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New Interferons

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Abstract

New interferons (IFNs) include members of the type I IFN family, such as IFN epsilon (IFNe), IFN tau, IFN omega, and IFN kappa, as well as the type III IFN family, also known as the IFN lambdas. By comparison the classical or ‘old’ IFNs comprise the 14 subtypes of IFN alpha and IFN beta, which are all members of the type I IFN family, as well as type II IFN gamma. In this article, we examine the new IFNs and specifically discuss their discovery, comparative structures, functions in physiology and disease, the signaling pathways they initiate, and their regulatory controls. We highlight IFNe that was discovered in our laboratory and characterized for its role in protecting the female reproductive tract from infections.

Introduction and Comparative Overview of the Classical (‘Old’) Interferons

Since the discovery of an antiviral activity by Nagano in 1953–54 (Nagano and Kojima, 1954), named the interferon by Isaacs and Lindenmann in 1957, we have seen the elaboration of this term to cover a broad family of cytokines with 28 members. This original activity became known as the type I interferon (IFN) family, which grew to comprise 14 IFN alpha (IFNα) subtypes and a single IFN beta (IFNβ) (originally called fibroblast IFN). It was later discovered in 1965 (Wheelock, 1965) that lymphocytes stimulated by mitogens also produced an antiviral activity that was eventually distinguished by chemical properties (acid lability), then antigenicity, which was called immune IFN after the cells that produced it; it was subsequently cloned as the type II IFN gamma (IFNg) (Gray and Goeddel, 1982). For the purpose of this article, these IFNs will be considered as the ‘old’ IFNs, and we will discuss herein, the subsequently identified ‘new’ members of the type I IFN family (IFN omega (IFNω) in 1985; IFN tau (IFNτ) in 1996; IFN epsilon (IFNe) in 2004; IFN kappa (IFNκ) in 2001) and the IFN lambdas (IFNλs), the type III IFN family, discovered in 2003.

The IFNs derive their name from their definitive antiviral activity through which they were first described, although their potency varies by three orders of magnitude among the different types. The types of IFNs are distinguished by sequence identity, genomic locus, distinct cognate receptors, and to a lesser extent by cell of origin and stimulus (see Table 1). The ‘old,’ classical type I IFN family comprises the IFNαz subtypes and IFNβ, all encoded by genes in a genomic locus on HSA chromosome 9p (and the syntenic murine chromosome 4), which also contains the genes encoding the ‘new’ type I IFNs described below (Hardy et al., 2004). All type I IFNs bind their cognate cell surface receptors IFNAR1 and IFNAR2 and subsequently activate associated kinases Tyk2 and Jak1, respectively, leading to phosphorylation of the intracellular domains of the receptors and recruitment of signal transducers and activator of transcription (STAT) proteins. The type I (and to some extent type II) IFN signaling has been the prototype system for the discovery and characterization of the JAK/STAT pathway (Stark and Darnell, 2012). This pathway regulates the expression of thousands of so-called IFN-regulated genes (IRGs) (Rusinova et al., 2013), which encode the effector molecules of the various type I IFN properties, including the antiviral IRGs, namely 2′-5′ oligoadenylate synthetase, RNase L, PKR, viperin, and many of the so-called ‘viral restriction factors.’ Additional IRGs that regulate viral infection and replication have been elucidated by the studies of Schoggins et al. (Schoggins, 2014; Schoggins et al., 2014, 2011; Schoggins and Rice, 2011). Since their discovery as antiviral proteins, the ‘older’ IFNs have been further characterized as multifaceted cytokines that can modulate cell proliferation; survival; differentiation; and migration, and regulate virtually every effector cell of the innate and adaptive immune responses. They are involved in many pathologies including cancer, infectious, and inflammatory diseases; and IFN modulators are in use or in clinical trials for these conditions. While IFNs have a well-characterized protective role in host defense, excessive signaling is toxic, even lethal. Thus, the well-characterized and diverse pathways driving IFN signaling (Hertzog and Williams, 2013), are balanced by an intricate array of negative regulators to control potential side effects (Porritt and Hertzog, 2015). The large number of negative regulators and the nature of their targets, which function in many stages of the IFN production and action system, suggest the need to tightly regulate the response in a temporal and tissue-specific manner. It will be interesting to determine whether the ‘controls’ on signaling are the same for the ‘new’ IFNs as the older, well-characterized ones.

