The Jak-Stat Signaling Pathway of Interferons System: Snapshots

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ABSTRACT

Interferons (IFNs) are a family of small regulatory glycoproteins that play a central role in the defense against viral infections. Although IFNs have been initially discovered as antiviral factors, today they are known as an integral part of the cytokine network that affect a wide range of biological processes. IFNs exert their pleiotropic effects through their multisubunit cell surface receptors in a species specific manner that is believed to be controlled at the receptor and the post-receptor levels. Although IFN-mediated signaling and transcription activation of cellular gene expression is currently best understood in the context of the JAK-STAT signal transduction, additional IFNs signaling pathways may also act in certain conditions. The *Janus* family of tyrosine kinase (JAK) enzymes and two families of transcriptional regulators, signal transducer and activator of transcription (STATS) and IFN regulatory factors (IRFs), are the principal components of the JAK-STAT pathway. Overlapping subsets of JAKS are involved in signaling by type I (IFN-α/ß) and type II (IFN-γ IFNs, indicating that the receptor subunits confer specificity for activating particular JAK family members. A considerable cross talk can exist between separate signaling pathways. The emergence of new tools and approaches for study of IFNs signaling has been an exercise in coming to respect the level of complexity of IFNs system. For many years, IFNs have been satisfactorily used in many clinical trials. However, their serious side effects remain as the major concern in clinical use of IFNs. A better understanding of the exact mechanism involved in IFNs signaling pathways and the structure-function relationships of the IFNs system components will allow researchers to improve and expand the therapeutic potential of these naturally occurring molecules. IFNs actions are mediated through multiple signaling pathways. However, due to the space limitation, this review will focus primarily on the IFNs-mediated JAK-STAT pathway.

Keywords: Interferon, JAK-STAT, Signal Transduction

INTRODUCTION

Although interferons (IFNs) have been initially discovered as antiviral factors, today they are known as an integral part of the cytokines network that affect a wide range of biological processes including those regulating cell growth and proliferation, differentiation, extracellular matrix metabolism, programmed cell death, and modulation of immune responses. In recent years tremendous progress has been made toward understanding the basic mechanism involved in IFNs actions. This advancement set the stage for IFNs to be approved for clinical use. For more than a decade IFNs have been satisfactorily used in many clinical trials. However, their serious side effects remain as the major concern in clinical use of IFNs. Because IFNs are the best known naturally occurring antiviral factors, mechanisms involved in their antiviral actions have been thoroughly studied. Although considerable cross talk can exist between separate pathways of IFNs signaling network, due to space limitation and for simplicity this review has focused on the IFNs JAK-STATs signaling pathway. A better understanding of the exact mechanism involved in IFNs signaling and the structure-function relationships of the IFNs system components will allow researchers to improve and expand the therapeutic potential of these naturally occurring molecules.

