

Interferon- λ s: Special Immunomodulatory Agents and Potential Therapeutic Targets

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Abstract

Interferon (IFN)- λ s are a new addition to the old IFN family and share many similarities, such as antiviral and antiproliferative characteristics, with type I IFNs. IFN- λ s also exhibit unique characteristics in immunomodulation. Accumulating studies have indicated the interactions between IFN- λ s and immune cells, which lead to the regulation of the latter. IFN- λ s can influence dendritic cells (DCs) and their product, IFN- λ s-DCs, can then regulate the function of T cells. On the other hand, IFN- λ s can also directly affect T cells through inhibition of the T helper 2 cell (Th2) responses. IFN- λ s have varying immunomodulatory functions under different physiological conditions or in different organs and can inhibit tumor growth via regulation of the immune system. Diseases associated with IFN- λ s include asthma, allergy, and systemic lupus erythematosus. In this review, we summarize the current knowledge of the biology of IFN- λ s and their immunomodulatory function in relevant human diseases.

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Introduction

Interferons (IFNs) are defined by their ability to induce host defense to viral infection. There are three types of IFNs, known as types I, II, and III. Type III IFNs, also called IFN- λ s, are a new distinct type of IFN initially found in 2003 by two independent groups [1, 2]. Three closely positioned genes on human chromosome 19 were found to encode distinct but paralogous proteins, which were designated IFN- λ 1, IFN- λ 2, and IFN- λ 3 [or interleukin (IL)-29, IL-28A, and IL-28B, respectively] [1]. IFN- λ s are also related to the IL-10 family with regard to a classical four-helix bundle structure [3].

IFN- λ s and type I IFNs are similar in their expression patterns and biological activities, but research has shown that IFN- λ s also have their unique characteristics. Compared to type I IFNs, expression of IFN- λ s can be induced in response to a broader spectrum of stimuli, such as diverse viruses and various toll-like receptor (TLR) agonists [4].

Many studies have demonstrated that IFN- λ s play a unique role in antiviral defense [1, 5–8], with their influence on HBV or HCV persistence [9–11]. However, there is still little known about their function in immunomod-

ulation. This review summarizes the current understanding of the immunomodulatory activities of IFN- λ s and their significance in cancer and several immune diseases, such as asthma and SLE. These latest studies suggest that IFN- λ s will be a potential therapeutic target in clinical medicine.

Expression Pattern

Similar to type I IFNs, IFN- λ expression is in response to diverse viruses and various TLR agonists [2, 11, 12], and it is induced through transcriptional mechanisms involving IFN regulatory factors (IRFs), NF- κ B, and activator protein 1 (AP-1) [4, 13]. The similar expression patterns of type I and type III IFN genes are due to the common regulatory elements in their promoters [11, 14]. Nevertheless, the expression of IFN- λ s responds to a wider range of stimuli compared with type I IFN [4]. Further studies indicate that the IFN- λ 1 gene is regulated by IRF3 and IRF7, thus resembling the IFN- β gene, whereas IFN- λ 2/3 gene expression is mainly controlled by IRF7, resembling those of the IFN- α genes [13]. In addition, dendritic cells (DCs), monocytes, mast cells, and epithelial cells are the main IFN- λ -producing cells [15–20].

Receptor Complex and Signaling

Type III IFNs function through a heterodimeric IFN- λ receptor complex composed of a unique IFN- λ 1R1 chain and the IL-10R2 chain that is also the second subunit of the receptor complexes for IL-10, IL-22, and IL-26 [21, 22]. IFN- λ 1R1 can be alternatively spliced to produce two variant receptors with similar affinity to IFN- λ s, and it is possible that these IFN- λ receptor variants are involved in inhibiting ligand binding and/or signal transduction [23].

After IFN- λ s bind to IFN- λ R, they can activate downstream signaling pathways, such as the Jak-STAT pathway and the mitogen-activated protein kinases (MAPK). Engagement of these pathways by IFN- λ s results in recruitment of the IFN-stimulated gene factor 3 (ISGF3) complex to the promoter region of responsive target genes [24–26]. Additionally, IFN- λ s can also induce phosphorylation of protein kinase B (PKB) through the phosphatidylinositol 3-kinase (PI3K) pathway [27]. IFN types III and I induce a similar subset of genes, such as 2'-5'-oligoadenylate synthetase 1 (OAS1) and IFN-stimulated gene 56 (ISG56) [24].

