The interferons and their receptors—distribution and regulation

Nicole A de Weerd and Thao Nguyen

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 with 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. On the basis of this criteria the IFNs were initially classified into two types—the type I family composed of the acid-stable forms IFN-α and IFN-β, whereas the acid-labile form, IFN-γ, was classified as the lone type II IFN. In recent years, a third type of IFN has been described, IFN-λ. 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. However, although 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 in 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 cytokines and thus in the same protein family as IL-10, IL-19, IL-20, IL-22, IL-24, IL-26. 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-τ, IFN-ω, IFN-ζ. These cytokines can share as much as 100% homology (between certain IFN-α subtypes) to as little as ~20% homology (in a triad between IFN-α, IFN-β and IFN-ω subtypes). Although the most widely studied subtypes are IFN-α and IFN-β, 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 whereas IFN-τ is found only in ruminant animals. 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. In contrast, there is only one type II IFN, IFN-γ. IFN-γ 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. Now termed IFN-λs due to the common mode of viral induction they share with the type I IFNs, these cytokines have higher structural homology with IL-10/IL-22 rather than to the type I IFNs despite having higher amino-acid identity with the IFNs.

**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 (hCRs) 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. In the extracellular region, all members of this class of hCR...
have tandem domains consisting of ~100 amino acids each housing a type III fibronectin (FN 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 FN III domains. Interestingly, although the receptors are unique to each IFN type, 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 (see Figure 1). IFNAR2 exists as three isoforms transcribed from the same gene by exon skipping, alternative splicing and differential usage of polyadenylation sites. 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 Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling cascade. IFNAR2 also exists as a short transmembrane form lacking the intracellular domain (IFNAR2b) and a soluble form truncated before the transmembrane region (IFNAR2a), but possessing 11 additional carboxy-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 cell types where it is expressed. 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. Although 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.

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, α, 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 | IFNL1, IL10RB | JAK1, Tyk2, STAT-1,-2,-3,-4,-5, MAPK, PI3K, Akt |

Abbreviations: IFN, interferon; IL, interleukin.

Figure 1 Representation of the distinct receptor systems employed by type I, type II and type III IFNs for signal transduction. Ligand engagement of these receptors initiates a signaling cascade that utilizes the receptor-associated JAK kinases for receptor phosphorylation and subsequent STAT activation. STATs activated following type I and type III IFN receptor engagement can drive expression of genes with either ISRE or GAS elements in their promoters, whereas signaling via the type II IFN receptor complex almost exclusively drives the expression of genes with GAS promoters elements.
Structurally, while IFNAR2 is typical of all other class II hCRs, the low-affinity receptor IFNAR1 is 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 with 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 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 differential ligand engagement of a shared receptor 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 ligand engagement.19 Although IFNAR1 in the ternary complex structures was truncated before 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 tyrosine kinase 2 (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. Although 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-parallel 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.22 IFNGR1 has been shown to be pre-associated with IFNGR223 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 to Jak1 whereas IFNGR2 binds to 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

### Table 2 Cell type and tissue-specific presentation of IFN receptors

| Cell/tissue | Type I | Type II | Type III |
|-------------|--------|---------|----------|
| T cells     |        |         |          |
| CD4+        | +1     | +1      | +3       |
| CD8+        | +2     | +2      | +4       |
| Th1         | +5,6   | -5,6    | -5,6     |
| Th2         | +5,6   | -5,6    | -5,6     |
| B cells     | +4,9   | +4,9    | +10      |
| Astocytes   | +4,9   | +4,9    | +10      |
| NK cells    | +4,6   | +4,6    | +4,6     |
| Epithelial cells | +4,6 | +4,6 | +4,6 |
| Endothelial cells | +4,6 | +4,6 | +4,6 |
| Fibroblasts | +4,6   | +4,6    | +4,6     |
| Megakaryocytes | +4,6 | +4,6 | +4,6 |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Platelets   | +4,6   | +4,6    | +4,6     |
| Fibroblasts | +4,6   | +4,6    | +4,6     |
| Phagocytes  | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Serum       | +4,6   | +4,6    | +4,6     |
| Macrophages | +4,6   | +4,6    | +4,6     |
| Hepatocytes | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Platelets   | +4,6   | +4,6    | +4,6     |
| Fibroblasts | +4,6   | +4,6    | +4,6     |
| Phagocytes  | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Serum       | +4,6   | +4,6    | +4,6     |
| Macrophages | +4,6   | +4,6    | +4,6     |
| Hepatocytes | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Serum       | +4,6   | +4,6    | +4,6     |
| Macrophages | +4,6   | +4,6    | +4,6     |
| Hepatocytes | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |
| Serum       | +4,6   | +4,6    | +4,6     |
| Macrophages | +4,6   | +4,6    | +4,6     |
| Hepatocytes | +4,6   | +4,6    | +4,6     |
| Eosinophils | +4,6   | +4,6    | +4,6     |
| Myeloid cells | +4,6 | +4,6 | +4,6 |