INTERFERONS SYSTEM

Genes and Proteins. Interferons are a family of small regulatory glycoproteins that play a critical role in the defense against viral infections and regulation of cell growth, differentiation and immune responses (1-5). On the basis of chemical properties, gene structure, cellular source, and biological activities, the IFNs have been classified into six distinct IFNs known as IFN–α, IFN–ß, IFN-Δ, IFN-ω, IFN-tau and IFN–γ (4,5). In contrast to IFN–α gene which is a cluster of twenty - three interferon–α genes, including several pseudogenes, there is only a single gene for IFN-ß, IFN-ω and IFN–γ. The IFN–α, IFN–ß and IFN-ω genes are simple, lack introns, and located on the short arm of human chromosome 9 next to each other (6). Although it is believed that IFN–α and –ß may have a common ancestral gene, the proteins exhibit only 15-30% homology in amino acid sequence, therefore, they are antigenically different from each other. There are some evidence to show that the carboxy terminal amino acid residues are not critical for the maintenance of biological activities and receptor binding of IFN–α/β. The amino acid residues 139 to 151 are highly conserved among alpha interferons and IFN–ß suggesting that this region may participate in the formation of a biologically active or a receptor binding domain. This idea has been supported since both IFN–α and –ß share a common receptor on the surface of target cells. Since IFN–α, –ß and -ω have related molecular and functional properties, they are also known as type I interferons or viral interferons (4-6). With the exception of mouse embryonal carcinoma cells, almost all cells are capable of producing IFN–α and IFN-ß. IFN-ß, originally known as fibroblast interferon, is produced mainly by fibroblasts and epithelial cells, whereas, IFN-α is produced by leukocytes (7,8). Viral infection is one of the best known inducers of type I interferons. Regarding the mechanism of induction, IFN-α genes can be divided into two classes: IFN-α 4 gene which is an immediate-early gene and is synthesized rapidly without the need for protein synthesis, and a group of IFN-α genes, including IFN-α 2, IFN-α 5, IFN-α 6 and IFN-α 8, that are induced with delay and are synthesized more slowly and demand ongoing protein synthesis (6-9). IFN-γ or type II interferon, also termed immune interferon, differs from type I interferons at the level of structure and function (8-11). In contrast to type I interferon genes, the IFN–γ gene is relatively complex. It contains four exons and three introns and is located on different chromosome, the long arm of human chromosome 12. IFN–γ mRNA encodes a 166 amino acid protein which follow-

ing the cleavage of hydrophobic signal sequence leaves a mature 143–amino acid residue protein. The carboxy-terminal sequencing analysis has revealed that this portion of the molecule contains a large number of positively charged amino acids. Moreover, 1-6 carboxy terminal residues are susceptible to post-translational enzymatic degradation which may be responsible for the length and the charge heterogeneity seen in the mature protein (10). Unlike type I IFNs, IFN–γ forms a homodimer. Apparently the homodimer is the only form of the peptide that can bind to the specific IFN–γ receptor. Since the mature molecule is devoid of cysteine residue, two monomers are held together by non-covalent forces. Therefore, it is not unexpected that IFN–γ is sensitive to extremes of pH and heat. Both the carboxy- and amino-terminal regions of the molecule are critical for the biological activities and receptor binding of IFN–γ. IFN–γ exhibits two N-linked glycosylation sites. Although these carbohydrate moieties are not important for the IFN–γ biological activities, glycosylation appears to influence the stability of the molecule in circulation. T-lymphocyte and natural killer cells are the major cellular source of IFN–γ. Both antigenic and mitogenic stimuli are known to induce immune interferon (11). IFN–γ displays all the biological activities that have been ascribed to type I interferons. However, antiviral activity of IFN–γ is 10-100 fold lower than IFN–α /ß. On the other hand, IFN–γ is 100-1000 times more active as an immunomodulator compared with type I IFNs (12).

Receptors and Signal Transduction Pathways. IFNs exert their extensive and pleiotropic effects by binding to specific receptors on the surface of target cells in a species specific manner which is believed to be controlled at the receptor as well as post-receptor levels (13). Interferons receptors are ubiquitously expressed in all cells and even on the surface of most IFN-resistant cells. However, until recently, the structure and function of human IFN receptors were poorly elucidated mostly because the receptor number on the cell surface is very limited. Researchers cloned the human IFN-α and IFN-γ receptor genes by transfer of human DNA to mouse cells and by selection of mouse cells expressing the human IFN receptors (14-16). These receptors are now characterized and have been classified as the members of the cytokines receptor superfamily (16,17). In contrast to receptor protein kinases, most cytokines receptors, if not all, do not possess intrinsic protein kinase activity or catalytic domain and exhibit limited similarity in their cytoplasmic domain. Instead, the cytoplasmic domains of the receptors are associated with a protein tyrosine kinase whose activation requires ligand-binding interaction at the cell surface (16-18).

