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Lambda interferons in immunity and autoimmunity

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ABSTRACT

Type I IFNs are well known players in immunity and autoimmunity. They induce potent innate and adaptive immune responses essential for mediating host defenses against viral and bacterial infections but also driving inflammation during chronic inflammatory and autoimmune diseases. Lambda interferons (IFNλs) or type III IFNs, on the other hand, comprise a relatively new family of cytokines sharing homology and functional resemblance with type I IFNs but whose spectrum of activities remains poorly understood. Although IFNλs induce antiviral responses similar to type I IFNs, their restricted pattern of expression suggested that may have more specialized functions at specific body sites such as barrier surfaces. However, recent developments in the field have revealed broader roles of IFNλs in immunity against a diverse range of pathogens including viral, bacterial and fungal infections, and have highlighted unique non-redundant functions of IFNλs that cannot be compensated by type I IFNs. They have also positioned IFNλs as a non-inflammatory or immunoregulatory form of IFNs that possesses the antimicrobial functions of type I IFNs but lacks their pro-inflammatory effects, playing a crucial role in the fine tuning of immune defenses for optimal host protection and minimal host damage. Beyond infections, IFNλs are also emerging as important players in immunity against cancer and autoimmunity, with several studies now demonstrating up-regulation of these molecules at disease sites, and functional involvement in experimental animal models. Here, we critically assess recent advances in our understanding of the IFNλ biology, with emphasis to their emerging roles in cancer and autoimmune diseases, and discuss their potential therapeutic implications.

1. Introduction

Fifty years ago Isaacs & Lindenmann [1] described type I interferons as factors capable of 'interfering' with viral replication. In less than a decade later, Wheelock [2] added IFNγ or type II IFN, as another class of IFN secreted by activated lymphocytes upon antigenic stimulation sharing the ability with type I IFNs to 'interfere' with viral replication. However, it took another nearly 40 years, along with the completion of the Human Genome Project, for Kotenko, Sheppard and colleagues to uncover a third class of IFNs, termed lambda interferons (IFNλs), type III IFNs or interleukins 28 and 29 [3,4]. This pointed to a more subtle and disguised role of IFNλs in immunity and host defense that has delayed their discovery. Indeed, progress over the recent years has established IFNλs as cytokines that share many antiviral features with type I IFNs and that are difficult to be discriminated from. They are both triggered by viral infection and activate analogous downstream signaling cascades involving JAKs, STATs and interferon-regulated transcription factors (IRFs) [5]. They also induce seemingly similar antiviral responses enhancing viral resistance of cells and mediating viral clearance [6]. Many viruses thus encode inhibitors for both type I and type III IFNs, inhibiting their signaling response or production [7]. Moreover, they are both expressed in various types of cancer and autoimmune conditions, regulating diverse inflammatory and proliferative responses. Emerging evidence, however, indicates that type I and type III IFNs also exhibit important functional differences that are only now starting to become appreciated. In this article, we review current literature on the biological activities of IFNλs in the context of host defense, autoimmunity and cancer, compare them with type I IFNs, and highlight their therapeutic potential for the treatment of a diverse range of devastating diseases of our times.

2. IFNλ family members and IFNλ receptor signaling cascades

In humans, lambda interferons (IFNλs) are closely positioned on chromosome 19 and comprise four members; IFNλ1/IL29, IL28A/IFNλ2, IL28B/IFNλ3 and IFNλ4, with the latter being functional only in a subfraction of the population bearing the ΔG genotype [8,9]. In mice, IFNλs are represented by two members positioned on

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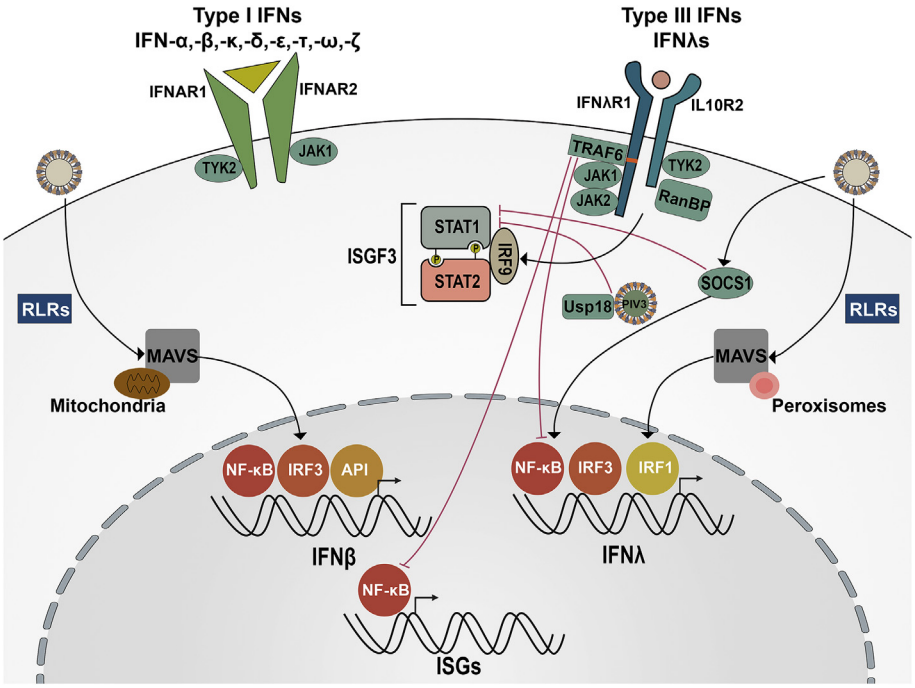

