The Interferons and their Receptors – Distribution and Regulation

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Abbreviations

CaMKII calcium/calmodulin kinase II; CK1α casein kinase 1α; CNS central nervous system; FBN-III fibronectin type III; GAS gamma activated sequence; hCR helical cytokine receptor; IFN interferon; IFNAR Interferon alpha beta receptor; IFNGR Interferon gamma receptor; IFNLR interferon lambda receptor; IL interleukin; IL10R Interleukin 10 receptor; IRF Interferon Response Factor; ISRE interferon stimulated response element; JAK Janus Kinase; LPS lipopolysaccharide; NF-AT Nuclear Factor of Activated T-cells; NK natural killer cells; NKT natural killer T cells; SOCS Suppressor of Cytokine Signaling; STAT Signal Transducer and Activator of Transcription; TCR T cell receptor; Th T helper lymphocytes; TLR Toll-like receptor; VV vaccinia virus; VSV Vesicular Stomatitis Virus; YLDV yaba-like disease virus.

Abstract

The interferons (IFNs) were originally described over 50 years ago, identified by their ability to confer viral resistance to cells. We now know that they are much more than just anti-viral cytokines collectively having roles in both innate and adaptive immune responses, in tumor surveillance and defense, and modulation of immune cell function. Three types of IFN have now been described, simply referred to as type I, II and III. Distinguishable by the unique receptors that they rely on for signal transduction, the three types of IFN have specific and varied roles in the maintenance of human health and defense against pathogens. In mounting an IFN-mediated immune response, the human body has developed the ability to regulate IFN mediated signal transduction. Like all cytokines the ability of a cell to respond to IFN is completely dependent on the presence of its cognate receptor on the surface of the target cell. Thus, one of the major mechanisms used by the human body to regulate the strength and duration of the IFN response is through regulation of receptor levels, thereby altering the cytokine-specific responsiveness of the target cell. This review will discuss the receptor system utilized by the type I IFNs and compare it to that of the type II and III IFNs which also regulate immune responses through controlling receptor level on the cell surface.

Keywords: interferon signaling; receptors; regulation

Discovered over 50 years ago, the interferons (IFNs) were first identified and are historically best known for their ability to elicit viral resistance to cells[1]. Based on this criteria the IFNs were initially classified into two types – the type I family composed of the acid stable forms IFNα and IFNβ, while the acid labile form, IFNγ, was classified as the lone type II IFN[2]. In recent years a third type of IFN has been described, IFNλ[3]. Originally termed interleukin (IL)-28a/b and IL-29, these proteins have been re-classified as IFNs based on the similar modes of induction and anti-viral activities they share with the type I and type II IFNs[3]. However, while the type I and type III IFNs are induced during a viral infection and are, at least in

part, involved in host defense against viruses, the type II IFN is primarily involved the allergic response, in host defense against intracellular pathogens and in control of tumors.

The cytokines that make up the three types of IFNs share basic secondary structural elements with an overall five helical bundle architecture. The IFNs are all classified as class II alpha-helical bundle cytokines and thus in the same protein family as interleukin(IL)-10, IL-19, IL-20, IL-22, IL-24, IL-26[4]. But besides a conserved overall helical-bundle fold, the IFNs otherwise share very limited homology, undoubtedly reflected by their use of distinct receptors for signal transduction. There are nine identified mammalian type I IFN subtypes including IFN-α of which there are 13 known subtypes, and single forms of IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-δ, IFN-τ, IFN-ν, IFN-ζ[4]. These cytokines can share as much as 100% homology (between certain IFNα subtypes) to as little as ~20% homology (in a triad between IFNα, IFNβ and IFNε subtypes). While the most widely studied subtypes are IFNα and IFNβ, evolutionary conservation would suggest that each subtype has unique and perhaps tissue-specific roles to play in human health and disease. However, not all subtypes are found in humans - IFN-δ is found only in pigs while IFN-τ is found only in ruminant animals[4]. The type I IFNs are acid stable, a feature which has assisted in the development of protocols for purification of these cytokines for therapeutic applications[5]. In contrast, there is only one type II IFN, IFNγ[4]. IFNγ is acid labile, a feature that distinguishes it from the type I IFNs. Also known as IL28A/IL28B and IL29, three type III IFNs have been identified[3]. Now termed IFNλs due to the common mode of viral induction they share with the type I IFNs, these cytokines have higher structurally homology with IL-10/IL-22 rather than to the type I IFNs despite having higher amino acid identity with the IFNs[6].

INTERFERON RECEPTOR SYSTEMS

The three IFN types are distinguished by the use of distinctive but related multi-chain cell-surface receptor complexes (see Figure 1, Table 1). All receptors involved in IFN signal transduction are classified as class II helical cytokine receptors (hCR) sharing homologous structural folds and basic structural elements with other proteins including tissue factor, and the receptors for IL-10, IL-20 and IL-22[4]. In the extracellular region, all members of this class of helical cytokine receptor have tandem domains consisting of ~100 amino acids each housing a type III fibronectin (FBN-III) domain with topology analogous to the immunoglobulin constant domain. With the exception of IFNAR1 which has a four-domain architecture, all other IFN receptors consist of two FBN-III domains[7]. Interestingly, while the receptors are unique to each IFN type receptor, components of each signaling complex namely IFNAR1, IFNAR2, IFNGR2 and IL10RB are encoded by genes clustered on human chromosome 21q22.1, suggesting common evolutionary conservation and thus a possible functional relationship between these systems..