Type I IFNs bind to a common receptor. The human IFN-α/ß receptor (IFNAR) is composed of two identified subunits, IFNAR-1 and IFNAR-2, both map to chromosome 21. The IFNAR-1 subunit has a single form whereas three different forms of IFNAR-2 are the results of alternative processing of the transcript. These forms are specified as long (2c), short (2b) and soluble (2a) (17-19). It appears to be a single specific receptor for IFN- γ which is distinct from that used by type I IFNs (10). However, like type I IFNs receptor, IFN-γ receptor consists of two components, IFNGR-1 and the associate IFNGR-2 protein. The human chromosomes 6 and 21 are both necessary for IFN–γ responsiveness indicating that receptor components are located on separate chromosomes. In addition, it has been shown that expression of the human IFN–γ receptor in mouse cells is not sufficient for human IFN–γ responsiveness and vice versa suggesting that species-specific molecule is involved in IFN–γ signal transduction (17-20). Although early reports show that IFN-γ receptor mediates its effects on target cells through classical signaling pathways such as calcium, serine/threonine protein kinases or ionic channel activation, it is now well established that a family of cytoplasmic protein known as JAK (Just Another Kinase or Janus, ancient Roman god of gates and doorways with two faces depicted in opposite directions, Kinase) play a central role in the IFN-mediated transcriptional activation signaling (10,18,19,21). The JAKs do not contain a ligand-binding domain, a transmembrane domain or a characteristic regulatory domain. However, they contain two kinase domains, an active domain (close to carboxy terminal) and a second kinase-like domain (in the amino terminal). Hitherto, four members of the JAK family,

Jak-1, Jak-2, Jak-3 and Tyk-2 have been identified. Three family members of JAKs, Tyk-2, Jak-1, and Jak-2, are involved in IFNs signaling system. The Tyk-2 and Jak-1 kinases are activated by IFN-α/ß and Jak-1 and Jak-2 function in IFN-γ signaling. Characterization of full-length cDNAs has revealed a great similarity between these enzymes suggesting that these three kinases constituted a unique subfamily of protein tyrosine kinases (13,18,21-24). Original works conducted by Darnell's and Stark's groups revealed the involvement of JAK kinases in IFNs signaling pathways (21). Taking advantage of a series of mutant cell types that have lost the ability to respond to IFN–α/ß or IFN–γ or both, they demonstrated that in a mutant, so called U1, who was unable to respond to IFN–α/ß but retained a normal response to IFN–γ, the IFN–α response was restored by transfection of an isolated human genomic fragment that encodes the human Tyk-2 (24). Using another mutant, so called U4, who lacked the ability to respond to either IFN–α or IFN–γ, they found that responsiveness to both IFNs was restored by introducing *Jak-1* gene (25). The third mutant, so called γ1, was deficient in IFN–γ response but retained normal IFN–α responsiveness. In this mutant, they found that the IFN–γ responsiveness was restored by introducing *Jak-2* gene (26). Taken together the results from these comprehensive investigations revealed that Tyk-2 & Jak-1 are essential for IFN–α/ß, and Jak-1 & Jak-2 are essential for IFN–γ signaling. Since two kinases have shown to be essential for each class of IFN signaling, they postulated that a kinase cascade may be involved in the process. However, the detection of tyrosine phosphorylated Jak-1 in IFN–α–treated U1 mutant and IFN–γ–treated γ1 mutant, and the detection of activated Tyk2 and Jak-2 in IFN–α/ß or IFN–γ–treated U4 mutant ruled out the existence of a kinase cascade in the JAKs–dependent IFNs signaling.

Recent studies using mice with targeted disruption of Jak-1 and/or Jak-2 not only confirmed the Darnell's and Stark's groups findings, but also have utterly established the essential developmental and physiological roles for these kinases (21,27-30). The involvement of overlapping subsets of JAKs in signaling by two types of IFNs indicates that receptor subunits, accessory molecules, and/or cytoplasmic domains of IFNs receptor confer specificity for binding or activating a particular JAK family member.