Abbreviations: CNS, central nervous system; DCs, dendritic cells; IFN, interferon; IL, interleukin; PBMCs, peripheral blood mononuclear cells.

1. ‘+’ represents cell type experimentally demonstrated to present IFN receptors on the surface or in a situation where this is inferred by responsiveness to the IFN type given.
2. ‘NS’ is used to demonstrate that the identity of the receptors were not specified.
3. ‘-’ represents cell type or tissue in which the presence of the relevant receptor components have not been demonstrated or are not reported.
4. The data for receptor distribution in the brain was also taken from the Allen Brain Atlas at www.brain-map.org.

### Type III IFN

Similar 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 IFNαs utilize one unique receptor (IFNLR1) but also one required for signal transduction by IL-10, IL-22 and IL-26 (IL10RB).1,26 The receptor-associated Jak kinases, JAK1 with IFNLR1 and Tyk2 with IL10RB are responsible for activation of the JAK/STAT pathway upon IFNα engagement of this receptor complex.7 As 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 (see Table 1). Much research has shown that specific combinations of STAT homo- and heterodimers activate target genes by 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. 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. GAS elements are generally recognized by STAT1, 3, 4, 5 homodimers and STAT1/2 or 1/3 heterodimers. 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, whereas STAT-3, -4, -5 and -6 can also be activated by IFNAR engagement in certain cell types (reviewed by Platanias). Although IFNγ signal transduction predominantly activates STAT1 homodimers, STAT3 homo- and STAT1–STAT3 heterodimers can also be generated. 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. However, in some cell types the type III IFNs can also induce the activation of STAT-3, -4 and -5. As 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 IFNβ induce a similar set of genes, albeit that the expression induced by IFNα was weaker than that of IFNα in certain cell types. 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 (see Table 1). The type I and type II IFNs have also been shown to activate and signal via the NFkB pathway, however, although experimental evidence does not exist to support the activation of the NFkB pathway directly following IFNα stimulation, bioinformatic analysis of the promoters of the three type III IFN genes suggests the presence of binding sites for NFkB. 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 tumor suppression and the growth inhibitory effects observed for IFNs (reviewed by Platanias).

EFFECTS OF IFNS DURING IMMUNE RESPONSES

Generally, IFNs are produced by the body to fight infection or in an allergic response. 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. Although 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. Although type I IFNs are protective in viral infection, IFNβ signaling causes lethality during certain bacterial infections but protection against certain protozoa and fungi. Although the mechanism of IFNβ toxicity in sepsis is yet to be fully elucidated, it is apparent that IFNβ engagement of IFNAR1 during
as 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 IFNs 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 IFNγ signaling are
generally widely distributed and found on the surface of most cell types
(see Table 2). Two major exceptions to this observation are in regards
to the specific absence of IFNGR2 on the surface of Th1 cells60,61 and
the low expression level of membrane-bound IFNAR2 in sections of
the human brain (see Table 2; www.brain-map.org). As IFNγ specifi-
cally 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 As 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
can also signal in this organ. This observation could also suggest that canonical type I IFN signaling must be downregulated in
the brain for protection of this critical region.