Fig. 1. Viral induction and downstream signaling of IFNλs, and comparison with type I IFNs. Viruses induce IFNλ gene expression through a peroxisomal mitochondrial antiviral-signaling protein (MAVS) signaling cascade while mitochondrial MAVS is employed for the induction of type I IFNs. IFNλs signal through a heterodimeric receptor complex comprising IFNλR1 and IL10R2 chains. Type I IFNs use IFNAR1 and IFNAR2. Although both IFNs activate the JAK-STAT pathway, unique molecules like JAK2 are only induced upon IFNλ signaling, ultimately leading to ISG induction. JAK: Janus activated kinase, STAT: Signal transducer and activator of transcription, ISG: Interferon stimulated genes.

chromosome 7; IFNλ2/IL28A and IFNλ3/IL28B [3,4,8]. The IFNλ receptor complex is a unique heterodimer consisting of IFNλR1 (IFNλRA or IL28RA) and IL10R2 (IL-10RB) which is shared with all IL-10 superfamily members. IFNλR1 confers ligand specificity and enables complex assembly with IL10R2 (IL-10RB) while IL10R2 is indispensable for signaling. IFNλ binds first IFNλR1 leading to the recruitment of IL10R2 and the formation of the ternary complex in a 1:1:1 ratio [10]. This triggers downstream signaling events, many of which are interestingly shared with type I IFNs as well (Fig. 1). More specifically, IFNλ receptor stimulation leads to the induction of the JAK-STAT pathway with key players being JAK1 and TYK2, phosphorylating Tyr residues of the IFNλR1 intracellular domain with subsequent activation of STAT1 and STAT2 [11–13]. STAT1-STAT2 heterodimers bind to IRF9, forming the Interferon Stimulating Gene Factor 3 or ISGF3 complex that translocates to the nucleus and binds to Interferon Stimulated Response Elements (ISREs) on the promoters of Interferon Stimulated Genes (ISGs), initiating their transcription [3,4]. Upregulation of ISGs can then contribute to the inhibition of viral replication, the induction of an antiviral state on neighboring cells and the inhibition of bacterial and parasitic infections [5]. Notably, this aforementioned signaling cascade is shared with type I IFNs making it difficult to distinguish transcriptional and functional disparities between type I and IFNλs responses (Fig. 1). Differences, however, in downstream signaling processes have been described including the fact that IFNλ-induced effects exhibit a delayed peak and a longer duration [14–18]. Differential utilization of downstream signaling components has been described as well. Specifically, IFNλs but not type I IFNs activate JAK2 affecting immune cell functions in a way type I IFNs cannot do [19,20], USP18 acts as a negative regulator of IFNλ signaling and inhibits the phosphorylation of STAT1 [22], while mitochondrial antiviral-signaling protein (MAVS) on peroxisomes can activate IRF1 to regulate IFNλ production [20]. Furthermore, it has been proposed that IFNλR1-adaptor molecules such as RanBP and TRAF-6, upregulate IRF9 and inhibit NF-kB, respectively [23,24].

3. IFNλ actions on epithelial cells and barrier surfaces

Respiratory, gastrointestinal and urogenital tracts constitute major physical barriers for pathogen entry, conferring protection from infections. They express pathogen recognition receptors (PRRs) that recognize diverse PAMPs and act to induce the production of antimicrobial mediators, including interferons. Therefore, it did not come as a surprise that IFNλs are most abundantly produced at these mucosal sites following infection [15,19,25]. What came as a surprise though was the fact that IFNλ production and IFNλR1 expression follows a very restricted expression pattern in sharp contrast to the type I IFN receptor (both IFNAR1 and IFNAR2 subunits) which is broadly distributed among virtually all nucleated cells. IFNλR1 is thus expressed on a very limited cell type spectrum; on cells of epithelial origin including epithelial cells of the respiratory, gastrointestinal and urogenital tracts, keratinocytes, hepatocytes and endothelial cells and a few innate immune cells, mostly neutrophil and DC subpopulations as discussed below [26]. IFNλ expression largely follows its receptor distribution as recently reviewed [26]. This selective IFNλ receptor presence and IFNλ responsiveness highlights the fact that IFNλs act locally through engagement of epithelial and immune cells, in cooperation with type I IFNs, to confer and fine-tune immunity and host protection at barrier surfaces (Fig. 2) [15,19]. Although, mucosal surfaces are inseparably linked to IFNλ biology, emerging studies are now beginning to unravel new functions of IFNλs at non-mucosal surfaces. Recently, in a study examining blood brain barrier (BBB) integrity researchers observed that IFNλR1$^{-/-}$ mice exhibited higher West Nile Virus (WNV) viral titers in the brain and spinal cord, in combination with increased BBB permeability, while IFNλ2 treatment was able to maintain BBB integrity and reduce brain viral titers upon lethal challenge [27]. Furthermore, in the context of thromboinflammation, IFNλ1 was reported to hinder neutrophil activation and extracellular trap formation (NETs) [28].

4. IFNλ pleiotropic effects on immune cells and host immunity

4.1. Dendritic cells

Dendritic cells (DCs) have a central role on immune responses as they are the sentinels of the body that sense pathogens, initiate immune responses and link innate with adaptive immunity. DCs were among the first cell types found to possess IFNλR1. This is now well established as both human and mouse plasmacytoid DCs (pDCs) [29,30], human