Interferon Omega

IFNo was discovered in 1985 during a low-stringency hybridization screen of the bovine genome with a human IFNa cDNA probe (Capon et al., 1985). The same study subsequently identified human IFNo (Capon et al., 1985). There is limited functional data available in the literature for IFNo. While it is induced after viral infection in human peripheral blood leukocytes (Adolf et al., 1990), it has been shown to have a role in protecting cats against parvovirus (Paltrinieri et al., 2007). Interestingly, while humans and mice have only one functional IFNo gene each, over 12 IFNo genes have
Table 1 Summary of key features of type I and type III IFNs

| Interferon | Expression pattern | Function | Species |
|------------|--------------------|----------|---------|
| Type I<sup>f</sup> | | | |
| IFNα<sub>2</sub> | Ubiquitous | Classical<sup>f</sup> | All species |
| IFNβ | Ubiquitous | Classical<sup>f</sup> | Pigs, cattle |
| IFNω | Reproductive tract: trophoblasts | Maternal–fetal interactions | Humans, rhesus macaque, mouse, cattle, dogs, birds, bats |
| IFNε<sub>2</sub> | Mucosal organs: Epithelial cells of predominantly the female reproductive tract and also gastrointestinal tract and lung | Basal immune protection via ISGs | |
| IFNε<sub>1</sub> | Immune cells: leukocytes | Classical<sup>f</sup> | Human, mice, sheep, cattle, bats, cats |
| IFNε<sub>3</sub> | Immune cells and skin: leukocytes, keratinocytes | Classical<sup>f</sup> | Humans, mice, sheep, cattle |
| IFNε<sub>4</sub> | Immune organs: spleen, thymus, lymph node | Classical<sup>f</sup> but less myelosuppressive activity than IFNε<sub>1</sub> | Mice |
| IFNε<sub>5</sub> | Reproductive tract: trophoblasts | Maternal–fetal interactions | Cattle, sheep |
| Type III<sup>f</sup> | | | |
| IFNκ<sub>1</sub> (IL-29) | Ubiquitous | Classical activity<sup>f</sup> is regulated at transcriptional level and through tissue-specific restriction of receptor expression, e.g., mucosal epithelial cells | All species |
| IFNκ<sub>2</sub> (IL-28A) | Ubiquitous | | All species |
| IFNκ<sub>3</sub> (IL-28B) | Ubiquitous | | All species |

*See text for relevant references.

<sup>f</sup>Cell and organ distribution of the ubiquitous type I IFNAR1 and IFNAR2 receptors and the more restricted expression of type III IL-10Rα and IL-28Rα receptors is reviewed in<sup>f</sup>.  
<sup>f</sup>Classical functions of IFNs include antiviral, antiproliferative, antitumor, and immunomodulatory functions.

been identified in each of bats, cats, and cattle (Walker and Roberts, 2009; Yang et al., 2007; Kepler et al., 2010).

The endogenous form of human IFNω was purified from peripheral blood leukocytes after Sendai virus infection (Adolf et al., 1990). The human IFNω protein shares 61% amino acid identity with human IFNα<sub>2</sub> but only 26.2% and 28.21% with human IFNβ and human IFNε<sub>2</sub>, respectively (see Table 2), but despite relative similarities in primary protein sequence, structural modeling predicts human IFNω is more similar to IFNβ than IFNα<sub>2</sub> (Figure 1(a) and 1(b)). However, of the limited studies reported for IFNω, this cytokine demonstrates binding affinities for both IFNAR1 and IFNAR2 comparable to human IFNβ, and a 5- to 10-fold more potent antiproliferative activity compared to human IFNα<sub>2</sub> subtypes (Jaks et al., 2007), with demonstrated antitumor activities in human cancer models (Horton et al., 1999). Beside activation of the canonical ISGF3 signaling pathway (Jaks et al., 2007), IFNω along with IFNα<sub>2</sub> and IFNβ has been shown to induce tyrosine phosphorylation of Crkl (Ahmad et al., 1997), an SH3/S12 domain–containing signaling adapter involved in signal transduction in chronic myeloid leukemia (ten Hoeve et al., 1994). IFNω also has disease associations, with reports of serum autoantibodies to this cytokine being a marker for autoimmune polyendocrine syndrome type I, a multifaceted autoimmune disease (Husebye et al., 2009; Cervato et al., 2010). The crystal structure of IFNω in complex with the extracellular domains of IFNAR2 and a truncated form of IFNAR1 has been determined (Thomas et al., 2011). When compared to these structures, it is clear that the ligand–receptor interfaces consist of anchor points that are residues conserved across IFN subtypes. Both the high-affinity interface (between IFNα<sub>2</sub> and IFNAR2) and the low-affinity interface (with IFNAR1) are similar to the structure of a mutant IFNα<sub>2</sub>-IFNAR2 and IFNβ-IFNAR1, respectively (Thomas et al., 2011; de Weerd et al., 2013). The mostly hydrophobic interface with IFNAR2 is localized around the ‘elbow’ between the two extracellular subdomains of IFNAR2; while the interface of IFNω with IFNAR1 is diffuse over the surface of the receptor with only two receptor residues on IFNAR1 identified as energetically critical for ligand binding, namely Tyr70 and Phe238 (Thomas et al., 2011). It has been shown recently that in the mouse system, IFNβ can bind to and signal through IFNAR1 independently of IFNAR2 (de Weerd et al., 2013). Given that IFNω has a similar IFNAR1 binding affinity and similar antiproliferative potency as IFNβ, it may be