Having bound to distinct cell surface receptors, IFNs induce transcriptional activities of a number of genes by activation of transcription factors (30-33). Transcription of most, if not all, IFNs – inducible genes is rapid, within minutes, and does not require new protein synthesis suggesting that rapid activation of a preexisting latent cytoplasmic transcription factor is involved in the process. The activated transcription factor is then translocated into the nucleus and mediates gene activation. Although the receptor, the ligands, and in some cases the responsive genes are different, a cis–acting sequence is present in the 5'-flanking region of all tested IFNs – inducible genes (32,33). This region is known as IFN-stimulated response element (ISRE). Using deletion analysis, site-directed mutagenesis, and transfection analysis, researchers have found that this consensus sequence for many IFN–α/ß- inducible genes is a 12-15 – base pair segment which is highly conserved in IFN–α/(ß)–stimulated genes (32,33). A consensus immediate response element has been also identified for IFN–γ–inducible genes. This consensus sequence is known as IFN–γ activation site (GAS). The promoter of overlapping genes contains both ISRE and GAS elements (34). The identities and the functional efficiency of ISRE and GAS of different genes have been evaluated by deletion and point mutation analysis. The consensus ISRE and GAS derived from several IFN- specific genes (ISGs) are well characterized (34-37).

For more than a decade, extensive investigations were carried out to understand the mechanisms involved in gene activation in response to type I and type II IFNs. It is now accepted that a family of latent cytoplasmic proteins, termed STATs (for signal transducers and activators of transcription), acts as JAKs substrate that after activation by tyrosine phosphorylation is translocated into the nucleus, binds to ISRE or GAS and activates ISGs. So far, seven members of the STAT regulatory protein family, Stat-1, Stat-2, Stat-3, Stat-4, Stat-5a, Stat-5b, and Stat-6 have been identi-

fied. Of the known STATs, the Stat-1 and Stat-2 transcription factors play crucial roles in IFN-mediated responses (35,38-40).

In addition to STATs, a family of transcriptional regulators, termed IFN regulatory factors (IRFs), are important in mediating IFN biological activities (41,42). Nine members of this family of transcriptional regulators are identified, and have been designated IRF-1 to IRF-9 (41). Biochemical analysis has revealed that the N-terminal region of these factors is homologous, and corresponds to their conserved DNA- binding domain. The IRFs act in conjunction with STATs to establish the IFNs signal transduction and gene expression. Moreover, these factors play important roles in the regulation of IFNs production and the onset of positive feedback loop in virally- infected cells (43). In particular, IRF-3 and IRF-7 have shown to be involved in the regulation of IFN-α/ß synthesis in response to viral infection (43,44).

In the case of IFN-α/ß, the major factor responsible for ISGs transcriptional activation is a trimeric complex consisting of Stat-1, Stat-2 and IRF-9, collectively termed ISGF3 (42). Apparently, the Stat-2 (113 kD) subunit is associated with IRF-9 (48 kD) in the cytoplasm in unstimulated cells. This pre-association can potentially help the dimerization with Stat-1 (91 kD) upon activation, and accelerates nuclear translocation of the complex (41,42). Translocated ISGF3 complex binds to the ISRE via the IRF-9 DNA binding domain, and activates transcription (45-47). Although the IRF-9 confers DNA binding activity, *in vitro* treatment of ISGF3 with phosphatases reduces its ability to bind DNA suggesting that phosphorylation of the Stats subunits is also important for the ISGF3–DNA binding ability (48). The Stat-1 protein exhibits 40% homology (in some regions up to 70% homology) with Stat-2 over a 715 amino acid region, indicating that the genes encoding these proteins are closely related but not identical. The N-terminal segment analysis of these proteins has identified one region of heptad leucine repeats in a potentially helical region (49). Therefore, a "leucine zipper" can be involved in the complex formation or dimerization of Stats. In addition, it has been noted that a short region in the C-terminal segment of these proteins is highly conserved and is similar to the putative Src homology 2 (SH2) domain found in various tyrosine kinases and substrates for these enzymes (49). Apparently, this domain (in particular Arg. 602) plays a critical role in phosphorylation of Stats (50). Since this domain exhibits the phosphotyrosine binding activity, it may also be involved in complex formation and dimerization of STAT members.