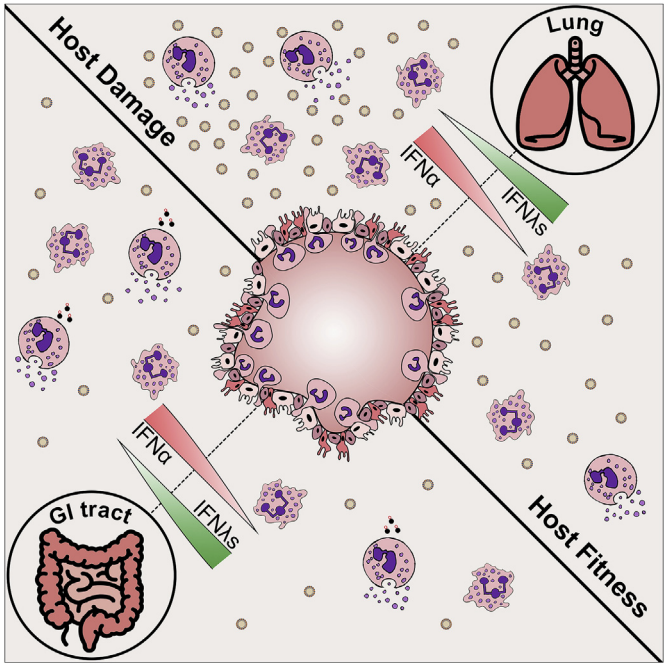

Fig. 2. IFNλs are major players in antimicrobial immunity and homeostasis at barrier surfaces. IFNλs constitute the frontline antimicrobial system in the respiratory and gastrointestinal tracts, conferring initial protection. When the microbial burden is high and host fitness is broken, type I IFNs take over, enhancing immune responses at the expense of collateral host damage.

monocyte-derived DCs [31,32] and mouse bone marrow-derived or lung sorted conventional DCs (cDCs) of the DC2 phenotype [33] have all been shown to express IFNλR1. Human and mouse pDCs [29,30,34–36], DC1 [37], DC2 [15,29,36,37] and human monocyte-derived DCs [31,32,38,39] can also express IFNλs upon activation with diverse stimuli including various TLR ligands [32,34–38] and IFNα [39]. IFNλs act on monocyte-derived and conventional DCs and can profoundly modulate their antigen presenting function by promoting Th1 skewing [33] and Foxp3+ Treg expansion [32]. Accordingly, IFNλR1$^{-/-}$ mice exhibit reduced Th1 development, augmented Th2 and Th17 responses and worsened allergic airway disease (AAD) while recombinant IFNλ administration in wild type animals exerts the opposite effects [33]. Increasing Th1 skewing following IFNλ treatment has also been reported to occur in human PBMC and T cell culture systems [40]. IFNλs may also act on pDCs as it has been reported that IFNλs can evoke type I IFNs and TNF production [41], induce high levels of these inflammatory cytokines in the presence of IL-3 [42], and upregulate co-stimulatory molecules like CD80 and CD86 [42], suggesting a new angle by which IFNλs can enhance immunity to viral and bacterial infections. Interestingly, immunofluorescence studies on biopsies from ulcerative colitis and Crohn's disease patients have revealed significantly increased IFNλ and CD11c positive cell co-localization, compared to healthy controls, pointing to CD11c^{+} DCs as important IFNλ-producers in human diseases as well [43]. However, further research is needed to define the effects IFNλs have on DCs.

4.2. Neutrophils

Neutrophils constitute a major component of the innate immune response; wherever there is pathogen invasion or tissue damage, neutrophils are the cells that arrive first at the site of infection to mediate front line defenses essential for host protection. While type I IFNs are long known to act on neutrophils [44], it has only recently been shown that IFNλR1 is also expressed on murine and human neutrophils and is functional [15,19,45]. IFNλ stimulation of neutrophils activates the canonical JAK-STAT pathway leading to ISG upregulation at levels similar to type I IFNs [15,19,45,46], indicating that IFNλs are an important regulator of neutrophil function. Accordingly, influenza virus infection of IFNλR1 knockout mice leads to higher viral load, increased neutrophil and total leukocyte cell numbers in the BAL and worsened lung function even at sublethal IAV doses [15]. This is dependent on IFNλR1 expression in neutrophils and respiratory epithelial cells, highlighting the importance of these two cell types in initial antiviral immunity [15]. This also extends beyond viral infections as an invasive aspergillosis study using *Aspergillus fumigatus* showed that IFNλ-mediated STAT1 activation in neutrophils is essential for protecting the host from fungal infection [46]. Moreover, in an acute pneumonia model based on *Staphylococcus aureus* infection, IFNλR1$^{-/-}$ mice exhibited increased bacterial clearance compared to WT mice and decreased IL-1β levels attributed to proteases released by neutrophils instead of caspase-1 and NLRP3 activation [47]. In the gut mucosa, IFNλs have also been shown to exhibit a protective role in the DSS-induced colitis mouse model [19,43,49] through a fine inhibitory role of IFNλs in the production of reactive oxygen species (ROS) by neutrophils, conferring intestinal mucosal protection during acute inflammation [19]. As neutrophil-mediated pathogen restriction is exerted through phagocytosis, ROS production and cytotoxic antimicrobial molecule release [50], striking is the effect that IFNλs down-regulate degranulation, ROS generation and NET release of neutrophils, without affecting their ability to engulf pathogens or secrete cytokines [51]. IFNλs are therefore emerging as key modulators of neutrophil-specific antimicrobial defenses in the context of distinct viral, bacterial and fungal infections.

4.3. Macrophages

Macrophages constitute a major innate immune population with a central role on host protection. Characterized by a broad phenotypical spectrum, ranging from pro-inflammatory M1-like to anti-inflammatory M2-like states, macrophages act to preserve tissue homeostasis and prevent infection [52]. There is evidence that IFNλs can be produced by macrophages as human monocyte-derived macrophages produce IFNλ following stimulation with Human Respiratory Syncytial Virus (HRSV) [53], Rhinovirus (RV) [54], the TLR3 and TLR4 agonists poly(I:C) or LPS [38]. However, this may not be a universal capacity of macrophages as other studies, especially in mouse macrophages, have failed to detect IFNλ expression [29]. Controversy also exists on the responsiveness of macrophages to IFNλs. It has been reported that IFNλs can act on human monocyte-derived macrophages and have a protective role upon HIV infection [48,55] while others have shown that IFNλ can enhance IFNγ-induced IL-12p40 production by monocyte-derived macrophages after R-848 stimulation, in sharp contrast to IFNα that exhibits a suppressive role. In experiments of the same context, IFNλ-pretreated monocyte-derived macrophages and subsequently stimulated with IFNγ and R-848, exhibited higher levels of pro-inflammatory cytokines than their IFNα counterparts [56]. However, other studies have not been able to demonstrate signaling of IFNλs such as ISG induction on these cells. Therefore, functionality of the IFNλR complex in macrophages, needs to be carefully re-evaluated, taking into account the diversity of macrophage populations and activation states.