The specificity of the IFN- λ response is regulated through limited receptor expression [8, 24]. Unlike the widespread expression of the receptor of type I IFN, the IFN- λ R is only expressed in skin, the respiratory tract, and the gastrointestinal tract. Only epithelial-like cells and, to a lesser extent, some immune cells respond to IFN- λ s [28]. Thus, IFN- λ s contribute to prevent viral invasion through the skin and mucosal surfaces [29–32].

Surprisingly, Witte et al. [23] reported that, despite the expression of IFN- λ receptor in immune cells, IFN- λ 2 and IFN- λ 1 did not activate STAT (signal transducer and activator of transcription) 1 or STAT3 at all in monocytes, T cells, or natural killer (NK) cells, and only minimal activation was observed in B cells, presumably because these cells depend on other pathways for STAT activation.

Different Functions of IFN- λ Subtypes

IFN- λ 2 and IFN- λ 3 are virtually identical, sharing 96% identical amino acids, whereas IFN- λ 1 has 81% homology to IFN- λ 2/3 [33], so many researchers assume that different subtypes of IFN- λ s have the same activity. Surprisingly, Dellgren et al. [34] found that IFN- λ 3 possesses the highest antiviral activity among all human IFN- λ subtypes, exhibiting a 2-fold higher activity compared to IFN- λ 1 and a 16-fold higher activity compared to IFN- λ 2. In addition, Liu et al. [35] found that IFN- λ 1 had a stronger ability than IFN- λ 2/3 to induce IL-12p40, TNF, and IL-10 production in monocyte-derived macrophages in response to R848 stimulation. Further research showed that IFN- λ 2 significantly reduced the expression of 89 genes by more than 2-fold in hepatic cells, while no significant downregulation of genes was observed following IFN- λ 1 stimulation [36]. Currently, there is still limited data to compare the biological activities of the three different IFN- λ s cytokines. It would be useful to figure out whether different subtypes are responsible for different aspects of their functions.

Antiviral and Antiproliferative Function

IFN- λ s possess antiviral activity [reviewed in 5, 7, 25]. Administration of exogenous IFN- λ s protects mice from the encephalomyocarditis virus (EMCV), herpes simplex virus-2 (HSV-2), influenza A virus, HCV, and other viruses. However, the IFN- λ -induced antiviral system alone cannot provide full protection against systemic vi-

rus infections; the functional type I IFN antiviral system is also required. The latest study shows that mice deficient for both type I and type III IFN receptors cannot efficiently control initial SARS-CoV replication in the lung [37]. In contrast to type I IFNs, antiviral protection of intestinal epithelial cells against rotaviruses mainly relies on the action of the type III IFNs antiviral system [38]. IFN- λ 3 single-nucleotide polymorphisms (SNP) can influence IFN- λ expression, which is also associated with mortality risk in HIV-infected patients [39] and prognosis in HCV patients [40–45].

IFN- λ s also elicit antiproliferation responses [46–48] and induce STAT activation more potently than type I IFNs. IFN- λ s lead to apoptosis or G1 phase arrest of cancer cells [49–51], although not all cell lines have the same susceptibility to IFN- λ s [51]. As discussed below, IFN- λ s can inhibit tumor growth through modulation of the immune system.

Immunomodulatory Functions of IFN- λ s

A study found a discrepancy between the observed antiviral activity *in vitro* and *in vivo*, suggesting that type III IFNs do have immunomodulatory properties [52]. The current understanding of the complex role of type III IFNs in overall immunity constitutes an important aspect of IFN- λ biology.

IFN- λ s and DCs

IFN- λ s have a close relationship with DCs. Although all cells infected by virus can produce IFN- λ s, DCs are the main source of IFN- λ s after specific stimulation of TLRs [16, 53–57]. A recent study measuring the expression of IFN subtypes in purified human myeloid DCs (mDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs in response to different TLR agonists revealed that the expression profiles of human IFN- λ s subtypes depend on the specific types of TLRs and immune cells [17].

