the risk of death and the standard therapy with pegylated IFN-α and ribavarin has been found to induce significantly lower rates of sustained virological response.[36] Recently, it was found that IFN-λ1 has, besides its antiviral activity, a relevant role in immunomodulatory responses. Specifically, it was noted that this cytokine regulates the development of T helper (TH) 1 and TH2 cells. Additionally, Srinivas et al showed a markedly IFN-λ1-dependent diminished IL-13 secretion in T cell cultures where IL-4 had been added. Therefore, IFN-λ1 appears to be an inhibitor of human TH2 responses directed towards IL-13.[37,38] Interestingly, there is a reciprocal control of IL-4 and IFN-λ secretion. Megjugorac et al showed that IL-4 stimulation of monocytes leads to an elevated secretion of IL-1 receptor antagonist, which acts directly on plasmacytoid DCs (pDCs) to augment their IFN-λ1 production and function.[39] Accordingly, there is a mechanism in regulating IFN-λ1 secretion and pDC function in which IFN-λ1 emerges as a cytokine with an immunomodulatory role for TH2 generation. Furthermore, IFN-λ leads to the generation of partially mature DCs with a tolerogenic phenotype. These DCs express high levels of major histocompatibility complex (MHC) I and MHC II but low levels of costimulatory molecules, and they have the ability to migrate to lymph nodes, once injected into immunodeficient mice. In addition, they showed the ability to induce mature DCs that where able to induce an IL-2-dependent proliferation of CD4+CD25+Foxp3+ T cell population with a regulatory phenotype.[40] Recently, it was found that the IL-28 cytokine expression was diminished in allergic asthma. Koltsida et al showed a novel role of IL-28 cytokines in TH1 generation and protection from allergic airway disease. Thus, beside high expression of IL-28Rα on the gut epithelium the lung epithelium reveals expression of the IFN-λ receptor and is therefore highly responsive to IFN-λ. The authors described an improvement of allergic airway disease after treating the mice with rIL-28A. Such treatment suppressed the TH2 and TH17 responses but induced local TH1 immune responses.[41] Abrogation of endogenous IL-28 cytokine signaling by IL-28Rα deficiency in mice aggravated experimental ovalbumin-mediated airway disease by increasing TH2 and TH17 responses as well as IgE levels.

IFN-λ and its antitumor activity

In addition to its antiviral activity, type I IFN (IFN-α/β) has been found to inhibit tumor cell growth. This observation suggested the potential benefit of type I IFN therapy in several forms of cancer. However, type I IFN is a pleiotropic cytokine with many effects on various cell types due to the wide expression of its receptor complex. Accordingly, numerous side effects have been noted in patients treated with type I IFNs.[42] The discovery of a new subgroup of IFNs (IFN-λ) with antiviral properties but more restricted receptor expression thus might represent a suitable alternative for cancer therapy. In fact, lambda IFNs revealed potent antitumor activity in murine models of cancer and have been proposed as novel tools for cancer treatment in patients.[19,43,44] Due to the fact that the cellular receptor expression differs between IFN-α and IFN-λ, such therapy may result in fewer side effects. Indeed, the receptor for IFN-λ is expressed only on a narrow range of cell types and the activity of IFN-λ appears to be more tissue specific.[28]