4.4. Natural killer cells

Most to date evidence points towards an indirect role of IFNλs in the regulation of NK cells. Although it has been reported that mouse NK cells express low levels of IFNλR1 [57,58], IFNλ stimulation does not induce ISG expression nor STAT1 phosphorylation, major downstream components of the IFNλ signaling pathway [59]. It has been shown that the combination of IFNα and IFNλ in the tumor microenvironment can promote tumor eradication, and the concerted action of these two interferons can promote NK-mediated antitumor immunity as discussed below [59]. However, this involves the indirect modulation of NK cell

function through IFNλ-mediated effects in tumor cell sensitization to NK-cell mediated tumor cytotoxicity in an NKG2D-dependent manner, in line with studies suggesting NK cell-unresponsiveness to IFNλs [60–62]. Although some evidence about IFNλ-augmented NK cell tumoricidal and other functions in concert with IFNα exists, further studies are needed to evaluate the efficacy of such combination therapy in preclinical animal models and ultimately in humans. In an influenza virus infection mouse model, IFNλ constitutive expression (through systemic hydrodynamic gene administration), protected infected mice and influenced NK proliferation rates and maturation state [58]. As IFNλs can affect NK cells through indirect effects, it is plausible to hypothesize that other IFNλ-responsive cells, such as DCs and neutrophils or even non-immune cells, might contribute to the augmented NK cell functions observed [51].

4.5. Lymphocytes

T and B cell lymphocytes are the orchestrators of adaptive immunity, directing pathogen-specific cell and antibody-mediated immune responses, and conferring long-term protection. T cells do not appear to express significant levels of IFNλ1 [63], and despite some early reports claiming that there is a slight expression on IFNλR1 mRNA levels, downstream signaling components like pSTAT1 are undetectable [64]. This seems to be the case for both human and mouse T cells, although current data do not exclude the possibility that some T cell populations may do so. Human B cells, on the other hand, seem to express significant levels of IFNλR1 [63,65] and respond to IFNλ with STAT1 phosphorylation [64] and ISG upregulation [65]. Mouse B cells may also express IFNλR1 as one study has claimed that IFNλ can act on mouse B cells and induce upregulation of TLR7 in a contact-NK cell mediated manner [66]. Whether such effects of IFNλs on B cells are functionally important, and can affect their biology, remains to be understood.

5. IFNλs in cancer immunity

5.1. Anti-proliferative and anti-tumor effects in vitro

Similarly to type I IFNs, IFNλs possess antiproliferative effects on several human cancer cell lines. In the BON1 pancreatic neuroendocrine tumor cell line, IFNλs exhibited the highest cell number reduction compared to IFNα treated cells. When apoptosis was further investigated, IFNλ1 was shown to induce the highest level of DNA fragmentation compared to IFNλ2 and IFNα, with all three cytokines inducing caspase-3 and poly (ADP-ribose) polymerase or PARP-cleavage [67]. In the mouse fibrosarcoma MCA205 cell line a wide range of IFNλ doses did not have any effect on its growth rate in culture [68] while on the stably transfected with the full-length IFNλR1 cDNA BW514 T lymphoma cell line, IFNλ1 inhibited its proliferation [69]. In a cohort of 12 adherent brain tumor-derived cell lines of astrocytoma and glioblastoma, IFNλ1 and IFNλ2 inhibited their expansion with good effective dose values for the 50% of the treated cells (ED_{50}). Interestingly, the glioblastoma LN319 cell line showed a strong dose-dependent IFNλ1 growth inhibition, with IFNλ1 having greater effects than IFNβ. Interestingly, ED_{50} values for various non-small Cell Lung Cancer (NSCLC) cell lines was also calculated [70] with 12 human NSCLC cell lines (see Table 1) treated with IFNλ exhibiting growth suppression. Furthermore, combinatorial treatment with IFNλ and IFNα on the large cell carcinoma OBA-LK1 cell line revealed augmented apoptotic DNA fragmentation and Annexin V cell positivity compared to each IFN alone. When cyclin-dependent kinase inhibitors were evaluated, IFNλ1 led to increased expression of $p21^{Waf1/Cip1}$ on OBA-LK1 and the adenocarcinoma 11–18 cell line [71]. Evidence from the human lung adenocarcinoma cell lines HCC 827 and NCI-H1650 indicates that IFNλ stimulation can suppress their growth [72]. In colorectal cancer-derived intestinal epithelial cell lines (IECs), it has been demonstrated that IFNλ1 and IFNλ2 decreased cell proliferation of the HCT116 cell line, with IFNλ2 exhibiting higher antiproliferative properties than IFNλ1 [73]. In contrast to the aforementioned direct IFNλ effects, it has been proposed that IFNγ treated HT29 colorectal adenocarcinoma cells can be sensitized to IFNλ-mediated apoptosis [74]. Another study has demonstrated that IFNλ1 can mediate growth suppression in the human esophageal carcinoma cell lines TE-11, YES-5 and T.Tn in a dose-dependent manner. Strikingly, combination of IFNλ1 with chemotherapeutic agents like cisplatin/CDDP or 5-fluorouracil/5-FU can augment anti-tumor effects in the aforementioned esophageal carcinoma cell lines in a dose-dependent manner but not in normal esophageal Het-1A cells [75]. Another study examined human cervical tissue samples from 154 women and demonstrated higher IFNλ1-3, IFNλR1 and *Isg15* message levels on Low Risk HPV (LR-HPV) patients compared to High Risk HPV patients (HR-HPV) and IFNλ1 levels were significantly decreased with abnormal cytological results. In that setting, a positive correlation between lower ISG expression on HR-HPV patients and progression towards a high-grade cervical lesions and cancer was proposed [76]. Analysis of the human melanoma MM-LH cell line also demonstrated growth suppression upon IFNλ stimulation [72]. In the F01 human melanoma cell line, IFNλ1 induced apoptosis in a dose-dependent manner as flow cytometric analysis with PI and Annexin V revealed , and the effect was synergistically enhanced by the presence of Bortezomib (also revealed by cleaved-PARP immunoblots) or Temozolomide. The same study revealed that six out of eight primary melanoma lesion were IFNλR1-positive while seven benign nevi samples were IFNλR1-negative [77]. Although, it has been reported that proliferation of mouse B16 melanoma cells constitutively expressing IFNλ2 (B16.IFNλ2) is not affected [78], another team has developed an *in vitro* melanoma B16ova cell/bone marrow coculture assay exploring IFNλs' actions in combination with vesicular stomatitis virus (VSV). Interestingly, NK, macrophage or $Gr1^+$ cell depletion led to decreased IFNλ levels in culture, and reduction of the cytotoxic effect on B16ova cells was observed upon VSV-treatment. Moreover, when B16ova cells were treated with IFNλ, NK cell-derived IFNγ production was observed [79]. Taken together, these studies suggest strong anti-proliferative activity of IFNλs that is potentially beneficial in cancer.