In contrast to 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, particularly keratinocytes and cells from the kidney, lungs and the gastro-
intestinal tract have been shown to express significant levels of IFNLR1
on their cell surface.56,63 Furthermore, dendritic cells56 have also been
shown to express IFNLR1.58 Although 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 develop-
ment of a ‘cytokine storm’ often associated with uncontrolled inflam-
mation 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 downregulation, ubiquitination and proteo-
lytic receptor degradation. Both clathrin-dependent and -independent
mechanism of endocytosis have been demonstrated to be involved in
the regulation of IFN receptor 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 downregulated.65

The extent and sustainment of the downregulation 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 in the human system, the
Tyk2 constitutively associated with this receptor 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
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 laboratory have recently shown
that SOCS1 negatively regulates type I IFN signaling via an interac-
tion with Tyk2 thereby controlling the activation status of the
IFNAR1-associated kinase.69 This association is ligand-dependent
as 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
subsequent ubiquitination and degradation of the receptor.21 In a ligand-dependent manner, Tyk2 is
required for the phosphorylation of Ser535 on the intracellular domain
of IFNAR1; however, at least another kinase, protein kinase D2 is also
capable of phosphorylating this site and therefore affecting the cell
surface presentation of IFNAR1. Phosphorylation of Ser535 and
subsequent ubiquitination and degradation of IFNAR1 is also report-
edly mediated by casein kinase 1z (CK1z) 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,61 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, UBAP43, has been shown to inhibit type I IFN-induced
JAK/STAT signaling by blocking the interaction between IFNAR2 and
JAK1.24

| 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 expres- | 65–71     |
|           | sion                        |           |
|           | Bacterial/protozoan infec-
|           | tion                        | 65–71     |
|           | Other cytokines            |           |
| Type III  | No information available  |           |

Abbreviations: IFN, interferon; LPS, lipopolysaccharide; SOCS1, suppressor of cytokine
signaling 1; TCR, T-cell receptor; VEGF, vascular endothelial growth factor.
References cited in the table are available in Supplementary Information.
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NA de Weerd and T Nguyen

Upon ligand engagement, the ternary IFNAR signaling complex is internalized rapidly by endocytosis. 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

Similar 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. 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 downregulated following engagement of the T-cell receptor (TCR) in naïve CD4+ T cells. This receptor down-modulation was found to be dependent on efficient nuclear translocation of nuclear factor of activated T-cells induced by TCR signaling. Upon ligand engagement of the receptor complex, IFNGR1 and IFNGR2 are internalized by endocytosis (reviewed by Claudinon et al.). 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. Alongside, IFNAR1, IFNGR1 and IFNGR2 have been shown to be associated with lipid rafts and signaling by the type II IFN signaling complex can be inhibited by the disruption of lipid raft microdomains. However, the association of IFNγ receptors with lipid rafts has been demonstrated to be both independent of ligand stimulation in certain cell types and dependent in others. It remains to be seen how these seemingly contrasting mechanisms of regulation of IFNγ 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 whereas IFNGR1 endocytosed in a clathrin-dependent manner routes IFNGR1 to be recycled to the cell surface (reviewed by Claudinon et al.). In contrast, after ligand binding the majority of IFNGR2 remains on the cell surface. In human T lymphocytes, ligand-dependent internalization IFNGR2 is regulated by intracellular trafficking between cytoplasmic stores and the cell surface, thereby limiting surface levels to regulate activity in these cells. IFNGR1 but not IFNGR2 cell surface levels have also been shown to be downregulated in macrophages following treatment with mycobacteria and stimulation with TLR2 agonists. The decrease in cell surface levels of IFNGR1 was shown to be dependent on clathrin and caveole-mediated endocytosis and proteasomal degradation. IFNGR1 has also been shown to be downregulated following infection with Leishmania donovani and Trypanosoma cruzi. Interestingly, the type I IFNs, particularly IFNβ, induced following infection with Listeria monocytogenes have been shown to downregulate IFNGR1 surface levels thereby antagonizing the type II IFN response to infection.