Type I IFN Despite their seemingly broad range of amino acid homologies, all type I IFNs signal through a common heterodimeric receptor composed of low (IFNAR1) and high affinity (IFNAR2) receptor components[4](see Figure 1). IFNAR2 exists as three isoforms transcribed from the same gene by exon skipping, alternative splicing and differential usage of polyadenylation sites[8]. The most well characterized form of IFNAR2, IFNAR2c, exists as a long transmembrane form with a full intracellular domain and is required for a complete type I IFN induced anti-viral response via the JAK/STAT signaling cascade[9]. IFNAR2 also exists as a short transmembrane form lacking the intracellular domain (IFNAR2b) and a soluble form truncated prior to the transmembrane region (IFNAR2a) but possessing 11 additional **carboxyl-terminal** hydrophobic amino acids not found in the extracellular domains of the other two

forms. IFNAR2b reportedly acts as a dominant negative regulator of type I IFN activity at least in cells types where it is expressed[10]. Studies in our laboratory have shown that the soluble form of IFNAR2 (IFNAR2a) is found circulating in the blood and can exhibit both agonistic and antagonistic properties in certain circumstances[11]. While the complete functionality of soluble IFNAR2 in type I IFN signal transduction requires further elucidation, soluble forms of receptors are clearly essential in other cytokine systems[12].

Structurally while IFNAR2 is typical of all other class II hCRs, the low affinity receptor IFNAR1 is structurally unique amongst the class II hCRs being comprised of four FBN-III domains in the extracellular domain[7]. The functional consequences of a receptor with such an unusually elongated architecture, as compared to all other members of the same protein family, are yet to be fully demonstrated. One of the most compelling questions about the functionality of the type I IFN receptor system is how so many ligands can signal through the same heterodimeric receptor but drive a diverse array of biological signals. Although IFNα2 and IFNβ bind competitively to the IFNAR receptor complex, a number of studies have shown that these cytokines engage the receptor components in ligand-specific manners[13-15]. The consequences of the different modes of receptor engagement by these two ligands are reflected in the distinct gene sets they induce and the disparate biological responses they generate[16]. The affinity of the various ligands for IFNAR1, the stability of the ternary complex and the number of receptors presented on a cells surface have all been shown to participate in dictating ligand-specific biological responses[16-18]. Recently the crystal structures of both extracellular ternary IFNα and IFNω IFNAR signaling complexes were determined [19]. From these structures it is apparent that the ligands have conserved anchor points for receptor engagement but also make ligand-specific receptor interactions that influence the biological outcome[19]. These structures confirm that it is the ligand-specific interactions that influence ternary complex stability, and that the affinity of the ligands for IFNAR1 defines the resultant biological outcome of the ligand engagement[19]. Although IFNAR1 in the ternary complex structures was truncated prior to the membrane proximal FBN-III domain, the structures have given us a greater understanding of differential ligand engagement of a shared receptor but also suggest that every ligand engages the receptor complex in its own particular way.

To transduce signals via the JAK/STAT pathway, IFNAR1 and IFNAR2 are associated with Tyk2 and JAK1, respectively, for the kinase activity required for receptor phosphorylation and STAT recruitment to the receptor complex[4]. In the human system, Tyk2 has been shown to be required for stability of IFNAR1 on the cell surface[20]. A similar role for the IFNAR2-associated JAK1 has not been demonstrated. While IFNAR1 and IFNAR2 have not been found to be pre-associated, they are both required for full type I IFN-dependent STAT activation and the development of an effective anti-viral state[21].

Type II IFN Unlike the type I IFNs which all appear to signal as monomeric cytokines, IFNγ signals as an anti-parellel homodimer[22]. The complex through which this cytokine signals is composed of four transmembrane-spanning receptors; two chains of each of the high affinity (IFNGR1) and low affinity receptors (IFNGR2)[4]. The IFNγ homodimer engages directly with the two IFNGR1 chains on opposing sides of the cytokine dimer and that the two IFNGR1 chains do not interact directly[22]. IFNGR1 has been shown to be pre-associated with IFNGR2[23] and although the ligand does not engage IFNGR2 directly, ligand-induced conformational changes in both receptors have been reported[23]. Despite the fact that both IFNGR1 and IFNGR2 are not always present together on the surface of all cells (see Table 2) both receptor components are required for full activity of IFNγ[24]. For signal transduction via the JAK/STAT pathway IFNGR1 binds JAK1 while IFNGR2 binds JAK2[25]. Although both kinases are necessary for signal transduction, only JAK1 has been demonstrated to be required for the formation of the full IFNγ signaling complex[23].

Type III IFN Similarly to the type I IFNs, the type III IFNs signal as monomeric cytokines engaging one copy of each of their low affinity and high affinity receptors. However, unlike both the type I and type II IFNs which employ their own dedicated receptors, the IFNλs utilize one unique receptor (IFNLR1) but also one required for signal transduction by IL-10, IL-22 and IL-26 (IL10RB)[3, 26]. The receptor associated JAK kinases, JAK1 with IFNLR1 and Tyk2 with IL10RB are responsible for activation of the JAK/STAT pathway upon IFNλ engagement of this receptor complex[7]. Since IL10RB is also common to the signaling complexes for IL-10, IL-22 and IL-26 it remains to be seen whether there is any functional cross-talk between the type III IFNs and these cytokines as a result of having a shared receptor.