5.2. Anti-proliferative and anti-tumor effects in vivo

Besides the *in vitro* studies, a potent anti-proliferative and antitumor role of IFNλs on murine models has also been proposed. In the B16 melanoma model in mice, overexpression of IFNλ2 in B16 melanoma cells remarkably delayed the development of tumors in the lung and reduced their size compared to the B16 parental cells [78]. This was associated with reduced vascularity in the tumors from the IFNλ2-overexpressing B16 cells and reduced immune infiltrates. On the contrary, engineering of IFNλ-unresponsive B16 cells resulted in decreased tumorigenicity compared to the parental cells, suggesting a direct antitumor effect of IFNλs in this model [78]. In another study, IFNλ transfected syngeneic Colon26 cells administered subcutaneously to BALB/c mice demonstrated retarded tumor growth compared to their un-transfected or mock-transfected controls [71]. Evidence that IFNλs can prevent metastatic tumor growth also exists. Intravenous injection of IFNλ-transfected B16/F10 cells in C57BL/6 mice prevented pulmonary metastasis while tumor sites exhibited increased cellular infiltrates. Interestingly, although $CD4^+/CD8^+$ antibody depletion had no effect on IFNλ-overexpressing B16F10 cell tumor growth, NK cell depletion through *anti*-asialo GM1 led to progressive tumor growth, implicating a major NK cell contribution to the elimination of the tumor [81]. On another setting, fibrosarcoma MCA205 cells retrovirally transduced to express IFNλ, reduced tumor growth and resulted in a significantly longer survival of the experimental animals in comparison to their non-transduced counterparts, with IFNλ demonstrating reduced metastatic lung foci [68]. Mechanistic studies using a bone marrow sublethal irradiation approach or antibody-based cell-specific depletion

Table 1
IFNλs exhibit anti-proliferative and anti-tumor activities against cancer cells qPCR: quantitative Polymerase Chain Reaction, WB: Western blot, NB: Northern blot, ED50: Effective dose 50, IC50: Inhibitory concentration 50.

Cancer Types	Cell lines	IFNλR Signaling Components	Antiproliferative activities	References
Human				
Colorectal cancer-derived Intestinal Epithelial Cellls (IECs)	Caco-2, DLD-1, SW480	qPCR (IFNλR1/IL10R2)	——	73
	HT29	qPCR (IFNλR1/IL10R2) WB pSAPK/JNK-1/-2, pAKT, pSTAT1	IFNγ pre-treated HT29 sensitized to IFNλ apoptosis	
	HCT116	qPCR (IFNλR1/IL10R2)	Decreased cell proliferation	
Glioblastoma	LN319	qPCR (IFNλR1/IL10R2)	Dose-dependent inhibition Low/modest sensitivity (ED50)	70
	LN229	–	Low/modest sensitivity (ED50)	
Hepatocyte Carcinoma	HepG2	–	Low/modest sensitivity (ED50)	
Osteosarcoma	MG63	–	Low/modest sensitivity (ED50)	
Bladder Carcinoma	SW480, T24/83	–	Intermediate/high sensitivity (ED50)	
Laryngeal Carcinoma	Hep2C	–	Intermediate/high sensitivity (ED50)	
Pancreatic Neuroendocrine Carcinoma	BON-1	qPCR (IFNλR1/IL10R2) WB pSTAT1/2/3	Higher cell reduction compared to IFNα	67
Oesophangeal Carcinoma	TE-1, TE-2, TE-10, YES-2, YES-4, YES-6,	NB (IFNλR1/IL10R2) qPCR (MxA, 2′,5′ Oas)	–	75
	TE-11, YES-5, T.Tn	NB (IFNλR1/IL10R2) qPCR (MxA, 2′,5′ Oas)	Dose-dependent	
Melanoma	RPM-MC 1106 MEL, A375, MEL39, SK MEL 5, 18105 MEL, Hs 294T	qPCR (IFNλR1/IL10R2)	——	77
	F01	qPCR (IFNλR1/IL10R2)	Dose-dependent apoptosis	
	MM-LH	WB (pSTAT1	Growth suppression	72
Squamous Cell Carcinoma	Sq-1	–	Intermediate sensitivity (IC50)	71
	Sq-19	Flow cytometry (IFNλR1)	Insensitive (IC50)	
	LK-2	–	Insensitive (IC50)	
	LK-79	–	Intermediate sensitivity (IC50)	
	EBC-1	–	Insensitive (IC50)	
Large Cell Carcinoma	OBA-LK1	Flow cytometry (IFNλR1)	Sensitive (IC50)	71
	86–2	–	Sensitive (IC50)	
	Lu99,	–	Insensitive (IC50)	
	NCI-H460	–	Insensitive (IC50)	
Adenocarcinoma	11–18	Flow cytometry (IFNλR1)	Direct antiproliferative effects	71
	LK-1	Flow cytometry (IFNλR1)	Intermediate sensitivity (IC50)	
	HCC 827	qPCR(IFNλR1/IL10R2) WB (pSTAT1)	Growth suppression	72
	NCI-H1975, NCI-H441	qPCR(IFNλR1/IL10R2)	–	
	NCI-H1650	qPCR(IFNλR1/IL10R2)	Growth suppression	
	NCI-H23	qPCR (IFNλR1/Il10R2) Flow cytometry (IFNλR1)	–	
Alveolar Cell Carcinoma	A549	Flow cytometry (pSTAT1)	Intermediate/high sensitivity (ED50)	70–72
Mesothelioma	NCI-H2052	qPCR (IFNλR1/IL10R2)	–	75
Mouse				
Melanoma	B16	ISGF3/pSTAT3	–	78
Fibrosarcoma	MCA205	PCR (IFNλR1/IL10R2) Flow cytometry (IFNλR1)	Reduced tumor growth	68
Hepatoma	BNL	pSTAT1	Reduced tumor growth	60