Table 2 Percentage homology of five human type I IFN subtypes as calculated using the ClustalW2 multiple protein sequence alignment program<sup>*</sup>

| Name    | Amino acids | Comparison | Amino acids | % Identity |
|---------|------------|------------|------------|------------|
| IFNα<sub>2</sub> | 188        | IFNβ<sub>2</sub> | 187        | 32.09      |
| IFNα<sub>2</sub> | 188        | IFNε<sub>1</sub> | 207        | 27.66      |
| IFNε<sub>1</sub> | 188        | IFNκ<sub>1</sub> | 195        | 61.17      |
| IFNκ<sub>1</sub> | 187        | IFNκ<sub>1</sub> | 208        | 30.32      |
| IFNκ<sub>1</sub> | 187        | IFNκ<sub>1</sub> | 207        | 34.22      |
| IFNκ<sub>1</sub> | 187        | IFNκ<sub>1</sub> | 195        | 26.2       |
| IFNκ<sub>1</sub> | 187        | IFNκ<sub>1</sub> | 208        | 36.9       |
| IFNκ<sub>1</sub> | 207        | IFNκ<sub>1</sub> | 195        | 28.21      |
| IFNκ<sub>1</sub> | 207        | IFNκ<sub>1</sub> | 208        | 28.02      |
| IFNκ<sub>1</sub> | 195        | IFNκ<sub>1</sub> | 208        | 28.21      |

<sup>*http://www.ebi.ac.uk/Tools/msa/clustalw2/.</sup>
Interferon Kappa

IFNκ was discovered in 2001 following screening of the Human Genome Services expressed sequence tags database for homologs within the IFN family (LaFleur et al., 2001). IFNκ is distinguishable from the IFNz and IFNβ subtypes by its constitutive expression in the absence of exogenous stimuli, particularly in dendritic cells, monocytes, and human epidermal keratinocytes (LaFleur et al., 2001; Nardelli et al., 2002). IFNκ is also inducible in monocytes following IFNγ stimulation (Nardelli et al., 2002), and in keratinocytes following viral infection, or IFNγ or IFNβ stimulation (LaFleur et al., 2001).

Besides the five helical bundle structure characteristic of all type I IFNs, IFNκ shares only limited amino acid identity with human IFNz2 (27.66%), IFNβ (34.22%), or human IFNε (28.02%) (see Table 2). Furthermore, it has an insertion of 13 amino acids (residues 135-147) leading to an extension of the loop between helices C and D of IFNκ that may protrude into the IFNAR1 binding domain, and thus could alter signaling (Figure 1(c)). Regardless, IFNκ has been shown to utilize both IFNAR1 and IFNAR2 to induce an IFN-stimulated response element–driven response, and the expression of IRGs characteristic of cellular responses to treatment with other type I IFNs (LaFleur et al., 2001). IFNκ has also been shown to induce production of tumor necrosis factor (TNF) and IL-10, suggesting a role for this cytokine in regulating immune cell function (Nardelli et al., 2002). Application of recombinant IFNκ has been shown to protect human cells from two types of viral infection in vitro (LaFleur et al., 2001). Interestingly, two studies have investigated IFNκ expression in keratinocytes infected with human papillomavirus (HPV) (DeCarlo et al., 2010; Reiser et al., 2011) with one group finding that HPV represses IFNκ expression in human keratinocytes in vitro and in vivo (Reiser et al., 2011; DeCarlo et al., 2010). The other study showed compartmentalized expression, in that keratinocytes from patients infected with HPV lacked IFNκ expression, whereas the stroma of cervical biopsy specimens showed elevated IFNκ expression that increased in relation to disease progression (DeCarlo et al., 2010).

Due to its constitutive expression in keratinocytes, the role of IFNκ has been investigated in skin diseases. Compared to samples from healthy controls, IFNκ is elevated in skin samples from patients with allergic contact dermatitis (Scarpioni et al., 2006), psoriasis and atopic dermatitis (Nardelli et al., 2002), and in a cohort of patients with increased susceptibility to melanoma and skin cancer (Puig-Butillé et al., 2014). There is also a report of an association between a single nucleotide polymorphism (SNP) upstream of the promoter of IFNκ and systemic lupus erythematosus in males, reportedly in the absence of additional SNPs associated with the type I IFN locus (Harley et al., 2010).

Interferon Epsilon

IFNε is a novel type I IFN discovered and characterized by the Hertzog laboratory (Hardy et al., 2004; Fung et al., 2013). It is found in the same genetic locus as the other type I IFNs and has approximately 30% or 37% amino acid identity with IFNω or β (Table 2), respectively, and subtle differences in 3D structure based on modeling (Figure 1). The regulation and expression of IFNε are different to the other type I IFNs suggesting a different function for this type I IFN. Whereas ‘classical’ type I IFNs are not expressed constitutively and are induced by pathogens via pathogen recognition receptor pathways, IFNε is constitutively and most abundantly expressed in the glandular endometrial epithelium of the female reproductive tract (FRT) where expression is not inducible by pathogens, but is regulated by the hormone changes of the menstrual cycle. IFNε gene expression levels are highest when estrogen is highest and lowest when progesterone levels are prominent. IFNε levels are significantly reduced at embryo implantation (day 4.5) in the mouse, consistent with progesterone regulation of IFNε. IFNε expression is barely detectable in postmenopausal women consistent with the other hormonal regulation data (Fung et al., 2013). Interestingly, IFNε is weakly, but significantly induced in human ectocervical epithelial cells following exposure to seminal fluid (Sharkey et al., 2007) and 8 h postcoitus in the mouse (Fung et al., 2013). Additionally, Matsumiya et al. (2007) determined that in the HeLa (human cervical cancer) cell line, the TNF cytokine can stabilize IFNε mRNA thus increasing IFNε synthesis to result in increased TNF-mediated STAT1 phosphorylation. This group has since
demonstrated a posttranslational regulation of IFNe expression under basal conditions by the importin 9 transporter protein, as identified by mass spectrometry on proteins in HeLa cell extracts that are bound to the 5’UTR of IFNe (Matsumiya et al., 2013).