PATHWAYS OF INTERFERON SIGNALING

All three types of IFN have some similarities and differences in the signal transduction pathways through which they exert their biological effects. All IFNs utilize the JAK/STAT pathway for signal transduction[7](see Table 1). Much research has shown that specific combinations of STAT homo- and heterodimers activate target genes through binding to either Interferon Response Factor 9 (IRF9) which couples the STAT/IRF complex to Interferon-Stimulated Response Elements (ISREs) or directly to GAS elements found in the promoter regions of IFN target genes[27]. ISRE-binding STAT combinations include STAT1/2 and STAT2/6 heterodimers and STAT2 homodimers, however IFNγ has been shown to induce ISRE-binding STAT1 homodimers[28]. GAS elements are generally recognized by STAT1, 3, 4, 5 homodimers and STAT1/2 or 1/3 heterodimers[27]. Despite co-reliance on the JAK/STAT pathway, the STATs that each of the IFN types activate may be different. For anti-viral activity, the type I IFNs activate primarily STAT-1 and -2, while STAT-3, -4, -5 and -6 can also be activated by IFNAR engagement in certain cell types (reviewed by[29]). Although IFNγ signal transduction predominantly activates STAT1 homodimers, STAT3 homo- and STAT1-STAT3 heterodimers can also be generated[27]. Like the type I IFNs, the type III IFNs activate both STAT1 and STAT2 and can therefore drive the transcription of genes with either ISRE or GAS elements[30]. However, in some cell types the type III IFNs can also induce the activation of STAT-3, -4 and -5[31]. Since the type I and type III IFNs utilize the same JAKs and STATs for signal transduction, it is not surprising that these cytokines have similar biological functions in certain instances. Indeed, it has been demonstrated that IFNα and IFNλ induce a similar set of genes, albeit that the expression induced by IFNλ was weaker than that of IFNα in certain cell types[32]. It seems that the importance of type III IFN signaling lies in the narrow range of cells that have the ability to respond to these cytokines (see below).

Besides the JAK/STAT pathway, type I, II and III IFNs can also activate other signaling pathways, including the MAPK and PI3-Kinase pathways[29, 32](see Table 1). The type I and type II IFNs have also been shown to activate and signal via the NFkB pathway[33, 34], however while experimental evidence does not exist to support the activation of the NFkB pathway directly following IFNλ stimulation, bioinformatic analysis of the promoters of the three type III IFN genes suggests the presence of binding sites for NFkB[29]. The type I and II IFNs have also been shown to activate a CRKL-dependent pathway important for activation of Rap1 and subsequent antagonism of the Ras pathway thus promoting tumour suppression and the growth inhibitory effects observed for IFNs[35](reviewed by [29])

EFFECTS OF INTERFERONS DURING IMMUNE RESPONSES

Generally IFNs are produced by the body to fight infection or in an allergic response[4]. Following induction, ligand binding to the IFN receptor complexes initiates the transduction of signals that culminate in the transcriptional activation of gene sets, the nature of which is dependent on a number of factors including the stimulus and the IFN type/subtype. While the defining activity of the IFNs is their ability to invoke an anti-viral response in the host organism, these cytokines are collectively involved in

many more immune responses. Of the IFNs, the type I IFNs have the broadest range of biological activities having both protective and counter-protective effects in different immune situations[36]. While type I IFNs are protective in viral infection, IFNβ signaling causes lethality during certain bacterial infections[36] but protection against certain protozoan and fungal infections [37-39]. While the mechanism of IFNβ toxicity in sepsis is yet to be fully elucidated, it is apparent that IFNβ engagement of IFNAR1 during sepsis initiates the transmission of these lethal signals; Tyk2 also has a role[40, 41]. Numerous studies have utilized IFNAR1-null mice or cells, or anti-IFNAR1 neutralizing antibodies to demonstrate the importance of this receptor and type I IFN signal transduction for the maintenance of health and prevention of disease. Using these resources, IFNAR1 has been shown to play a role in tumor surveillance and cancer immunoediting[42], and to alter the cell cycle, inhibit cell growth and suppress cancer[43]. This receptor also transmits signals involved in regulation of the immune system through the promotion of B cell survival[44, 45], induction of cross-priming of T cells[46, 47], enhancement of humoral immunity[48], and regulation of natural killer (NK) cell function[49] (reviewed in[50]). Interestingly, the type I IFNs have also been shown to be components in seemingly conflicting activities of cell survival[51], and in the promotion[52] and prevention of apoptosis[44]. These contrasting biological outcomes of IFN signaling may be due to differential receptor expression levels on the target cell and/or cell-specific expression of components of the IFNAR receptor or at present unknown cell-specific regulatory mechanisms or elements that restrict IFN activities in certain cell types.

One organ in which IFNβ has significant importance is the CNS where, in the absence of IFNα[53], IFNβ has been shown to be vital for viral immunity and protection from autoimmune disease such as experimental autoimmune encephalomyelitis (EAE)[54]. In contrary to the lethality resulting from the IFNβ/IFNAR1 association seen in sepsis, this ligand-receptor interaction is protective in the CNS[54]. In an elegant study by Prinz and colleagues, cell-specific knockdown of IFNAR1 in CNS cells allowed the identification of myeloid cells as the effector target cell of IFNβ activity in a model of EAE[55, 56]. In contrast, knockdown of IFNAR1 on B cells, T cells and neuroectodermal cells had no effect on disease progression[55]. This study suggests that despite the ubiquitous expression of the type I IFN receptor on all these cell types, the cell-specific regulation of IFN signal transduction suggests that there are as yet unknown mechanisms or elements that restrict IFN signaling in off-target cells. It remains to be seen the exact nature of these cell-specific regulatory mechanisms.