strategies, indicated that the antitumor action of IFNλ was mediated through NK, CD8 T cells and neutrophils but not CD4 T cells, supporting the notion that IFNλs possess potent immunotherapeutic effects in cancer. They also suggested that IFNλs mediated their antitumor function indirectly through the activation of immune cells while IFNα exhibited a direct effect on the tumor cells themselves, claiming an important difference on the underlying antitumor mechanism of the two interferon systems [68]. Moreover, in a melanoma mouse model based on B16 ovalbumin-overexpressing tumor cells, IFNλ was found to augment VSV-mediated tumor reduction [79]. In line with these results, in a BNL hepatoma BALB/c mouse model, syngeneic BNL hepatoma cell-derived tumors expressing IFNλ showed increased intratumoral NK cell infiltration [60]. Notably, when splenic NK cells isolated from mice injected with BNL.IFNλ cells were depleted using antibodies, reduced cytotoxicity was observed, supporting NK cells' importance on the IFNλ-mediated antitumor response [60]. In a follow up paper, an IFNα/IFNλ combination therapy was reported to be more efficient than individual therapies, promoting tumor remission on the BNL hepatoma model which was also related to increased NK cell infiltration [59]. Another study used a xenograft model based on luciferase-expressing HCC827 human lung cancer cells transiently transfected to express IFNλ2. Strikingly, it found that seven days after tumor inoculation, tumor derived photons (counted with an *in vivo* luminescent imaging system) were significantly reduced in IFNλ2-transfecting HCC827 cells compared to mock transfected [72]. In a different xenograft study where OBA-LK1 or LK-1 NSCLC cell lines were implanted into SCID mice forming palpable tumor nodules, intratumoral IFNλ1 administration reduced tumor volume in a dose-dependent manner compared to PBS treated mice. Moreover, systemic IFNλ1 administration in OBA-LK1-established tumors also reduced tumor volume with immunohistochemical (IHC) analysis revealing higher p21 accumulation and lower Ki-67 cell positivity although vascularity remained unaffected. Strikingly, treatment with a combination of IFNλ and IFNα exhibited the greatest antitumor activity compared to IFN monotherapy [71]. In the breast cancer spontaneous PyVmT mouse model of mammary tumorigenesis, initial evidence showed that Usp18 knock-out mice had reduced tumor growth and increased $CD4^+$ T cell infiltrates as flow cytometric and immunofluorescence analyses revealed. Trying to

explain the increased T cell infiltrates, Usp18-deficient tumor tissue was shown to have higher CXCL10 levels and a Th1 polarized cytokine network that could cause mammary tumor inhibition [22].

6. IFNλs in autoimmunity

6.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation in the peripheral synovial joints, which are infiltrated by blood-derived cells, mostly T cells, macrophages and autoreactive B cells. Although pro-inflammatory cytokines such as TNF, IL-1 and IL-6 are well-studied pivotal molecules involved in disease pathophysiology [82] type I IFNs are also considered to be important [83,84]. IFNα and IFNβ are upregulated in the RA synovium and type I IFN related genes are increased in the PBMC compartment of RA patients, suggesting an active role in the disease process [83]. Interestingly, IFNλs mRNA and protein levels are also up-regulated in the serum, PBMCs and synovial fluid of RA patients [85–88], although it remains unclear whether these correlate with RA disease markers [85,86]. A relatively recent study has identified increased IFNλ1$^+$ cells in the RA synovium lining layer compared to the healthy synovium, as well as increased IFNλ1$^+$ macrophages with IHC and IF respectively [89]. Moreover, studies have proposed that IFNλR1 is expressed in both human primary RA synovial fibroblasts (RA-FLSs), MH7A cells [89] and osteoarthritis synovial fibroblasts (OA-FLSs) [90], rendering them responsive to IFNλ stimulation. In line with that, it has been proposed that IFNλ1 and IFNλR1 are expressed in the osteoarthritis (OA) synovium lining layer [90]. Functionally, IFNλ1 has been reported to increase the production of the pro-inflammatory cytokines IL-6 and IL-8, and the matrix metalloproteinase MMP3, in both mRNA and protein level, in the RA-FLS cell line MH7A [89,90]. It has further been shown to up-regulate TLR2, TLR3 and TLR4 expression in RA-FLS [90]. These data suggest a mechanism by which IFNλs may be involved in the recruitment of immune cells to the inflamed synovium contributing to the chronicity of the disease. Further studies on the effects of IFNλs on synovial macrophages are needed in order to elucidate their potential involvement in RA pathogenesis [91]. In collagen-induced arthritis (CIA) in mice, an animal model that replicates many features of human RA, exogenous administration of IFNλ ameliorated disease, reducing Th17 and γδ T cell numbers without perturbing humoral autoantigen immune responses. This was through the inhibition of IL-1β-expressing neutrophil recruitment to the inflamed joints, highlighting IFNλs' importance on neutrophil-driven inflammation [45]. Despite these encouraging results, more studies are needed to shed light into IFNλs' anti-inflammatory and/or pro-inflammatory possibilities proposed by the above studies. Interestingly, there has also been one study where IFNλ1 was identified as an intraocular biomarker for juvenile idiopathic arthritis-associated uveitis [92], implying that IFNλs may be important players in rare autoimmune diseases as well.