While most functional studies to date have assessed the importance of IFNe in mice, IFNe is highly conserved and the protein has been studied recently in several species, including humans (Fung et al., 2013), rhesus macaques (Demers et al., 2014), dogs (Yang et al., 2013), and bovine cells (Guo et al., 2015). IFNe signals through IFNAR1 and IFNAR2 to induce typical IRGs such as ISG15, 2’–5’oligoadenylate synthetase, and IFN regulatory factor (IRF) 7. Whether IFNe also utilizes the novel IFNAR1-only signaling axis as shown for IFNβ (de Weerd et al., 2013) or initiates novel downstream signaling mechanisms in specific mucosal cell types remains to be determined.

Mice lacking IFNe are healthy and fertile suggesting the expression of IFNe in the FRT is not necessary for reproduction and development, but may be important in the immune defense of this important site. The importance of IFNe in inflammatory conditions of the FRT (e.g., endometriosis, pelvic inflammatory disease, or choioamnionitis in pregnancy) has not been determined. IFNe−/− mice are more susceptible to infection with Chlamydia muridarum bacteria and treatment of mice with recombinant IFNe can protect against vaginal infection (Fung et al., 2013). These results are in stark contrast to previous studies that indicated that other type I IFNs exacerbated the pathogenesis of C. muridarum disease by activating cytotoxic T cells, which were largely responsible for the inflammatory cell damage in infection (Nagarajan et al., 2008). Thus IFNe performs different, and in this case opposite, functions to other type I IFNs. This difference in activity is difficult to explain for IFN ligands that act via the same receptors. The unique expression pattern, regulation, and impacts on localized mucosal infections suggest a unique biological function for IFNe.

The epithelial expression of IFNe (Fung et al., 2013; Demers et al., 2014) represents an important innate factor in mucosal immune defense against pathogens as is seen for Chlamydia and herpes simplex virus 2 infection of mice (Fung et al., 2013). As mentioned, however, IFNe levels are not directly affected by these pathogens but rather by hormones that alter immune system in the FRT and can increase susceptibility to sexually transmitted infections (reviewed in Wira et al., 2015). While type I IFNs are well characterized for their anti-pathogen effects, many pathogens have developed mechanisms to evade the type I IFN response and thus, IFNe, with its unusual induction and expression patterns, may circumvent such strategies and thus offer an avenue for the development of novel therapies in FRT infections.

IFNe has recently been reported to be expressed in the epithelium of the lungs and intestines (Demers et al., 2014) in nonhuman primate studies and in the male reproductive tract of rhesus macaques and mice (Demers et al., 2014; Hermant et al., 2013). Once verified, any functional significance of these expression patterns will require further investigation. Of note, a SNP (rs2039381) resulting in a truncated IFNe protein has a significant association with the autoimmune skin disorder vitiligo (Cho et al., 2013), again indicating a possible function of IFNe outside the FRT.

Type I IFNs are known to affect the functions and development of innate and adaptive immune cell responses. Indeed IFNe−/− mice have reduced natural killer cells in the FRT, potentially contributing to the increased susceptibility of these mice to Chlamydia infection. Furthermore, IFNe was claimed to boost the adaptive immune response in vaccine adjuvant studies (Xi et al., 2012; Day et al., 2008). However, these effects were observed using adenoviral vectors containing the IFNe gene, and since IFNe was not quantified in these experiments, it is difficult to attribute the biological functions to IFNe directly. Furthermore, our data (unpublished) suggest that recombinant murine IFNe has approximately 100-fold less antiviral and antiproliferative activities and reduced immunoregulatory activity, compared with other type I IFNs, an observation which has also been demonstrated for IFNe in other species (Yang et al., 2013; Guo et al., 2015).