In contrast to the type I IFNs, IFNγ is induced in NK and NKT cells, CD8 T cells and Th1 CD4 effector T cells, has roles in immunity against viruses, intracellular bacteria and tumors and is generally anti-inflammatory in allergy and asthma[57]. This cytokine thus has a very distinctive activity profile as compared to the type I IFNs. As mentioned, the type III IFNs utilize the same receptor-associated JAKs and signal transduction pathways and thus induce very similar biological responses to the type I IFNs[30]. Furthermore, both IFN types are induced during a viral infection and are protective against viral pathogens. Where type III IFNs are unique from the type I cytokines is in the narrow range of cells able to respond to these cytokines as dictated by the presence of their receptor on the surface of these cells [30]. The type III IFNs are active against viral pathogens such as encephalomyocarditis virus and vesicular stomatitis virus (VSV) in several different cell types [3, 26, 58] and hepatitis B virus in hepatocytes[59].

INTERFERON RECEPTOR DISTRIBUTION

Apart from the fact that the different IFN types use distinct transmembrane receptors for signal transduction, it is clear that there is a great deal of redundancy in the use of JAKs, STATs and in the alternative signaling pathways employed by the cytokines to transduce their signals. In particular, it would seem that the type I and type III IFNs may have some redundancy since they are both induced by

viral infection and utilize identical JAKs and STATs for an effective anti-viral response. However, since the ability of cells to respond to cytokines is absolutely dependent on the presentation of the required receptor components on the cell surface, it is apparent that due to the strictly regulated distribution of IFN receptor components, the different types of IFN have either widespread or cell/tissue-specific functions based on the presentation of their receptors on the surfaces of target cells. The receptors for the type I and II IFNs, and the IL10RB involved in IFNλ signaling are generally widely distributed and found on the surface of most cell types (see Table 2). Two major exceptions to this observation is in regards to the specific absence of IFNGR2 on the surface of Th1 cells[60,61] and the low expression level of membrane-bound IFNAR2 in sections of the human brain(see Table 2; www.brain-map.org). Since IFNγ specifically inhibits the activation of Th2 cells but not Th1 cells, regulation of the surface expression of IFNGR2 in this way restricts responsiveness of Th2 cells to this cytokine[62]. Since we know that type I IFN (IFNβ) signaling is important in the brain, the low IFNAR2 expression suggests that either this receptor is not necessary for IFN signaling in this organ, that signaling via the complete IFNAR signaling complex is restricted to cells that have membrane-bound IFNAR2 or that soluble IFNAR2 contributes to signaling in this organ. This observation could also suggest that canonical type I IFN signaling must be down-regulated in the brain for protection of this critical region.

In contrast to the type I and type II IFN receptor distribution, the cell surface expression of the high affinity receptor for the type III IFNs, IFNLR1 is more restricted thereby limiting cell-specific responsiveness to these cytokines (see Table 2). Cells of epithelial origin[30, 58], particularly keratinocytes and cells from the kidney, lungs and the gastrointestinal tract have been shown to express significant levels of IFNLR1 on their cell surface[58, 63]. Furthermore, dendritic cells[58] have also been shown to express IFNLR1[58]. While it is clear that the cellular specificity of response to the type III IFNs lies with the restricted expression of IFNLR1, the receptor it shares with IL-10, IL-22, and IL-26, IL-10RB is widely distributed on the surface of many different cell types[64].

FACTORS THAT REGULATE INTERFERON RECEPTOR PRESENTATION

Receptor engagement by the IFNs initiates signaling cascades that lead to the desired biological response. However, the response must be restrained in order to limit cellular responses and avoid the development of a 'cytokine storm' often associated with inflammation and lethality. Mechanisms underlying regulation of IFN signaling are multi-factorial and can involve induction of negative regulators such as Suppressor of Cytokine Signaling (SOCS) proteins, ligand-induced receptor down-regulation, ubiquitination and proteolytic receptor degradation. Both clathrin-dependent and –independent mechanism of endocytosis have been demonstrated to be involved in the regulation of IFN receptors levels on the surface of target cells. Information in this section is summarized in Table 3.

Type I IFN Regulation of type I IFN signaling can occur via basal, ligand-dependent and –independent diminution of surface receptor levels, receptor ubiquitination promoting degradation and may involve other and varied mechanisms. To complicate the matter further, the mechanisms of regulation vary between the two receptors and also upon the ligand stimulus. Basally, the decay of IFNAR1 has been shown to be more pronounced than that seen for IFNAR2 in certain cell types, reflecting differential regulation of the two receptors[65]. Also following the exogenous application of type I IFNs, IFNAR1 and IFNAR2 have both been shown to be differentially down regulated[65]. The extent and sustainment of the down regulation has been shown to be different for each receptor and has also been shown to vary with the ligand applied[65]. With respect to IFNAR1, the tyrosine kinase Tyk2 is constitutively associated with this receptor[66] and at least in the human system has been shown to be involved in aiding stability of this receptor on the cell surface. The interaction between IFNAR1 and Tyk2 not only regulates surface

expression levels of the receptor but has also been demonstrated to also impede degradation of IFNAR1[20]. Recently a linear endocytic motif has been identified within the intracellular domain of IFNAR1; it is hypothesized that Tyk2 may mask this motif thereby regulating receptor trafficking[67]. Studies in our lab have recently shown that SOCS-1 negatively regulates type I IFN signaling[68] via an interaction with Tyk2 controlling the activation status of the IFNAR1 associated kinase[69]. This association is ligand dependent since type I IFN engagement of IFNAR induces expression of SOCS1 via the JAK/STAT pathway and regulates signaling in a negative feedback loop.