IFN- λ s can also impact DCs. There are two kinds of DCs in human periphery blood: pDCs and mDCs. The steady-state expression of IFN- λ R1 in pDCs is significantly greater than that of peripheral blood mononuclear cells (PBMCs) or general DCs, suggesting that pDCs are among the most IFN- λ -responsive cell types in the periphery [58, 59]. pDCs treated with IFN- λ 1 exhibit enhanced expressions of the homing molecules CCR7 and

CD62L, co-culture molecules CD80 and ICOS-L, and reduced production of IL-10, IL-13, and IFN- γ [58].

Human mDCs matured with lipopolysaccharide (LPS) in the presence of IFN- λ 1 secrete less IL-10 and more IL-12 than those not exposed to IFN- λ 1 [60, 61]. However, Mennechet and Uzé [62] found that IFN- λ s induced only a subset of human monocyte-derived DC maturation markers and did not induce IL-12. IFN- λ -treated DCs specifically induce proliferation of a CD4+CD25+Foxp3+ T cell subset with suppressive activity on T cell proliferation [62].

Although further studies are needed at this time, we hypothesize that the initial state of mDCs would influence the function of IFN- λ s on themselves. IFN- λ -treated mDCs display a partially matured phenotype and induce regulatory T cells (Tregs) [62], whereas after maturation by LPS stimulation, IFN- λ s can promote mDCs to facilitate the T helper 1 (Th1) response and diminish the Th2 response [60, 61].

IFN- λ s and CD4+ T Cells

IFN- λ 1 can modulate the secretion of Th1 or Th2 cytokines by CD4+ T cells by inhibiting the secretion of IL-4, IL-5, and IL-13 and promoting the secretion of IFN- γ [63]. Furthermore, IFN- λ 1 can suppress differentiation towards a Th2 phenotype [53]. Compared to IL-4 and IL-5, IFN- λ 1 preferentially inhibits IL-13 production [64] through a decrease in the Th2-restricted transcription factor GATA3 [63]. Th2 cytokines, in turn, also impact IFN- λ production. IL-4-responsive monocytes secrete IL-1 receptor antagonist (IL-Ra), which then acts on pDCs to elevate their IFN- λ 1 output [53]. In this way, IL-4 and IFN- λ 1 comprise a feedback loop which represents a natural checkpoint for the control of Th2 cytokine production. IFN- λ 1 can work against this loss of the CD62LCCR7 population of CD4+ T cells [63] and make memory T cells incapable of entry into the periphery or differentiation.

Intriguingly, an animal experiment showed that neither T cell differentiation nor cytokine production of already differentiated Th0, Th1, or Th2 cells is affected by IFN- λ 2 directly [61]. It has been shown that human herpesvirus type 6B (HHV-6B)-induced alterations in the Th1/Th2 balance are mediated mainly through IFN- α instead of IFN- λ 1 [57]. This controversy may be caused by different research approaches and models.

Table 1. Immunoregulatory functions of IFN- λ s

Subtype	Target cell	Effect and possible mechanism	Overall impression	References
$\lambda 1$	pDC	increase the expression of the homing molecules CCR7 and CD62L; upregulate co-stimulatory molecules CD80 and ICOS-L, and reduce stimulation of IL-10, IL-13, and IFN- γ production from allogeneic T cells	contribute to pDC activity and prolong pDC survival	58, 59
$\lambda 1, \lambda 2$	mDC (without LPS)	induce partial maturation of DCs; high levels of major MHC class I and MHC class II; express CCR7; low levels of costimulatory molecules, and retained phagocytic ability	induce partial maturation of mDCs	62
$\lambda 1, \lambda 2$	mDC	profoundly inhibit the generation of Th2 and Th17 responses; enhance Th1 polarization, and augment IL-12 secretion	promote mDC maturation	60, 61
$\lambda 1$	CD4+ T cell	alter the Th1/Th2 development of naive human T cells; diminish the development of Th2 cells and lower the secretion of IL-13, and induce CD3+ T cell apoptosis	inhibit Th2, promote Th1, and induce apoptosis	60, 64, 73
$\lambda 1, \lambda 2$	Treg	IL-2-dependent proliferation of CD4+CD25+Foxp3+ T cells	induce proliferation of Treg	62
$\lambda 3$	CD8+ T cell	increase CTL killing activity, and enhance antigen-specific cytolytic degranulation	promote killing activity	65, 66
$\lambda 1, \lambda 2/3$	NK	do not enhance NK cytotoxic activity and chemotaxis directly	no direct influence on NK	67, 68, 74
$\lambda 1$	PBMC	elevate chemokines mRNA levels of CXCL9, CXCL10, and CXCL11, and upregulate IL-6, IL-8, and IL-10	activate PBMC	70, 71
$\lambda 1$	monocyte	upregulate IL-6, IL-8, and IL-10; change morphology, and more motile	activate monocyte	71
$\lambda 1$	macrophage	upregulate IL-6, IL-8, and IL-10; increase TLR-induced IL-12p40 production, and upregulate IFN- γ R1	activate macrophage	35, 71
$\lambda 2/3$	B cell	enhance TLR7 on B cells	unclear	75