**Interferon Tau**

IFNe is not the only type I IFN of importance in the FRT. IFNτ is produced by trophoblasts and was first recognized as a pregnancy recognition signal, albeit only in ruminant species such as cattle and sheep (Spencer et al., 1996). IFNτ is located in the type I IFN cluster in the bovine genome on chromosome 8 (Walker and Roberts, 2009) and its trophoblast expression can be regulated by ETS2 (Ezashi and Roberts, 2004) though it can also be induced by pathogens. More recently, IFNτ has been characterized for anti-inflammatory effects and induction of several ISGs, including IRF2 that may protect the conceptus from the maternal immune system and promote development (Choi et al., 2003, 2001). Similarly, in pigs, IFNβ (delta) was identified in trophoblasts during the preimplantation period in the uterus (Lefevre et al., 1998). Although originally it was thought that IFNe might represent the human and murine equivalents of IFNτ, it is notable that ruminant species have both IFNτ and IFNe gene expression, suggesting different functions consistent with their expression by different cells and in response to different stimuli.

**Type III IFNs (IFNλ)**

The existence of a separate antiviral immune system other than the type I IFNs is evident by the observation that antiviral immunity, in some instances, can still be activated in the absence of the type I IFN receptor (Pulit-Penaloza et al., 2012; Pelletier et al., 2013). In 2003, a new family of antiviral IFNs, the type III IFNs, was first described (Kotenko et al., 2003; Sheppard et al., 2003). This family consisted of three cytokines, IFNλ1 (IL-29), IFNλ2 (IL-28A), and IFNλ3 (IL-28B) identified on human chromosome 19 (q13.13 region) (Kotenko et al., 2003; Sheppard et al., 2003). A fourth member, IFNλ4, was identified later in 2013 and its expression and function is still being fully determined (Prokunina-Olsson et al., 2013). Although the function of type III IFNs overlaps with type I IFNs, they are structurally more similar to the IL-10 cytokine family and interact with a distinct receptor complex to initiate signaling (Gad et al., 2009). It is the restricted
expression of this receptor complex which gives type III IFNs more specificity than type I IFNs.

Type III IFNs can be produced by many cell types, including by epithelial and immune cells. Similar to the type I IFNs, the type III IFNs are strongly induced in response to viral infection through activation of several pattern recognition receptor pathways, including those initiated by viral nucleic acids, such as Toll-like receptors (TLRs 3, 7/8, 9) and RIG-like receptors (RLRs; RIG-I, Mda5) (Onoguchi et al., 2007). Their induction is mediated through the activation of the transcription factors IRF3, IRF7, and NF-κB, although subtle differences exist in transcription factor activation in the regulation of type I and III IFN (Osterlund et al., 2007; Thomson et al., 2009; Iversen et al., 2010). This differential regulation at the transcriptional level may account for the observation that IFNγ expression is more tissue-restricted than the type I IFNs: for example, one study found that IFNγ expression was highly inducible upon stimulation in liver but not in the brain, whereas IFNα/β were upregulated in both organs (Sommereyns et al., 2008).

Additionally, a recent study identified a unique mechanism whereby intestinal epithelial cells, known to be high IFNγ producers, can selectively upregulate type III IFNs, and not type I IFNs, through activation of a novel RLR pathway in a pexinosome-dependent manner and through activation of the transcription factors IRF1, NF-κB, and IRF3 (Odendall et al., 2014). It is noteworthy that IFNα genes do not have NF-κB sites in their promoters.

The type III IFNs activate antiviral responses through engagement of their receptor complex, which consists of a subunit of the IL-10 receptor, IL-10Rβ, and a unique receptor chain IL-28Rα. Upon engagement with this receptor, receptor-associated JAK kinases (Tyk2 and Jak1, as in the IFNAR complex) are activated, leading to the phosphorylation and activation of members of the STAT family of transcription factors, including ISGF3a, in a mechanism similar to type I IFN-induced signaling (Dumoutier et al., 2004). This leads to the upregulation of genes with antiviral functions, similar to the type I IFNs. Indeed type I and type III IRG signatures have been shown to be redundant and no distinct type III IFN gene profile has yet been identified (Crotta et al., 2013; Zhou et al., 2007).

It is the restricted expression of IL-28Rα that makes the type III IFN response more specialized than the more ubiquitous type I IFN response. IL-28Rα is predominantly expressed by epithelial cells at mucosal surfaces, including the gastrointestinal tract, reproductive tract, and respiratory tract, and by some immune cell subsets such as dendritic cells (Mordstein et al., 2010; Sommereyns et al., 2008; Witte et al., 2009). Subsequently, the type III IFNs have emerged as major protective factors at mucosal sites. For example, type III IFNs protect airway epithelial cells from respiratory viruses such as influenza A and severe acute respiratory syndrome coronavirus (Mordstein et al., 2008, 2010). In the intestine, type III IFNs, and not type I IFNs, protect intestinal epithelium from enteric viruses (Pott et al., 2011; Mahlakõiv et al., 2015). However, this family of cytokines are proving to have more diverse roles than just antiviral immunity, with a recent focus shifting to their role in allergic asthma, where they not only control bronchial rhinovirus infection, an infection that can trigger asthma exacerbations, but also act directly on local adaptive immune cells to suppress Th2-mediated asthmatic responses (Koch and Finotto, 2015). Indeed, type III IFNs may play an important anti-inflammatory role in autoimmune diseases, with a recent study finding that type III IFNs block and reverse collagen-induced arthritis via suppression of IL-1β-producing neutrophil infiltration, therefore blocking Th17 and γδ T cell responses (Blazek et al., 2015). Many of these emerging roles for the type III IFNs have been elucidated as a consequence of the recently generated IL-28Rα knockout mouse, and more physiological roles may be revealed as studies continue (Ank et al., 2008; Egli et al., 2014).