The intracellular domain of IFNAR1 contains a degron, a linear motif that directs initiation of receptor degradation via a ubiquitin-dependent pathway[70]. A conserved serine residue (Ser535) within this motif is the target of kinases; phosphorylation of this serine leads to the recruitment of $SCF^{\beta Trcp}$ E3 ubiquitin ligase, ubiquitination and degradation of the receptor[71]. In a ligand-dependent manner, Tyk2 is required for the phosphorylation of S^{535} on the intracellular domain of IFNAR1, however at least one other kinase, protein kinase D2 is also capable of phosphorylating this site[72] and therefore affecting the cell surface presentation of IFNAR1. Phosphorylation of Ser535 and subsequent ubiquitination and degradation of IFNAR1 is also reportedly mediated by casein kinase 1α (CK1α) in a ligand- and JAK kinase-independent manner[73] suggesting that there are multiple levels of regulation for this receptor. Interestingly, although IFNAR1 is ubiquitinated following IFN stimulation IFNAR2 is not[65], suggesting differing mechanisms of regulation of these two receptors on the surface of cells. However, a ubiquitin specific protease that is known to be involved in the ISGylation and regulation of certain cellular substrates, UBP43, has been shown to inhibit type I IFN induced JAK/STAT signaling by blocking the interaction between IFNAR2 and JAK1[74].

Upon ligand engagement, the ternary IFNAR signaling complex is internalized rapidly by endocytosis[75, 76]. While heavily ubiquitinated IFNAR1 is routed for lysosomal degradation, the fate of IFNAR2 seems to depend on the cytokine stimulus[65]. Upon receptor engagement, internalized IFNAR2 has been shown to be either recycled to the cell surface (upon IFNα stimulation) or routed towards degradation (upon IFNβ stimulation)[65]. Endocytosis of the ternary signaling complex has been reported to occur in a clathrin-dependent manner resulting in lysosomal degradation of the IFNAR1 chain[77]. Endocytosis of the IFNAR signaling complex results in lysosomal degradation of the IFNAR1 chain[78]. However, after ligand binding, IFNAR1 has been shown to be associated with lipid rafts[79] often associated with caveolae-dependent endocytosis although the use of this pathway for the regulation of this receptor on the cell surface has not been directly shown[75]. It is unclear as to whether IFNAR2 can also be found in such lipid rafts or whether this is an IFNAR1-specific association.

In the human system, a number of other IFNAR immunoregulatory pathways have been demonstrated that are both ligand-dependent and -independent in nature. In mature dendritic cells, following lipopolysaccharide (LPS) stimulation and subsequent IFNβ induction IFNAR1 and IFNAR2 levels were shown to be down-regulated from the surface of the cells[80]. This study also showed that while IFNAR2 levels returned to maximal after 24 hours the levels of IFNAR1 remained low supporting the suggestion of differential regulatory constraints on the two receptors[80]. Bcr-abl signaling in chronic myeloid leukemia cells has been demonstrated to accelerate the degradation of IFNAR1 in a protein kinase D2-dependent manner[81], attenuating type I IFN signaling in these cells. Similarly P38, a stress-activated protein kinase, has been demonstrated to be an important regulator of IFNAR1 surface levels through participation in the phosphorylation of IFNAR1-S^{532} and subsequent ubiquitination and degradation of this receptor[82]. Angiogenesis is stimulated by VEGF but inhibited by type I IFNs[83]. It has recently been demonstrated that VEGF can directly antagonize type I IFN signaling by promoting the protein kinase D2-dependent down regulation of IFNAR1[84].

Many and varied mechanisms are utilized by the host to regulate type I IFN signal transduction; these mechanisms protect the host from the harmful effects of an uncontrolled immune response and also help to maintain homeostasis. In the type I IFN system, the literature suggests that the level of regulation that is applied to IFNAR1 is more stringent than for IFNAR2 implying necessity to do so. Taken from this, it would seem that IFNAR1 is the key to driving signaling via the type I IFNs and that in some instances type I IFN signaling can be strictly regulated through control of IFNAR1 surface levels.

Type II IFN Similarly to the type I IFN receptors, the IFNγ receptors IFNGR1 and IFNGR2 are regulated by distinct mechanisms. The negative regulator SOCS1, which suppresses type I IFN signaling also suppresses signaling via the type II IFN receptor complex specifically through a phosphotyrosine-specific interaction with IFNGR1[85]. It remains to be seen whether SOCS1 directly affects the regulation of the IFNγ receptor components on the cell surface as it does for IFNAR1 in the type I IFN system described above. In a ligand-independent manner, IFNGR1 has been shown to be down-regulated following engagement of the T-cell receptor (TCR) in naïve CD4+ T cells[86]. This receptor down-modulation was found to be dependent on efficient nuclear translocation of Nuclear Factor of Activated T-cells (NF-AT) induced by TCR signaling[86].

Upon ligand engagement of the receptor complex, IFNGR1 and IFNGR2 are internalized by endocytosis (reviewed by[75]). In execution of this process, both caveolae- and clathrin-dependent mechanisms have been reportedly associated with regulation of the type II IFN receptors on the surface of cells[75]. Alongside IFNAR1, IFNGR1 and IFNGR2 have been shown to be associated with lipid rafts[79] and signaling by the type II IFN signaling complex can be inhibited by the disruption of lipid raft microdomains[87]. However, the association of IFNGR components with lipid rafts has been demonstrated to be both independent of ligand stimulation in certain cell types and dependent in others[87]. It remains to be seen how these seemingly contrasting mechanisms of regulation of IFNGR surface levels may confer cell-specific constraints on signal transduction by the ternary IFNγ signaling complex.