6.2. Systemic & cutaneous lupus erythematosus

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease conferred by autoreactive T and B cell hyperactivity, increased autoantibody production and immune complex formation that leads to pivotal tissue damage and organ dysfunction. Type I IFNs have a well-established role in the pathogenesis and progression of SLE and Cutaneous Lupus Erythematosus (CLE), with agents blocking IFNα signaling being promising experimental therapeutics in the clinic [93,94]. However, there are very few reports on IFNλs, with some suggesting elevated IFNλ protein levels in the serum and mRNA levels in PBMCs of SLE patients compared to healthy individuals [95–98]. Interestingly, serum IFNλ protein levels positively correlate with anti-nucleosome Abs, *anti*-dsDNA Abs, lymphopenia, glomerulonephritis, arthritis and disease activity of SLE patients [95,99]. Moreover, treatment of PBMCs isolated from SLE patients with IFNλ for 72 h resulted in increased IL-8, IP-10 and MIG chemokine secretion compared to PBMCs from healthy individuals [97]. These data indicate that IFNλ levels correlate with SLE, although further studies are needed to dissect the specific role of this cytokine family in the disease process. Other studies have focused on CLE and observed that IFNλ and IFNλR were strongly expressed in the epidermis of CLE skin lesions [98]. Interestingly, IFNλ induced the secretion of the pro-inflammatory cytokines IL-6, IL-8, CCL3 and CXCL9 but not CXCL10 from human keratinocytes, and supernatants from IFNλ1-treated keratinocytes could significantly enhance recruitment of PBMCs in transwell assays. Finally, using IHC co-localization of CXCL9 (expressed within the whole epidermis) with IFNλ, and CXCL10 (expressed in basal epidermal areas) with IFNα on CLE skin lesions could be observed. IFNλ may further play a role on lupus nephritis (LN) as type I IFNs do, although this needs further elucidation [100].

6.3. Sjögren's syndrome

Sjögren's syndrome (SjS) is a chronic, systemic autoimmune disease characterized by focal lymphocytic infiltrates of the exocrine glands [101] and sicca symptoms [104], with many etiological factors contributing to the disease process [102] and leading to a variety of clinical manifestations [103]. In SjS an augmented type I IFN signature in the tissues and peripheral blood of patients has been reported, correlating in many cases with *anti*-SSA/Ro antibody titers [82,105–107]. In a particular study, when minor salivary glands (MSGs) from SjS patients were classified depending on the grade of the inflammatory lesion into three groups, IHC examination revealed a significantly higher epithelial expression of IFNλ2 and elevated IFNλ1 serum levels compared to sicca-complaining individuals [108]. Furthermore, TLR3 stimulation led to IFNλ production in both primary epithelial cells from salivary glands of SjS patients and on immortalized cell lines [108]. However, larger studies are required in order to decipher IFNλs' role in SjS.

6.4. Systemic sclerosis

Scleroderma or systemic sclerosis (SSc) is an autoimmune disease of unclear etiology characterized by extracellular matrix (ECM) deposition leading to vasculopathy and internal organ/skin fibrosis [82]. In one study, serum IFNλ and IFNγ levels were shown to be significantly elevated in SSc patients compared to healthy individuals. Moreover, IFNλ1 serum levels of SSc patients were found to be positively correlated with IFNγ levels, and following the classification of patients according to the presence or absence of each organ involvement, a positive correlation of IFNγ and myositis was demonstrated [109]. The potential involvement of IFNλs in SSc deserves therefore further attention.

6.5. Psoriasis/atopic dermatitis

Psoriasis vulgaris (or psoriasis) and atopic dermatitis (AD) are the most common chronic autoimmune skin diseases characterized by patches of abnormal skin, and dermal T cell and other immune populations infiltrations. The hyperproliferation of keratinocytes affects skin barrier integrity, disrupting the stratum corneum with the consequence of cutaneous infections. Notably, viral and bacterial infections are found at higher frequency in AD than psoriasis patients [110]. IFNλ, but not type-I IFNs, was recently shown to be responsible for the elevated ISG levels on psoriatic lesions compared to AD lesions [111], confirming the former observation and providing clues for the underlying mechanism involved. Moreover, IF studies indicated co-localization of IFNλ1 with RORγt$^+$ cells, implying that Th17 cells may contribute to IFNλ1 production in psoriasis. In line with that, *in vitro* differentiation of human CD4$^+$ T cells into T cell subpopulations outlined Th17 cells as potential producers of IFNλ1, both at the mRNA and