The clinical importance of the type III IFNs was highlighted in 2009 when a genome-wide association study revealed several SNPs in the IFNλ gene locus that were highly associated with both spontaneous clearance of hepatitis C virus (HCV) and IFNα treatment induced clearance of HCV (Thomas et al., 2009; Suppiah et al., 2009; Ge et al., 2009). The SNPs with the strongest associations were identified in the novel IFNλ4 gene. One of these SNPs, rs368234815, results in a frameshift mutation that gives rise to the expression of IFNλ4 (Prokunina-Olsson et al., 2013). However, why expression of IFNλ4, and strong IFNλ4 induced antiviral activity, is a disadvantage in HCV infection is unknown (Hamming et al., 2013; Terzyńska-Dyla et al., 2014).

The tissue-specific nature of the type III IFNs have made them an attractive therapeutic option as they can elicit similar responses to the type I IFNs, which have been used as therapies against viral infections and cancers for decades, but without inducing the systemic side effects observed with type I IFN treatment. Pegylated IFNα1 has successfully completed Phase II clinical trials for the treatment of HCV (Muir et al., 2014). Interestingly, type III IFNs can overcome the desensitization to IFNα signaling that occurs in HCV patients treated with therapeutic IFNα, making it an attractive complementary therapy for patients exhibiting IFNα refractoriness (Makowska et al., 2011). Thus, despite only subtle differences detected between type I and the type III IFN system tested in vitro, there may be major differences in vivo, possibly due to differences in the regulation of signaling cascades activated in vivo. Additionally, IFNλ has shown some effectiveness in several murine tumor models (Lasfar et al., 2006; Sato et al., 2006), which requires additional study.

This novel and exciting class of type III IFNs are emerging as key effectors in localized antiviral responses and could play a role in the pathogenesis of a variety of other diseases. Already, the discovery that SNPs in the type III IFN locus are highly associated with disease, and therapeutic response in HCV has revolutionized the treatment of this disease. Their ability to act like type I IFNs, yet in a much more localized and specialized manner due to their restricted receptor expression, demonstrates their potential for treating the diseases that respond to type I IFN therapy, albeit in a more precise manner to overcome the issues of tolerance and off-target effects.

Conclusions, Comparison, and Summary

The identification of the traditional type I IFNs over 60 years ago revolutionized our understanding of how the immune response was regulated and led to new treatments for a variety of human diseases, including viral infections, cancers, and autoimmune diseases. Despite the side effects associated with the off-target effects of these IFNs, they are still the main therapy for treating...
many diseases. However, the IFN family has greatly expanded in the past decade, and although some of these novel members have been significantly characterized, there is still much unknown about some of the newer IFNs. So, what do these new IFNs add to our knowledge and perception of the IFN family of cytokines and their roles in physiological and pathological processes? What is clear from recent characterizations of the type III IFN family and IFNε is that these novel IFNs play important functional roles, not only in immune functions, but in normal homeostasis. The clinical relevance of newer IFN research is apparent from the recent example of how better understanding of type III IFNs, especially SNPs in these genes, has changed the way HCV is treated clinically. Indeed, the strong link between SNPs in type III IFN genes and viral infection highlights the possibility that uncharacterized SNPs in other novel IFNs may have potent functional consequences on the immune response and may underlie other human disease pathologies or therapeutic responses. Another exciting aspect of many of these novel IFNs is that although they may exhibit similar functions to the traditional IFNs, they are often produced in a more specialized manner, with some even being expressed constitutively at low levels within some organs. Their signaling occurs through well-characterized receptors, but there may be differences in these signal transduction pathways that are yet to be characterized. This research raises the possibility that the use of some of these novel IFNs therapeutically may be able to harness the wide range of beneficial effects induced by traditional IFNs, while overcoming issues of tolerance and side effects.

**See also:** Cytokines and Their Receptors: Interferon α/β; Interferon γ: An Overview of Its Functions in Health and Disease; The IL-20 Subfamily of Cytokines and Their Receptors; Viral Anticytokine Strategies. Signal Transduction: Jak-STAT Signaling Pathways; Structural Biology of JAK/STAT Cytokines and Their Receptors.

**References**

Adolf, G.R., Maurer-Fogy, I., Kaisler, I., Cantell, K. 1990. Purification and characterization of natural human interferon omega 1. Two alternative cleavage sites for the signal peptide. J. Biol. Chem. 265, 9290–9295.

Ahmad, S., Alayyed, Y.M., Druker, B.J., Platanihas, L.C., 1997. The type I interferon receptor mediates tyrosine phosphorylation of the CrkI adaptor protein. J. Biol. Chem. 272, 29991–29994.