IFN- λ s and CD8+ T Cells

IFN- λ s can increase the killing activity of cytotoxic T lymphocytes (CTL). Using DNA vaccination, peripheral CD8+ T cells from animals that were administered with IFN- $\lambda 3$ show substantially increased cytotoxic responses [65]. IFN- $\lambda 3$ is able to increase the percentage of splenic CD8+ T cells and reduce Treg cell populations [66], and the CD8+ T cells are more granular and have higher antigen-specific cytolytic degranulation compared to cells taken from the animals that received IL-12 as an adjuvant. NK cells and CTL actually contribute to IFN- λ -induced immune protection of mice with tumor injection [67–69]. Nevertheless, further experiments showed that IFN- λ s cannot directly work on NK cells and CD8+ T cells in vitro [67, 68]. Thus, it remains unclear whether IFN- λ s have any effect on DCs to influence NK cells and CD8+ T cells, or if IFN- λ s can change IL-12 and IFN- γ production, which then contributes to the cytolysis of NK cells and CTL.

IFN- λ and Monocytes/Macrophages

IFN- $\lambda 1$ induces IL-6, IL-8, IL-10, chemokine (C-X-C motif) ligand (CXCL) 9, CXCL10, and CXCL11 in human PBMCs [70, 71]. Examination of purified cell populations isolated from PBMCs demonstrates that monocytes and macrophages are the major IFN- $\lambda 1$ -responsive cellular subsets. IFN- $\lambda 1$ -treated macrophages upregulate the surface expression of the IFN- γ R1 chain and therefore are more responsive to IFN- γ [35]. All of this indicates that IFN- λ s activate both monocytes and macrophages, and may therefore be important in activating innate immune responses at the site of viral infection. However, the latest research has found that IFN- $\lambda 1$ sensitized monocytes and macrophages to IL-10 stimulation and seemed to inhibit pro-inflammatory responses [72] (table 1) (fig. 1).