In case of the IFN–γ inducible genes, there must be additional pathways. IFN–γ induces expression of a set of polypeptides including major histocompatibility (MHC) class II antigens and guanylate binding protein, in HeLa cells but not in human fibroblasts, with a slower kinetics which needs new protein synthesis (51-53). Therefore, these genes may not be activated by modification of preexisting transcription factors. For simplicity, however, this review focuses on the signaling pathways involved in immediate transcriptional activation by IFN-γ. The IFN-α/ß and IFN-γ signaling pathways share a common member of STAT family. The immediate cellular response to IFN-γ also involves tyrosine phosphorylation of a preexisting latent cytoplasmic Stat-1α protein, initially called IFN-γ- stimulated factor (GSF) or IFN–γ– activated factor (GAF). Having bind to its receptor, IFN-γ induces tyrosine phosphorylation of the IFNGR-1 receptor subunit followed by subsequent recruitment and serine phosphorylation of Stat-1α (54,55). After activation, Stat-1α is dimerized via reciprocal SH2 domain followed by translocation to the nucleus and participates in formation of transcriptional factor complex which recognizes GAS sequence and activates IFN-γ- stimulated genes (40,54,55). Darnell's group had previously reported that the residue tyrosine 701 is the only site on Stat-1α that is phosphorylated in response to IFN-γ and that this phosphorylation is essential for immediate IFN-γ-dependent transcriptional activation (56). However, recent works show that serine phosphorylation at the position 727 of the transcriptional domain of Stat-1α enhances transcription of IFN-γ-regulated target genes, particularly the genes involved in cell growth control, by recruitment of transcriptional co-activators, p300/CBP

and BRCA1 (57). The Stat-1ß (84-kD protein, a truncated form of 91-kD Stat-1α) acts in parallel with Stat-1α after IFN-γ stimulation, only Stat-1α has shown to act by itself as a direct GAS activating protein. This indicates that 38 C-terminal residue of Stat-1α may play a key role in GAS/GAF activation and that Stat-1ß may compete with Stat-1α; therefore, playing a negative role if it is abundant in particular cell or particular condition. The proposed pathways of signal transductional activation on cells treated with IFN-α/ß or IFN-γ are shown in Fig. 1.

The mechanism involved in the IFNs signaling pathways has provided an explanation for some of the interactions between IFN–α/ß and IFN–γ, including the synergistic effect of IFN-γ on the transcriptional induction of IFN-α/ß-stimulated genes (53,58,59). In some cell types although IFN-γ does not induce expression of ISGs, pretreatment of these cells with IFN-γ has a profound effect on subsequent IFN-α/ß stimulation (59). This effect can be due to the accumulation of IRF-9, which is produced in response to IFN-γ. The presence of large amounts of this factor may facilitate the activation of ISGF3 complex and subsequently intensifies the transcriptional activity of IFN-α/ß –activated genes. Particular sensitivity to viral infection of the double–knockout mice lacking both the IFN-γ receptor and the IFN-α/ß receptor supports the role of IFN-γ in intensification of IFN-α/ß actions (58).