Ank, N., Iversen, M.B., Bartholdy, C., Staeheli, P., Hartmann, R., Jensen, U.B., Dagnna-Hansen, F., Thomsen, A.R., Chen, Z., Haugen, H., Klucher, K., Paludan, S.R., 2008. An important role for type III interferon (IFN-lambda/IL-28) in TRL-induced antiviral activity. J. Immunol. 180, 2474–2485.

Blazek, K., Eames, H.L., Weiss, M., Byrne, A.J., Perocheau, D., Pease, J.E., Doyle, S., Egli, A., Santer, D.M., O’Shea, D., Tyrrell, D.L., Houghton, M., 2014. The impact of the interferon-lambda family on the innate and adaptive immune response to viral infections. Emerg. Microbe. Infect. 3, e51.

Choi, T., Roberts, R.M., 2004. Regulation of interferon-tau (IFN-tau) gene promoters by growth factors that target the Ets-2 composite enhancer: a possible model for maternal control of IFN-tau production by the conceptus during early pregnancy. Endocrinology 145, 4452–4460.

Fung, K.Y., Mangan, N.E., Cumming, H., Horvat, J.C., Mayall, J.R., Stifter, S.A., De Weert, N., Rosiman, L.C., Rossjohn, J., Robertson, S.A., Schijenken, J.E., Parker, B., Gangret, C.E., Nguyen, H.P., Carr, D.J., Hansbro, P.M., Hertzog, P.J., 2013. Interferon-epsilon protects the female reproductive tract from viral and bacterial infection. Science 339, 1088–1092.

Gad, H.H., Delgiren, C., Hammond, O.J., Vends, S., Paludan, S.R., Hartmann, R., 2009. Interferon-lambda is functionally an interferon but structurally related to the interferon-10 family. J. Biol. Chem. 284, 20869–20875.

Ge, D., Fellay, J., Thompson, A.J., Simon, J.S., Shihama, K.V., Urban, T.J., Heinzen, E.L., Oiu, P., Bertelsen, A.H., Muir, A.J., Sulikowski, M., Michutshon, J.G., Goldstein, D.B., 2009. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 461, 399–401.

Gray, P.W., Goddell, D.V., 1982. Structure of the human immune interferon gene. Nature 298, 859–863.

Guo, Y., Gao, M., Bao, J., Luo, X., Liu, Y., An, D., Zhang, H., Ma, B., Wang, J., 2015. Molecular cloning and characterization of a novel bovine IFN-epsilon. Gene 558, 25–30.

Hamming, O.J., Terczyńska-Dyla, E., Venn, G., Dijkman, R., Jorgensen, S.E., Ahktar, H., Siupka, P., Pietschmann, T., Thiel, V., Hartmann, R., 2013. Interferon lambda 4 signals via the IFN lambda receptor to regulate antiviral activity against HCV and coronaviruses. EMBO J. 32, 3055–3065.

Hardy, M.P., Owczarek, C.M., Jermin, L.S., Eijdbak, M., Hertzog, P.J., 2004. Characterization of the type I interferon locus and identification of novel genes. Genomics 84, 331–345.

Harley, I.T., Newbold, T.B., Stormont, R.M., Kaufman, K.M., Glenn, S.B., Franke, B.S., Kelly, J.A., Klipatrick, J.R., Hutchings, D., Divers, J., Bruner, G.R., Edberg, J.C., Mcgwin Jr., G., Petri, M.A., Ramsey-Goldman, R., Reveille, J.D., Vila-Perez, L.M., Merrill, J.T., Gilkeson, G.S., Vye, T.J., Alarcon-Riquelme, M.E., Cho, S.K., Jacobo, C.A., Alarcon, G.S., Moser, K.L., Gaffney, P.M., Kimberly, R.P., Bae, S.C., Langefeld, C.D., Harley, J.B., Guthridge, J.M., James, J.A., 2010. The role of genetic variation near interferon-kappa in systemic lupus erythematosus. J. Biomed. Biotechnol. 2010.

Hernmant, F., Francis, C., Clotman, F., Michiels, T., 2013. IFN-epsilon is constitutively expressed by cells of the reproductive tract and is inefficiently secreted by fibroblasts and cell lines. PLoS One 8, e71320.

Hertzog, P.J., Williams, B.R., 2013. Fine tuning type I interferon responses. Cytokine Growth Factor Rev. 24, 217–225.

Horton, H.M., Hernandez, P., Parker, S.E., Barnhart, K.M., 1999. Antitumor effects of interferon-omega: in vivo therapy of human tumor xenografts in nude mice. Cancer Res. 59, 4064–4068.

Husebye, E.S., Perheentupa, J., Rautenma, R., Kampe, O., 2009. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. J. Intern. Med. 265, 514–529.
Nagarajan, U.M., Prantner, D., Sikes, J.D., Andrews Jr., C.W., Goodwin, A.M., Nagano, Y., Kojima, Y., 1954. Pouvoir immunisant du virus vaccinal inactivé par des rayons ultraviolets. Comptes rendus des séances de la Société de biologie et de ses filiales 148, 1700–1702.