The two IFNγ receptors are differentially regulated upon internalization via endocytic pathways. It seems that the endocytic pathway in which IFNGR1 is engaged routes the receptor through alternative intracellular pathways. Reports suggest that lipid raft-associated IFNGR1 is routed to the nucleus to transduce signals via its associated STAT1[87] whereas IFNGR1 endocytosed in a clathrin-dependent manner routes IFNGR1 to be recycled to the cells surface (reviewed by[75]). In contrast, after ligand binding the majority of IFNGR2 remains on the cell surface[88]. Upon ligand-dependent internalization IFNGR2 is regulated by intracellular trafficking between cytoplasmic stores and the cell surface thereby limiting surface levels to regulate activity in human T lymphocytes[89]. IFNGR1 but not IFNGR2 cell surface levels have also been shown to be down regulated in macrophages following treatment with mycobacteria and stimulation with TLR2 agonists[90]. The decrease in cell surface levels of IFNGR1 was shown to be dependent on clathrin and caveolae-mediated endocytosis and proteasomal degradation[90]. IFNGR1 has also been shown to be down-regulated following infection with *Leishmania donovani*[91] and *Trypanosoma cruzi*[92]. Interestingly, the type I IFNs, particularly IFNβ, induced following infection with *Listeria monocytogenes* have been shown to down-regulate IFNGR1 surface levels thereby antagonizing the type II IFN response to infection[93].

Other cytokines can reportedly regulate the surface presentation of the type II IFN receptor components. Firstly, the type III IFN, IFNλ3 (IL-29) has been shown to upregulate IFNGR1 levels on the surface of macrophages[94] demonstrating functional cross-talk between the type II and III IFNs. The type I IFNs have also been implicated in the regulation of the type II IFN receptors[94]. However unlike the effect of IFNλ, the type I IFNs have been shown to down-regulate IFNGR1 levels thereby rendering the

macrophages unresponsive to IFNγ treatment[94]. Likewise, IFNα/β signaling has been shown to down-regulate surface levels of IFNGR1 on *Listeria monocytogenes* infected macrophages[93]. The application of exogenous IFNβ has also been shown to have the same affect on IFNGR1 levels in a mouse model of mycobacterial infection (reviewed by[93]). Since the type II IFNs have a protective role in the immune response to bacterial infections, the functional benefit that antagonism of IFNγ responsiveness has on the immune response of the host organism by the type I IFNs remains to be seen.

Type III IFN Most probably due to the relatively limited number of research groups working on elucidating the functionality of the type III IFNs as compared to the type I or type II IFNs, there is at present minimal information on whether and how the type III receptors are regulated following IFNλ signal transduction. As far as can be gleaned from the current literature, there is no information available on whether they are regulated basally or upon ligand binding, whether they are internalized by endocytosis or any other mechanism. However, since expression of the receptors is restricted to cells of epithelial origin it is clear that basal expression of the receptors plays a major part in the regulation of IFNλ signaling. However, due to the role that Tyk2 plays in facilitating SOCS1-mediated regulation of IFNAR1 surface levels, and since Tyk2 is part of the type III IFN receptor complex through an interaction with IL10RB, it is possible that SOCS1 also has a role to play in the regulation of type III receptor surface expression. However, experimental evidence to this effect has yet to be demonstrated.

Virally-induced down-regulation of IFN receptors As a strategy for dampening the host immune response, certain viruses have developed mechanisms to down-regulate receptors from both the type I and II IFNs. No information is currently available as to whether viruses can influence the presentation or regulate signaling via the receptors for the type III IFNs. The viruses that target type I IFN signal transduction through down-regulation of receptor levels are Hepatitis C virus, Herpes simplex virus, VSV, Severs Acute respiratory syndrome Coronavirus and West Nile virus (WNV). Via a ligand-independent, P38-activated pathway reliant on CK1α, HSV and VSV were shown to induce a phosphorylation-dependent down-regulation of IFNAR1 in the absence of classical STAT-driven IFN signaling[78, 95]. Similarly a virally-expressed, accessory protein from the SARS coronavirus has been shown to induce stress within the infected host leading to activation of a ligand-independent phosphorylation and degradation of IFNAR1[96]. WNV infection has recently been shown to dampen type I IFN responses by inducing a decrease in IFNAR1 levels and by inhibiting surface accumulation of this receptor in infected cells, a mechanism hypothesized to involve viral non-structural proteins activating protein degradation pathways[97]. In the same study WNV was shown not to effect IFNAR2 surface expression[97]. Immunomodulation of IFNGR1 surface levels is also attributed to two proteins encoded by the human tumor-inducing virus, Kaposi's sarcoma-associated herpesvirus[98]. Both K3 and K5 proteins encoded by the virus were shown to down-regulate surface levels of IFNGR1 and induce its degradation thereby reducing responsiveness of the host cells to IFNγ[98].

Virally-encoded IFN receptor mimetics Apart from their effects on cell surface presentation of the IFN receptors, a number of viruses encode and secrete IFN receptor mimetics that directly bind the IFNs preventing an interaction with their receptors thereby neutralizing cytokine activity[99-102]. Mimetics of the IFNγ receptor are encoded by vaccinia virus (VV), myxoma virus, ectromelia virus, cowpox virus, camelpox virus, and yaba-like disease virus (YLDV)[99-106 107]. Similarly, VV and many other poxviruses also encode a soluble receptor mimetic that antagonizes type I IFN signaling[103-105, 107, 108]. Orthopoxviruses, such as YLDV encode orthologues of the type I IFN antagonist described above and have been shown to neutralize the activity of both type I and type III IFNs[107].