Other IFN types 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 demonstrating functional cross-talk between the type II and III IFNs. As mentioned above, the type I IFNs have also been implicated in the regulation of the type II IFN receptors. However, unlike the effect of IFNλ, the type I IFNs have been shown to downregulate IFNGR1 levels, thereby rendering the macrophages unresponsive to IFNγ treatment. 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 Rayamajhi et al.). As 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 with 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 ascertained 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, as expression of the receptors is restricted to cells of epithelial origin it is clear that basal expression of the receptors has a major part in the
regulation of IFNα signaling. Due to the role that Tyk2 has 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 in the regulation of type III receptor surface expression. Experimental evidence to this effect has yet to be demonstrated.

Virally induced downregulation of IFN receptors
As a strategy for dampening the host immune response, certain viruses have developed mechanisms to downregulate 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 downregulation of receptor levels are Hepatitis C virus, Herpes simplex virus, HSV, Severe Acute respiratory syndrome (SARS) Coronavirus and West Nile virus (WNV). Via a ligand-independent, P38-activated pathway reliant on CK1ε, HSV and VSV were shown to induce a phosphorylation-dependent down regulation of IFNAR1 in the absence of classical STAT-driven IFN signaling. 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. 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. In the same study WNV was shown not to effect IFNAR2 surface expression. Immunomodulation of IFNγR1 surface levels is also attributed to two proteins encoded by the human tumor-inducing virus, Kaposi’s sarcoma-associated herpesvirus. Both K3 and K5 proteins encoded by the virus were shown to downregulate surface levels of IFNγR1 and induce its degradation, thereby reducing responsiveness of the host cells to IFNγ.

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. Mimetics of the IFNy receptor are encoded by vaccinia virus (VV), myxoma virus, ectromelia virus, cowpox virus, camelpox virus and yaba-like virus (YLDV). Similarly, VV and many other poxviruses also encode a soluble receptor mimetic that antagonizes type I IFN signaling. 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.

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 downregulate 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. As 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/organisms 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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Trends in interferon signaling: an update

K. J. Lee, J. H. Kim, J. S. Kim, S. Lee, M. S. Uematsu, S. Akira, S. H. Lee and Y. Koyabu

1. Introduction

Interferons (IFNs) are a family of cytokines that are produced by host cells in response to viral infection or other stimuli and play a crucial role in the innate immune response. They are divided into three main types: type I (IFN-alpha and IFN-beta), type II (IFN-gamma), and type III (IFN-lambda, IFN-omega). Each type has distinct regulatory mechanisms that allow for the coordinated and specific responses to infections.

2. Type I IFNs

Type I IFNs are produced by cells infected with viruses or other pathogens and are involved in the recruitment of immune cells and the induction of antiviral genes. They are synthesized as large precursor molecules that are processed into mature IFN-alpha/beta by the cell membrane. Upon secretion, IFNs bind to their receptors, which are present on the surface of many cell types.

3. Type II IFNs

Type II IFNs, or IFN-gamma, are produced by T helper cells (Th1) and natural killer cells (NK cells) and are involved in the activation of macrophages and the induction of Th1-like responses. They bind to the IFN-gamma receptor, which consists of the IFN-gamma receptor 1 and IFN-gamma receptor 2 subunits.

4. Type III IFNs

Type III IFNs, or IFN-lambda, are produced by cells infected with viruses and are involved in the induction of antiviral genes and the modulation of the innate immune response. They bind to the IFN-lambda receptor, which is composed of the IFN-lambda receptor 1 and IFN-lambda receptor 2 subunits.

5. IFN Signaling Pathways

IFNs bind to their receptors on the cell surface, which leads to the activation of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) family of proteins. The activated JAK-STAT complex then translocates to the nucleus, where it regulates the transcription of IFN-responsive genes.

6. Conclusion

IFNs are critical components of the innate immune response, playing a crucial role in the recognition and elimination of pathogens. Understanding the mechanisms of IFN signaling is essential for the development of targeted therapies for infectious diseases.

7. Future Directions

Further research is needed to elucidate the complex regulations and mechanisms of IFN signaling in order to develop effective therapeutic strategies for the treatment of viral infections.

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