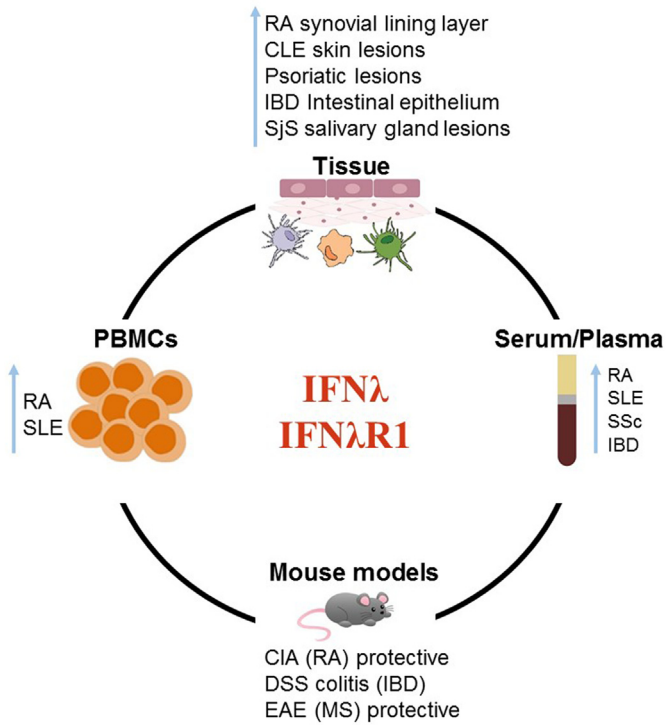

Fig. 3. Emerging roles of IFNλs in autoimmune diseases. IFNλs and their receptor have been reported to be expressed in several autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), psoriasis, atopic dermatitis (AD), systemic sclerosis (SSc), inflammatory bowel disease (IBD) and Sjögren's syndrome (SjS). Experimental mouse models of autoimmune diseases have also been used, providing key insight into the functional involvement of IFNλs in autoimmunity.

protein level, with IFNλ1 expression positively correlating with RORγt and negatively correlating with GATA3 [111].

6.6. Inflammatory bowel disease

Inflammatory bowel disease (IBD) encompasses two major chronic inflammatory diseases: Crohn's disease and Ulcerative colitis. These share many overlapping clinical features and are characterized by gastrointestinal tract inflammation and intestinal mucosal barrier disruption, with genetic and environmental risk factors involved in disease manifestation and progression. It has recently been reported that IBD patients have increased IFNλ and IFNλR1 transcript levels compared to controls [43]. Moreover, higher IFNλR1 protein levels were also detected in intestinal epithelial cells (IECs) of IBD patients compared to healthy individuals [43]. In DSS-induced and oxazolone experimental colitis in mice, IFNλR1$^{-/-}$ mice exhibited a worsened intestinal inflammatory phenotype while IFNλ was shown to play an important role in driving mucosal healing *in vivo* [112].

6.7. Multiple sclerosis

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS) characterized by CNS inflammation, nerve cell demyelination with progressive neurological dysfunction and clinical heterogeneity [82]. IFNβ is currently one of the best front-line treatments for MS, reducing its relapse rate [82], although multiple rounds of doses are needed with type I IFN activity varying among patients and phases of the disease [113]. A limited amount of studies have investigated IFNλs' involvement in MS. In one study it has been proposed that no significant associations between IFNλ3 polymorphisms and IFNβ-treatment in MS exist [114] while in another one, *ifnlr1* genetic locus was also not associated with MS pathogenesis [115]. Extending beyond human studies, evidence for a potential role of IFNλs in experimental autoimmune encephalomyelitis (EAE), a mouse model commonly used to simulate features of MS, was obtained. Vaccination of mice with proteolipid protein (PLP130-151) fused to chicken ovalbumin (OVA) and protein sigma 1 (pσ1) was able to induce tolerance, delaying disease's onset and dramatically decreasing its clinical score. Vaccination efficacy was proposed to be associated with the increase of CD25$^-$ CD4$^+$ FoxP3+ T cells producing IFNλs [116]. More studies are therefore needed both in MS patients and experimental mouse models to clarify the role of IFNλs in this disease. The emerging roles of IFNλs in autoimmune disorders are schematically shown in Fig. 3.

7. Concluding remarks

The discovery of IFNλs or type III IFNs has challenged the primacy of type I IFNs in antimicrobial defenses in the body, and has broken a dogma that has dominated the field for 50 years. Although IFNλs share many of the antimicrobial activities with type I IFNs, including the upregulation of ISGs and the induction of antiviral immunity, they also exhibit important functional differences; they are non-inflammatory or even possess immunoregulatory functions, and they are particularly important at body barriers such as the respiratory and gastrointestinal tracts. They also work cooperatively with type I IFNs to fine-tune immunity for optimal protection and minimal host damage. Inactivation or insufficiency of either of the two IFN systems therefore suffices to cause damage and lead to acute injury during infection. This raises unique new opportunities for therapeutic intervention as IFNλs enhance antimicrobial responses without having the pro-inflammatory and tissue damaging side effects of type I IFNs.

Extending beyond host immunity, IFNλs are also emerging as important players in diverse other conditions beyond infections including autoimmunity and cancer. Although the field is at its infancy, results from experimental animal models point to protective immunoregulatory effects of IFNλs in an expanding number of autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis. Similarly, early studies in cancer indicate that IFNλs possess potent anti-proliferative and antitumor effects both in cancer cell lines *in vitro* and animal models *in vivo*, and have therefore tremendous immunotherapeutic potential. This brings IFNλs in the spotlight for the treatment of a wide range of devastating diseases beyond infections, and highlights the urgent need to deepen our understanding in the biology of IFNλs without prejudice, expanding to areas that would not conventionally fit to our current view of IFNλs as antiviral cytokines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.102319.

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