CONCLUSIONS AND FUTURE DIRECTIONS

As with all cytokines and immunomodulatory molecules the activity of IFNs must be tightly regulated to prevent deleterious effects while still mediating a targeted and efficacious immune response. IFN signal transduction is controlled at many levels, but initially through presentation of the high and low affinity receptors expressed on target cells. The fact that viruses have evolved methods to down-regulate IFN signaling, either by reducing IFN receptor expression or through production of IFN receptor mimetics, emphasizes the importance of the receptors as a key regulatory step in transducing IFN responses. Since the IFNAR receptors are generally widely expressed, the type I IFNs have a broad range of target cells. This contrasts with the type II and type III IFNs which show restricted cell-specific activity due to the limited expression of components of their receptors. Regardless of the almost ubiquitous nature of type I IFN signaling, there are isolated examples of differential receptor expression for IFNAR2 with low levels of IFNAR2 message reported in the brain. To understand the implications of this to IFN signal transduction there is a need for detailed studies of the relative levels of IFNAR1 and IFNAR2 protein expression in particular cell types/organs and during different cellular processes. Furthermore, even though the effects of most IFNs have been shown to be protective, IFNβ is the exception showing lethality in some models of bacterial infection but protection against viruses and autoimmune disease. Perhaps the process by which IFNβ transduces such contrasting functions involves differential use of the IFNARs in certain circumstances, thus leading to the induction of alternative gene sets. These examples of selective use or targeting of the IFNAR components may herald other as yet unidentified instances of differential IFNAR signaling during the regulation of immune responses by type I IFNs. This is an area that requires further study to fully elucidate the complete spectrum of regulatory constraints on IFN signal transduction.

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Table 1: The receptor systems and accessory signaling molecules used by the three IFN types for signal transduction.

IFN type	Interferons	Receptor	Signaling molecules
Type I	α (13 types), β, δ, ε, κ, τ, ω, ζ	IFNAR1, IFNAR2	JAK1, Tyk2 STAT-1, -2, -3, -4, -5 MAPK, PI3K, Akt, NFκB p53, PRMT1
Type II	γ	IFNGR1, IFNGR2	JAK1, JAK2 STAT-1,-2, -3, -5 MAPK , PI3K, Akt, NFκB
Type III	λ	IFNLR1, IL10RB	JAK1, Tyk2 STAT-1, -2, -3, -4, -5 MAPK , PI3K, Akt

Table 2: Cell type and tissue specific presentation of IFN receptors. '+' represents cell types experimentally demonstrated to present IFN receptors on the surface or for which this is inferred by responsiveness to the IFN type given. '-' represents cell types that have been demonstrated to be negative. 'ND' represents cell types or tissues in which the presence of the relevant receptor components have not been demonstrated or are not reported as being found. 'NS' is used to demonstrate that the identity of the receptors were not specified. # data for receptor distribution in the brain was also taken from the Allen Brain Atlas at **www.brain-map.org**.

Cell/tissue		Interferon Receptor					
		Type I		Type II		Type III	
		IFNAR1	IFNAR2	IFNGR1	IFNGR2	IFNLR1	IL10R
T cells	CD4+	+[1]	+[1]	+[3]	+[3]	-[7]	+[8]
	CD8+	+[2]	+[2]	+[4]	-[4]	-[7]	+[8]
	Th1			+[5, 6]	-[5, 6]		
	Th2			+[5, 6]	+[5, 6]		
B cells		+[1, 9]	+[1, 9]	+[10]	+[10]	-[7]	+[11]
Astrocytes		+NS[12]		+NS[13]		-	+[13]
NK cells		+[14]	+[14]	+[15]	+[15]	-	ND
Epithelial cells		+[16]	+[16]	+/-[10]	+/-[10]	+[7, 17]	+[18]
Endothelial cells		+NS[19]		+[20]	+[20]	-[17]	+[21]
Plasmacytoid DCs		+[22]	+[22]	+[3]	+[3]	+[7]	+[23]
PBMCs		+[24]	+[24]	+[25]	+[25]	ND	+[26]
Tumor/cancer cells		+[27-29]	+[27-29]	+[15]	+[15]	ND	ND
Macrophages		+[30]	+[30]	+[10]	+[10]	-[7]	+[31]
Hepatocytes		+[32]	+[32]	+ low[10]	+ low[10]	+[33]	+[34]
Platelets		-[35]	-[35]	+[15]	+[15]	ND	+[36]
Fibroblasts		+[37]	ND	+[15]	+[15]	-[7]	+[38]
Phagocytes		ND	ND	+[15]	+[15]	ND	+
Eosinophils		+[39]	+[39]	+[40]	ND	+[41]	+[8]
Myeloid cells		+[42]	ND	ND	ND	ND	+[26]
Serum		ND	+(soluble)[11]	ND	ND	ND	ND
Erythrocytes		ND	ND	-[15]	-[15]	ND	+[43]
Keratinocytes		+[44]	+[44]	+[45]	+[45]	+[7]	+[46]
Mouse oocytes		ND	ND	+[47]	+[47]	ND	ND
Megakaryocytes		+[35]	+[35]	ND	ND	ND	ND
Kidney		ND	ND	ND	ND	+[17, 48]	+[49]
Brain		+/-[42] #	Low #	Low #	+/- #	+/-[17] #	Low[50]
CNS		+[42]	ND	+[51]	+[51]	ND	+[13]
Liver		+[52]	+[52]	low[10]	low[10]	-[17]	+[49]
Lung		+[53]	+[53]	ND	ND	+[17, 48]	+[49]
Gastrointestinal tract		+[54]	+[54]	+[10]	+[10]	+[48]	+[49]
Preimplantation embryos		ND	ND	+[47]	+[47]	ND	ND

Table 3: Mechanisms of regulation of cell surface levels of the receptors for type I, type II and type III IFNs.