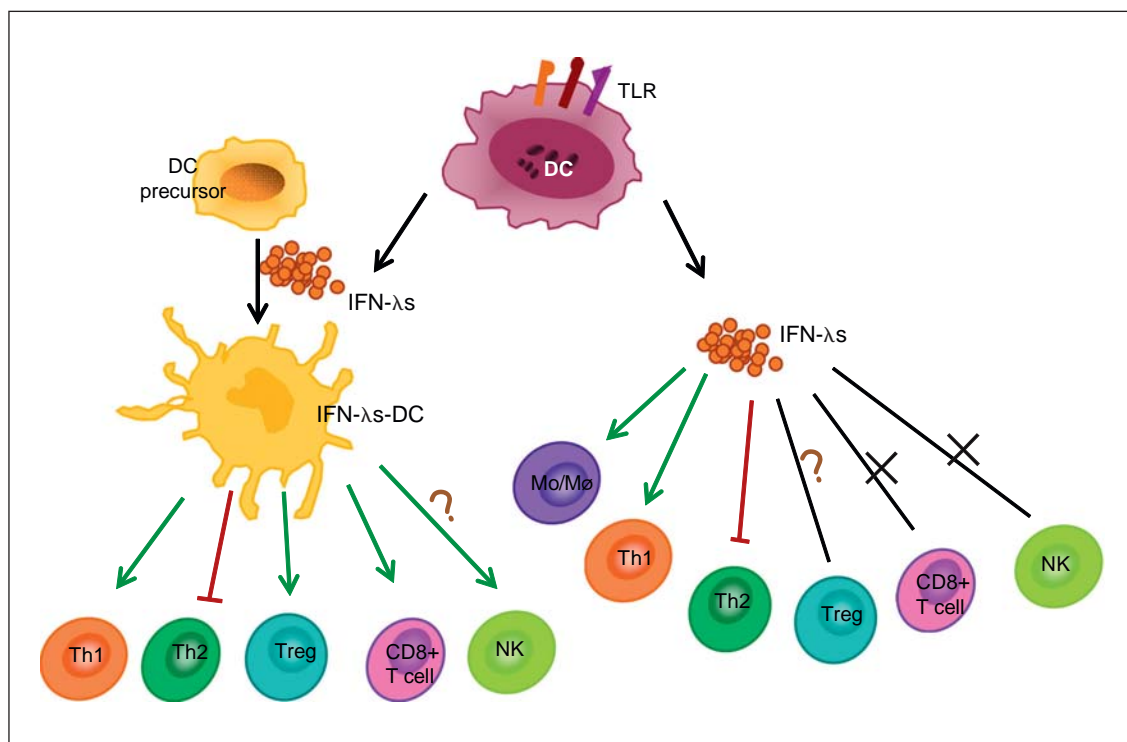


Fig. 1. Immunomodulatory functions of type III IFN. IFN- λ R is expressed in DCs, T cells, and NK cells. DCs can produce IFN- λ s in response to the stimulation of TLRs, and IFN- λ s can also affect DCs, resulting in the change of MHC, CCR7, and costimulatory molecules. IFN- λ s-DCs or IFN- λ s themselves can influence the function of T cells, including promotion of Th1, inhibition of Th2,

activation of Mo/M ϕ , and changing the proportion of Treg and the cytotoxicity of CD8+ T cells. Cross marks = IFN- λ s could not work directly on this kind of cells; question marks = the pathway was not completely confirmed; green color = promote; red color = inhibit.

Relationship of IFN- λ s in Disease

Growing tumors acquire the ability to resist immune recognition and immune-mediated injury [76]. In addition, allergy and systemic lupus erythematosus (SLE) have a hypothetical Th2 cell-cytokine predominance. Since IFN- λ s have a special immunomodulatory function, they may play a role in the pathogenesis or therapy of these diseases.

Cancer

Type III IFNs can elicit antitumor activities through both a direct effect on tumor cells themselves and an indirect effect on the antitumor immune responses. The direct antitumor activity of type III IFNs is associated with cell cycle arrest at the G1 phase and apoptosis [51, 77]. For human non-small cell lung cancer (NSCLC), Fu-

jie et al. [78] found that IFN- λ 1 significantly inhibited the in vitro growth of a wide range of NSCLC lines in a dose-dependent fashion.

IFN- λ s can also work on the immune system to inhibit tumor growth. The proliferation of cancer cells with constitutive expression of IFN- λ s is not affected in vitro, but the in vivo tumorigenicity is either suppressed or completely abolished when cells are injected subcutaneously into mice [68, 79], suggesting that IFN- λ s engage host mechanisms to inhibit tumor growth. NK cells probably play a critical role in IFN- λ -mediated protection against tumors [50, 67, 69, 80], as IFN- λ s sensitize tumor cells to NK cell recognition and activation, and depletion of NK cells inhibits IFN- λ -induced antitumor activity. In addition, Numasaki et al. [68] proposed that polymorphonuclear neutrophils and CD8+ T cells also play equally important roles in IFN- λ 2/3-mediated inhibition of MCA205 fibrosarcoma growth, while Sato et al. [69] found that the response of CD8+ T cells is weak in a mu-

rine colon26 cancer model. The increased secretion of IL-12 and IFN- γ may also contribute to the immunocytotoxicity induced by IFN- λ s [67, 68].

With regard to whether IFN- λ -induced antitumor activity is associated with an antiangiogenic response, research showed that IFN- λ s did not affect tumor vascularity in human NSCLC [78], a BNL hepatoma model [67], and esophageal carcinoma [50]. However, Lasfar et al. [79] found that tumors derived from B16.IFN- λ 2 cells were less vascular than B16 tumors. Importantly, these experiments were carried out using different subtypes of IFN- λ s, leaving the exact relationship between IFN- λ s and angiogenesis an open question.