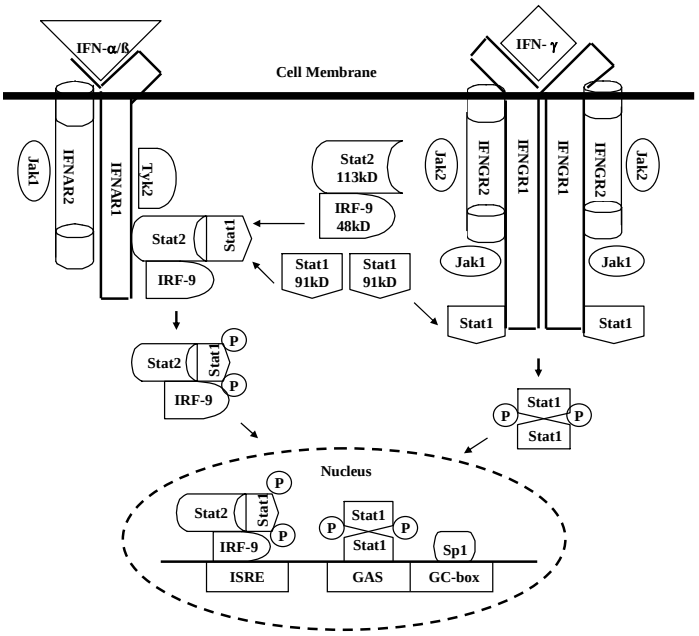

Figure 1. Schematic representation of the IFNs /JAK-STAT signaling engine. The ligand IFN binds to its cognate receptor subunit and induces JAKs kinase activation that leads to phosphorylation and subsequent translocation-in case of IFN-along with IRF-9-to the nucleus. The complex binds to corresponding *cis*-acting DNA element and activates the transcription of IFN-inducible genes. See the text for the details

NEGATIVE REGULATORS OF IFNs SIGNALING

Growing body of evidence shows that both cellular and viral proteins can function as negative regulators and antagonists of JAK-STAT-mediated signaling and gene activation (60,61).

Among cellular proteins, the members of suppressors of cytokines signaling (SOCS)/ STAT-induced STAT inhibitors (SSI)/cytokines-inducible SH2 protein (CIS) and protein inhibitors of activated Stat (PIAS), are known to function as negative regulators of JAK-STAT signaling

(60,61). Most cytokines, if not all, induce SOCS family members. For example, IFN-γ induces SOCS-1 that binds to the kinase domain of all four members of JAK kinases and inhibits its signaling process of both types of IFNs. Interestingly certain viruses may suppress the IFN signaling by rapid induction of a particular SOCS family member in order to replicate efficiently (62). The most recent study conducted by Yokato and colleagues revealed that the induced SOCS-3 by herpes simplex virus-1 (HSV-1) in the host T-cell line CCRF-CEM and FL cells is required for efficient replication of the virus (63). The induction is shown to be different among several tested cell types of human cell line, indicating that SOCs-3 may determine the efficient HSV-1 replication in a cell type specific manner (63). In contrast to SOCSs which inhibits JAK kinases, PIAS family members directly bind and block the DNA binding activity of STATs. Treatment with IFNs or IL-6 leads to association of PIAS-1 and PIAS-3 with Stat-1 and Stat-3, respectively, blocking DNA binding-activity and Stats-mediated gene activation (64).

Potentially, protein phosphatases can block almost all cell surface receptor-mediated signaling pathways, including cytokines receptor-mediated signaling pathways. Regarding IFNs signaling, SH2- domain containing protein tyrosine phosphatase-1 (SHPTP-1) is known to interact with JAKS, catalyzing their dephosphorylation and, thereby, suppressing IFNs signaling process (65, 66). Ironically, study with a dominant negative form of SHPTP-2D revealed that this phosphatase is required for IFN-α /ß –induced gene activation, indicating that SHPTPs may play a dual role in the IFNs signaling systems (66).