Interferon	Mechanism of regulation	Reference
Type I	Tyk2 association	[55]
	SOCS1	[56]
	Ubiquitination	[57, 58]
	Endocytosis	[55]
	Lysosomal degradation	[59]
	LPS	[60]
	Bcr-abl	[61]
	P38	[62]
	VEGF	[63]
Type II	TCR activation	[64]
	Endocytosis	[65]
	Differential basal expression	[5, 6, 15]
	Bacterial/Protozoan infection	[66-70]
	Other cytokines	[69-71]
Type III	No information available	

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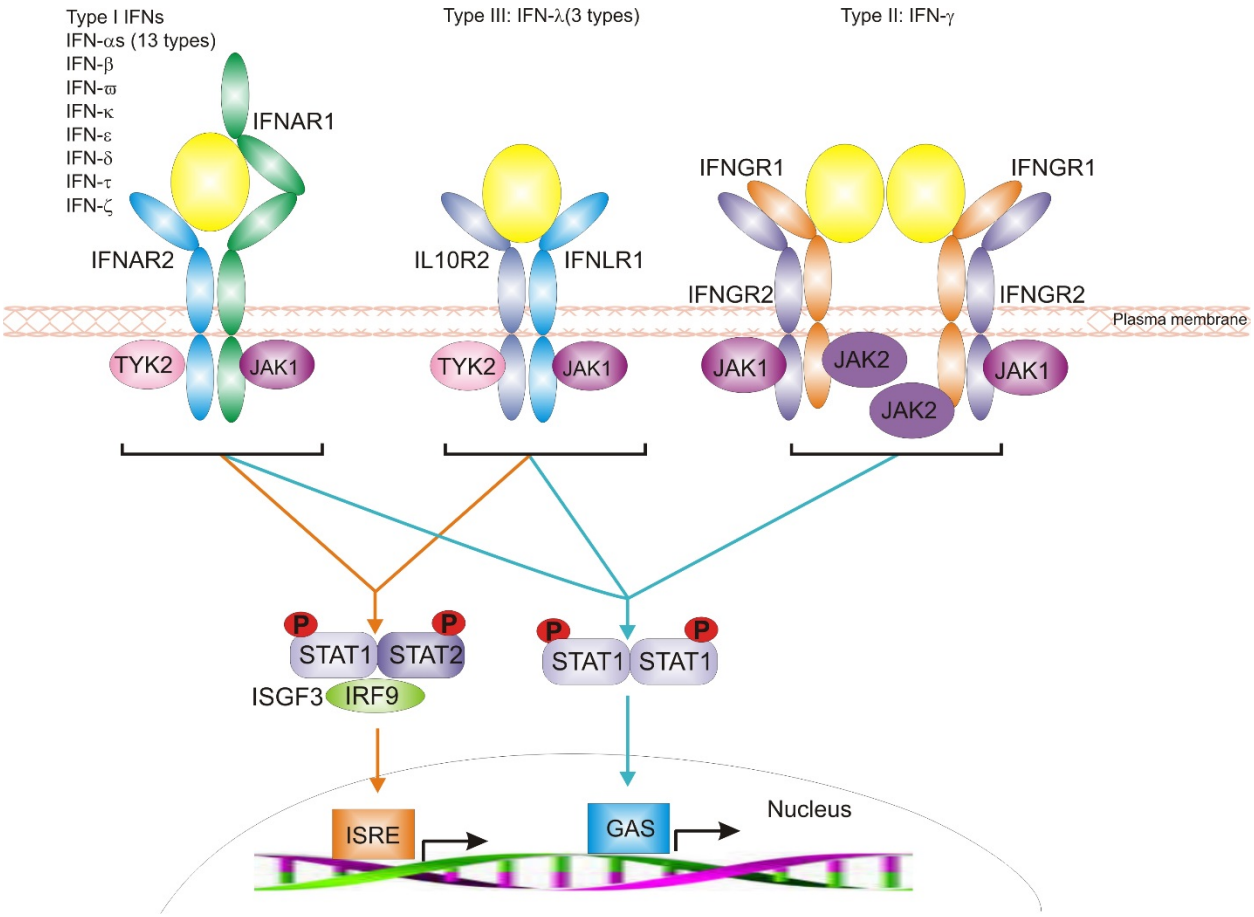
Figures


Type I IFNs
IFN-αs (13 types)
IFN-β
IFN-ϖ
IFN-κ
IFN-ε
IFN-δ
IFN-τ
IFN-ζ
Type III: IFN-λ(3 types)
Type II: IFN-γ
IFNAR1
IFNAR2
IL10R2
IFNLR1
IFNGR1
IFNGR1
IFNGR2
IFNGR2
Plasma membrane
TYK2
JAK1
TYK2
JAK1
JAK1
JAK2
JAK2
JAK1
P
P
STAT1
STAT2
ISGF3
IRF9
P
P
STAT1
STAT1
ISRE
GAS
Nucleus