First clinical trials with pegylated-IFN-λ1 in patients with chronic HCV infection encouraged the idea that IFN-λ is a promising therapeutic agent as an alternative to IFN-α.[45,46] In contrast to the IFN-α receptor, the type III IFN receptor was mainly detected on tumor cells and many tumor cell lines. Studies in tumor cells lines have addressed the antiproliferative and antiapoptotic effects of lambda IFNs. For instance, Dumoutier et al showed that IFN-λ1 inhibited growth of the murine BW5147 thymoma cell line but failed to inhibit the proliferation of the B lymphoma cell line Daudi.[47] It was also found that IFN-λ inhibits cell growth in the human glioblastoma LN319 cell line[48] and additionally induces apoptosis in human neuroendocrine BON1 tumor cells,[49] the human keratinocyte cell line HaCaT, and the human fibrosarcoma 2fTGH cell line[50] as well as in murine melanoma and colon cancer cells.[43] Thus, in contrast to IFN-α, IFN-λ could promote apoptosis in different cell lines and was more effective in inducing an antiproliferative effect associated with the induction of apoptosis. Interestingly, the combination of both IFNs augmented the effects on antiproliferative responses. As most solid tumors are of epithelial origin and as the IL-28Rα is predominantly expressed on epithelial cells, it appears likely that type III IFNs have proapoptotic effects in cancer cells. Indeed, a proapoptotic effect of IFN-λ in colorectal adenocarcinoma HT29 cells was noted that leads to caspase activation,

externalization of phosphatidylserin, DNA fragmentation, and cell death.[51] Another recent finding in colon26 and murine melanoma B16 cell lines revealed a functional IFN-λ receptor expression on the tumor cell surface. Transient transduction of IFN-λ enhanced MHC I and surface Fas (CD95) expression and suppressed cell proliferation by induction of $p21^{Waf/Cip1}$ and activation of caspase 3 and 7 activity. These findings indicated that lambda IFNs favor the induction of apoptosis in tumor cells accompanied with cell cycle arrest.[43] However, the antitumor activity of IFN-λ was mediated by tumor apoptosis and NK cell-mediated immunological tumor destruction. Another recent study confirmed these results in a different tumor cell line. In this series of studies, it was also discovered that the antitumor activity was partially dependent on IFN-γ but independent of IL-12, IL-17, and IL-23. Concomitant systemic administration of IL-12 augmented IL-28-mediated antitumor activity in the presence or absence of IFN-γ.[44] In summary, virus-induced IL-28 expression by innate immune cells may be used for lysis of tumor cells and reduction of tumor burdens.[52–54] Consistent with this concept, Wongthida et al identified that IL-28, induced by viral activation of innate immune cells, is a key modulator of antiviral and antitumor activity in B16 ova tumors.[55] They showed also that the vesicular stromatitis virus activity depends on host CD8+ and natural killer cells. They clear the virus, and lambda IFNs have both direct and indirect antitumor activity.[56,57] IFN-λ1 also induced G1 phase arrest or apoptosis in oesophageal carcinoma cells.[58] These data suggest that IFN-λ1 might be a useful therapeutic agent for oesophageal carcinoma without marked damage of surrounding tissues.

In summary, these results illustrate that IFN-λ has therapeutic properties for the clinical treatment of human malignancies and for suppression of tumor growth in vivo. As initial studies with recombinant lambda interferons in HCV infection showed relatively few side effects, such therapy might be both safe and effective. Controlled clinical trials addressing this concept are highly warranted.

Conclusion

The main role of IFNs is to inhibit viral replication in infected cells as well as to protect uninfected cells from viruses. The lambda IFNs IL-28A, IL-28B, and IL-29 are a new class of IFNs with potent antiviral and antitumor activities. These cytokines are produced in response to viral infections by various cell types including dendritic cells and macrophages. Although signaling events induced by lambda IFNs are similar to those of type I IFNs, lambda IFNs interact with a different, unique receptor complex that has a more restricted expression pattern compared with receptors for type I IFNs. For that reason type III IFNs have a higher tissue specificity than type I IFNs. Additionally, variations found in the IL-28B gene appear to influence the kinetics of viral response to therapy, as shown for patients with HCV infection bearing the C/C genotype. Because of the tissue specificity of type III IFNs and the predominant expression of their receptor on epithelial cells, these cytokines appear to be a promising new approach for the treatment of several cancer forms in humans. Consistently, various studies have identified potent antitumor effects of lambda IFNs on cancer cells ex vivo or in animal models of cancer in vivo. Thus, lambda IFNs have opened new therapeutical strategies for viral infections and tumor immunity.

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Disclosure

The authors report no conflict of interest in relation to this work.

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