Nagarajan, U.M., Prantner, D., Sikes, J.D., Andrews Jr., C.W., Goodwin, A.M., Nagano, Y., Kojima, Y., 1954. Pouvoir immunisant du virus vaccinal inactivé par des rayons ultraviolets. Comptes rendus des séances de la Société de biologie et de ses filiales 148, 1700–1702.
Spencer, T.E., Ott, T.L., Bazer, F.W., 1996. tau-Interferon: pregnancy recognition signal in ruminants. Proc. Soc. Exp. Biol. Med. 213, 215–229.

Stark, G.R., Darnell Jr., J.E., 2012. The JAK-STAT pathway at twenty. Immunity 36, 503–514.

Suppiah, V., Moldovan, M., Ahlenstiel, G., Berg, T., Weitman, M., Abate, M.L., Bassendine, M., Spengler, U., Dore, G.J., Powell, E., Rondan, S., Sheridin, D., Smeddle, A., Fragiomelli, V., Muller, T., Bahlo, M., Stewart, G.J., Booth, D.R., George, J., 2009. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat. Genet. 41, 1100–1104.

Terczyńska-Dyła, E., Bibert, S., Duong, F.H., Krol, I., Jørgensen, S., Collinet, E., Kutalik, Z., Aubert, V., Cerny, A., Kaiser, L., Malinverni, R., Mangia, A., Moradpour, D., Müllhaupt, B., Negro, F., Santoro, R., Semela, D., Semmo, N., Heim, M.H., Bochud, P.Y., Hartmann, R., Group, S.H.C.C.S., 2014. Reduced IFN-lambda activity is associated with improved HCV clearance and reduced expression of interferon-stimulated genes. Nat. Commun. 5, 5699.

Thomas, C., Moraga, I., Levin, D., Krutzik, P.O., Podoplelova, Y., Trejo, A., Lee, C., Yarden, G., Vock, S.E., Glenn, J.S., Nolan, G.P., Pehler, J., Schreiber, G., Garcia, K.C., 2011. Structural linkage between ligand discrimination and receptor activation by type I interferons. Cell 146, 621–632.

Thomas, D.L., Thio, C.L., Martin, M.P., Gi, Y., Ge, D., Gr’Huigen, C., Kidd, J., Kidd, K., Khakoo, S.I., Alexander, G., Goedert, J.J., Kirk, G.D., Donfield, S.M., Rosen, H.R., Tobler, L.H., Bunch, M.P., McHutchison, J.G., Goldstein, D.B., Carrington, M., 2009. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461, 796–801.

Thomson, S.J., Goh, F.S., Banks, H., Krausgruber, T., Kotenko, S.V., Foxwell, B.M., Udalova, I.A., 2009. The role of transposable elements in the regulation of IFN-lambda1 gene expression. Proc. Natl. Acad. Sci. U.S.A. 106, 11564–11569.

de Weerd, N.A., Vivian, J.P., Nguyen, T.K., Mangan, N.E., Gould, J.A., Braniff, S.J., Zaker-Tabrizi, L., Fung, K.Y., Forster, S.C., Beddow, T., Reid, H.H., Rossjohn, J., Hertzog, P.J., 2013. Structural basis of a unique interferon-beta signaling axis mediated via the receptor IFNAR1. Nat. Immunol. 14, 901–907.

Walker, A.M., Roberts, R.M., 2009. Characterization of the bovine type I IFN locus: rearrangements, expansions, and novel subfamilies. BMC Genom. 10, 187.

Wheelock, E.F., 1965. Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin. Science 149, 310–311.

Wira, C.R., Rodriguez-Garcia, M., Patel, M.V., 2015. The role of sex hormones in immune protection of the female reproductive tract. Nat. Rev. Immunol. 15.

Witte, K., Gruetz, G., Volk, H.D., Looman, A.C., Asadullah, K., Sterry, W., Sabat, R., Wolk, K., 2009. Despite IFN-lambda receptor expression, blood immune cells, but not keratinocytes or melanocytes, have an impaired response to type III interferons: implications for therapeutic applications of these cytokines. Genes Immun. 10, 702–714.

Xi, Y., Day, S.L., Jackson, R.J., Ranasinghe, C., 2012. Role of novel type I interferon epsilon in viral infection and mucosal immunity. Mucosal Immunol. 5, 560–566.

Yang, L., Xu, L., Li, Y., Li, J., Bi, Y., Liu, W., 2013. Molecular and functional characterization of canine interferon-epsilon. J. Interferon Cytokine Res. 33, 760–768.

Yang, L.M., Xue, G.H., Sun, L., Zhu, Y.P., Liu, W.J., 2007. Cloning and characterization of a novel feline IFN-omega. J. Interferon Cytokine Res. 27, 119–127.

Zhou, Z., Hamming, O.J., Ark, N., Paludan, S.R., Nielsen, A.L., Hartmann, R., 2007. Type III interferon (IFN) induces a type I IFN-like response in a restricted subset of cells through signaling pathways involving both the Jak-STAT pathway and the mitogen-activated protein kinases. J. Virol. 81, 7749–7758.