Viral proteins are the best known antagonists of IFNs signaling pathways (67-70). Although viruses use multiple strategies to impair IFNs actions, molecular mimicry is the most common tactic used by viruses (68,69). Using mimicry mechanisms, viruses antagonize the IFNs signaling, thereby impairing the development of antiviral condition. Viruses may block IFN-mediated signaling pathway at the pre- and post-receptor levels. For instance, several strains of poxviruses encode soluble IFN-γ receptor homologues (vIFN-γRc). Once synthesized and secreted into the media of poxvirus-infected cells, these soluble receptors bind IFN-γ, and prevent them from interacting with their natural receptors to evoke an antiviral action (68,69). It is noteworthy that the vIFN-γRc M-T7 gene product, the first known poxvirus IFNs receptor homologue, is a critical virulence factor for poxvirus pathogenesis (67). Likewise, the vIFN-α/ß receptor homologues, B18R and B19R gene products, secreted by vaccinia virus and several additional orthopoxviruses bind different IFN-α subspecies as well as IFN-ß and prevent activation of IFN-α/ß signaling pathway (68,69). Adenovirus, papillomavirus, and human herpesvirus 8 (HHV-8) block the pathway at the post- receptor levels; at a point upstream of the activation of ISGF3. These DNA viruses block the IFN-mediated signaling mainly by production of IRFs homologues (vIRF) or proteins that can bind and specifically inactivate the IRFs (67). Human papillomavirus, for example, produces the oncoprotein E6 that binds selectively to cellular IRF-3, but not to IRF-2 and IRF-9, and block the antiviral response (70). HHV-8, a gamma herpesvirus associated with Kaposi's sarcoma, synthesizes a vIRF that acts as a repressor of transcriptional activation induced by either type I or type II IFNs (67,71,72). A different strategy of antagonism may occur in other herpesviruses. In varicella-zoster virus the expression of Stat-1 and Jak-2 proteins is inhibited, whereas in cytomegalovirus –infected cells there is a specific decrease in the level of Jak-1 due to its enhanced degradation (67,71). Several RNA viruses use similar mechanisms of antagonism. In case of mumps virus, enhanced proteosome-mediated degradation of Stat-1, and in case of Sendai virus, impaired synthesis of Stat-1 by protein C hinder IFNs actions (73-75).

CONCLUSION

In spite of the growing body of information about the biological activities and signaling pathways of IFNs, many questions remain to be answered. What is the significance of sharing JAK1 by both types of IFNs? Why do so many IFN-α genes exist? Do they all compete for the same receptor? Do they use same signaling pathway and exhibit the same biological activities? Although, targeted disruption of the single IFN-ß gene on chromosome 4 leads to high susceptibility to viral infection, why has less attention been given to IFN-ß? In addition to Stat-1 and Stat-2, other STAT factors, Stat-3, Stat-4, Stat-5, and Stat-6 have also been observed to be activated by IFNs. What is the significances of activation of different STAT factors and their contribution to cell-type-restricted signaling in response to IFNs? Do different IFNAR-2 isoforms confer any specificity for activating different Stat factors? If they do, what are the biological significances? Do these specifications play roles in the type I interferon-mediated actions? Why does IFN–γ activate one gene with two different kinetics? Under certain conditions, in addition to JAK-STAT signaling pathway, the RNA-dependent protein kinase, mitogen activated protein kinase and phosphatidylinositol 3-kinase operate in response to IFN-γ. Surprisingly, some genes are activated by IFN-γ only in the absence of Stat1. This is of special significance in those viral infections where Stat-1 function is antagonized. Therefore, it is possible that an extensive network allows considerable cross talk between separate pathways involved in IFNs signaling with respect to the IFNs actions. Complexity of the IFNs signaling network is not unexpected because IFNs are involved in the control of integrated processes such as cell death, survival, proliferation and differentiation. Searching for the specific effector molecules in the network can lead to further insights into the mechanisms of viral pathogenesis and synthesis of regulatory molecules that are pivotal in mammalian cell life. For more than a decade IFNs have been satisfactorily used in many clinical trials. However, serious side effects such as neuropsychiatric, cardiovascular and hypersensitivity disorders remain as the major concern in clinical use of IFNs. A better understanding of the exact mechanism involved in IFNs signaling pathways and the structure–function relationships of the IFNs system components will allow researchers to improve and expand the therapeutic potential of these naturally occurring molecules.

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