The animal experiments reviewed above indicate that immune cells, cytokines, and antiangiogenesis are possible mechanisms of IFN- λ -mediated protection against tumor. Surprisingly, recent studies showed that IFN- λ 1 induced myeloma cell growth and protected cancer cells from dexamethasone-induced cell death [81]. In another study, intratumoral injections of 400 ng IFN- λ 1 did not mediate significant suppression of A549 growth *in vivo* [78]. These inconsistent results may suggest a context-dependent mechanism of action for IFN- λ s in different types of tumors.

The potential application of IFN- λ s in cancer treatment has been proposed [reviewed in 28, 82]. Due to the restricted expression of IFN- λ receptors, the adverse side effects are slight and two phase 1 clinical trials have shown good patient tolerance with IFN- λ s. Application of IFN- λ s will help to modulate the Th1/Th2 balance in cancer patients and break immune tolerance. IFN- λ s in combination with IFN- $\alpha/\beta/\gamma$ or chemotherapeutic agents can provide a new choice for cancer therapy [51, 74, 78].

Asthma

Researchers have observed deficient induction of IFN- λ s by rhinovirus in primary bronchial epithelial cells and alveolar macrophages of patients with asthma exacerbation [83] and human cystic fibrosis [84]. Another discovery is that an SNP rs12979860, which is located 3 kb upstream of IFN- λ 3 and influences the production of IFN- λ s, is correlated with the immune state in children who develop allergic disease [85], and a relationship between higher levels of a pro-inflammatory cytokine profile at birth with diminished levels of IFN- λ s is observed over time in children who carry the SNP.

IFN- λ s are thought to inhibit GATA3 expression and suppress Th2-type immune responses [60, 63, 64], which

are the hallmarks of allergic diseases [86]. This is further supported by the recent study by Koltsida et al. [61], which shows that IFN- λ s can promote Th1 immunity and suppress Th2 responses in the mouse model of allergic asthma [87]. The novel effects of IFN- λ 2 on T cell differentiation are not observed in IFN- γ -deficient mice or mice depleted of IL-12p40, indicating that IFN- λ 2 induces Th1 effect or function via IL-12 and IFN- γ [87]. IFN- λ s are likely the principal IFNs produced during innate responses to respiratory viruses in bronchial epithelial cells [88], and key modulators of the Th2 response [89]. All of this suggests that defective type III IFNs in response to rhinovirus lead to a stronger Th2 response and subsequent allergic diseases. Recent studies have shed further light on the regulation of IFN- λ 1 promoter activity in human airway epithelial cells and have shown that BLIMP-1 and ZEB1 may be negative regulators of IFN- λ 1 expression [15]. Moriwaki et al. [90] indicated that IL-13, a crucial cytokine responsible for asthma pathogenesis, suppresses dsRNA-induced expression of IFN- λ s in airway epithelial cells and alveolar macrophages, and contributes to the impairment of the antiviral defense in asthmatics.

However, Bullens et al. [91] reported that asthma patients have higher mRNA expression of IFN- λ 2/3 in sputum than healthy individuals. Moreover, the serum level of IFN- λ s is also higher in asthma patients in exacerbation [18]. These studies indicated that IFN- λ s are involved in the pathogenesis of allergic inflammation [18, 91]. Thus, the role of IFN- λ s in asthma is somewhat controversial, but the mainstream views are that the deficiency of IFN- λ s leads to hyperfunction of Th2 cells, and an IFN- λ supplement would alleviate asthmatic symptoms.

Systemic Lupus Erythematosus

IFN- λ 1 mRNA expression and serum protein levels in patients with SLE are higher compared to normal controls, suggesting that IFN- λ 1 is probably involved in the renal disorder and arthritis progression of SLE and associated with disease progression. IFN- λ 1 stimulates the production of CXCL10 (IP-10), CXCL9 (MIG), and IL-8 by PBMCs from SLE patients [92]. These chemokines play an important role in the inflammation process of SLE by recruiting leukocytes to inflammatory sites and promoting disease aggravation. Recently, the expression of IFN- λ 2/3 was found to be high in activated CD4+ T cells of SLE patients [93]. Significantly, enhanced IFN- λ 1 could also be measured in the serum of cutaneous lupus erythematosus patients with active skin lesions. Functional analyses re-

Table 2. IFN- λ s and relevant diseases

Subtype	Experimental system	Effect and possible mechanism	References
$\lambda 1, \lambda 2/3$	antitumor function in mice	regulate innate and adaptive immune responses of NK, T cells, and DCs, and antiangiogenesis	50, 67–69, 79, 80
$\lambda 1, \lambda 2/3$	asthma	modulate lung DC function to promote Th1 immune skewing and suppress allergic airway disease, and decreased IFN- λ production correlating with severity of rhinovirus-induced asthma exacerbation and virus load	18, 19, 61, 83, 84, 90
$\lambda 2$	Con A-induced hepatitis	induce Th1 cytokine production and T cell-mediated liver injury	96
$\lambda 1, \lambda 2/3$	SLE	significantly enhanced in patients with SLE, and stimulate the production of CXCL10 (IP-10), CXCL9 (MIG), and IL-8	92–94
λ	food allergy	controversial: induced apoptosis of T cells or intestinal epithelial cells, and suppressed or induced antigen-specific Th2 cell-mediated inflammation	73, 95

vealed that human keratinocytes are able to produce high levels of IFN- $\lambda 1$ but only low amounts of IFN- $\alpha/\beta/\gamma$ in response to immunostimulatory nucleic acids [94].

In SLE patients, IFN- λ secretion is enhanced and leads to upregulation of several inflammatory proteins, and cytokine imbalances contribute to immune dysfunction, trigger inflammation, and induce organ damage. Therefore, there is a potential to use anti-IFN- λ monoclonal antibodies to neutralize excess IFN- λ s in SLE patients.

Food Allergy

He et al. [73] found that IFN- λ s are involved in the development and maintenance of oral tolerance in the intestines of mice. Interaction between IFN- λ s and their receptor induces apoptosis of T cells and their subsequent phagocytosis by DCs, which leads to the generation of tolerogenic DCs and Tregs in vitro and in vivo. On the other hand, IFN- λ -treated DCs retain their phagocytic ability and induce Treg proliferation [62]. Thus, IFN- λ s are functional in the generation of tolerogenic DCs and Tregs, keeping the immune activation in control and helping to restore immune homeostasis. Surprisingly, He et al. [95] also reported that eosinophils express IFN- λ s that can induce intestinal epithelial barrier dysfunction and promote the initiation of aberrant Th2 polarization in the intestine. So it remains to be further investigated whether IFN- λ s are involved in the development of oral tolerance or food allergy (table 2).

Concluding Remarks

It has been widely accepted that type I IFNs play an exclusive role as early mediators of the innate response to viruses, as well as regulators of the subsequent responses from components of the adaptive immune system [97]. IFN- α -DCs can play a role in the generation of antitumor T cell immunity and in the pathogenesis of some autoimmune disorders [98]. IFN- λ s are new members of the IFN family of cytokines, and many research studies have shown that type III IFNs and type I IFNs share lots of biological similarities. The therapeutic efficacy could be augmented and the side effects could be reduced when both IFN types are used in combination [78, 99].

We believe IFN- λ s not only assist type I IFNs but also modulate the immune response independently. IFN- λ s can function via DCs and also directly work on T cells. Under physiological conditions, IFN- λ s promote differentiation of immune cells and activate the immune system. However, under pathological conditions, their abnormal secretion is associated with the pathogenesis of immunological diseases, such as cancer, SLE, asthma, and food allergy. In consideration of its immunomodulatory function, IFN- λ s have potential as a new target of treatment in these diseases. Potential applications include inhibition of the activity of IFN- λ to ameliorate symptoms of SLE patients, or supplementation of IFN- λ s to modulate the imbalance of T helper cells in cancer patients.

In summary, the newly discovered IFN- λ s and their special functions have attracted great attention to the old IFN family. It has been realized that the immunomodulatory activities of IFN- λ s are complex and intriguing. We hypothesize that IFN- λ s possibly have dual characteristics, functioning diversely in different circumstances. Al-

though further studies to elucidate the mechanism of the function of IFN- λ s are needed, the current evidence suggests that IFN- λ s have great therapeutic potential, and can provide novel strategies for the clinical treatment of many diseases.

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