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Signal Transduction by Type I Interferons

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ABSTRACT

The two classes of interferons, type I (IFNα, IFNβ, IFNω, and IFNτ) and type II (IFNγ) are pleiotropic cytokines that exhibit antiviral, antiproliferative, and immunomodulatory effects on their target cells. This article summarizes the advances made in elucidating the molecular events that mediate the biological responses to type I interferons.

INTRODUCTION

The interferons (IFNs) are a family of cytokines that exhibit pleiotropic intracellular effects generally categorized into antiviral, antiproliferative, and immunomodulatory roles (46,73). First isolated as agents of antiviral activity, the IFNs were later subdivided into two classes based on structural and functional differences (37). The type I IFNs include IFNα and IFNβ, which are produced by leukocytes and fibroblasts, respectively, as well as IFNω and IFNτ. In contrast, the only type II IFN, IFNγ, is produced by $CD8^+$ T cells, $CD4^+$ Th0 and Th1 cells, and natural killer (NK) cells. The goal of this article is to summarize the recent findings in the signal transduction pathways initiated by type I IFNs.

TYPE I INTERFERONS AND THEIR ACTIONS

The major representatives, IFNα and IFNβ, are both 4-α-helical bundle cytokines that bind to a common cell surface receptor. Fourteen human genes and 4 pseudogenes have been identified for IFNα, although the consequences of the existence of these multiple gene products remains elusive. Conversely, IFNβ is a single gene product exhibiting 13%–30% similarity to the IFNα protein products and is thought to have arisen by gene duplication and gene conversion of the IFNα locus. The IFNα and IFNβ loci lie adjacent to one another on human chromosome 9 and murine chromosome 4 and share a similar intronless gene structure (reviewed in Reference 74).

Most cells have the capability of synthesizing type I IFNs in response to viral infection or following contact with double-stranded RNA (dsRNA). Upon viral infection, biosynthesis of the type I IFNs is rapid, as their extracellular presence can be detected within 6 hours following infection.

Type I IFNs stimulate the synthesis of several antiviral gene products such as the 2′–5′ oligoadenylate synthetase. This enzyme is activated by the presence of dsRNA, a viral replication intermediate, to polymerize ATP into 2′–5′ oligomers. The oligomers, in turn, activate RNAse L, a constitutively expressed single-stranded RNA (ssRNA) ribonuclease, thereby inhibiting viral RNA production and viral protein synthesis. Protein kinase R (PKR), a serine/threonine kinase is also induced by IFNα/β. PKR phosphorylates the eIF-2 elongation factor, inhibiting its activity and disrupting protein translation (100).

The growth inhibitory effects of type I IFNs have been well documented, though many mediators responsible for the antiproliferative action of IFNs remain undefined. Various growth-modulating factors have been implicated in this process (22,42,58), and the elucidation of the IFN antiproliferative pathways has been hampered by the inconsistencies between cell systems. While the IFN-mediated induction of IRF-1, a documented tumor suppressor (103,104), appears to be a ubiquitous event, the modulated expression or posttranslational modifica-

tion of several cell cycle control proteins such as cyclin D3, p27kip, phosphoRb, and c-myc (42,106,117) in response to interferon stimulation varies between cell types or cell lines.

IFNs also induce intracellular processes, which modulate the host immune response to infection. For instance, upregulated expression of major histocompatibility complex (MHC) class I molecules in response to type I IFNs increases presentation of viral antigens on the surface of virally infected cells and targets them for cytotoxic $CD8^+$ T cell activity (100).

TYPE I INTERFERON RECEPTOR

IFNs initiate their biological effects by binding to their respective cognate cell surface receptors. All type I IFNs bind to a common receptor (IFNAR), whereas IFNγ utilizes a distinct receptor, IFNGR, both of which are ubiquitously expressed. Similar to other cytokine receptors, the IFN receptors display a high degree of species specificity in ligand recognition (73).

The type I IFN receptor exists as a multichain structure composed of IFNAR1 (α-subunit) (114) and IFNAR2 (β-subunit) (19,70). Both chains, each encoded by a distinct gene localized on human chromosome 21q22.1, exist as two membrane-bound splice variants. The 110-kDa IFNAR1 alone only binds one species of IFNα (IFNαB2), but is required for signaling by all type I IFNs. A short splice variant, IFNAR1s, lacks the extracellular subdomain encoded by exons 4 and 5 of the IFNAR1 gene, rendering the receptor insensitive to IFNαB2 and IFNαF, while binding of IFNαA and IFNω is maintained (reviewed in Reference 74). Alternative processing of the IFNAR2 RNA also yields two related proteins. The long 100-kDa IFNAR2c in a complex with IFNAR1 results in a fully functional type I IFN receptor (19,70). In contrast, expression of the short, cytoplasmic truncated form, IFNAR2b, in IFNAR2-deficient cells generates a low affinity binding site but no functional receptor (56). Interestingly, only IFNβ, but not IFNα, stimulation allows for the co-immunoprecipitation of IFNAR1 with IFNAR2c (78). This unique response transcends into the specific activation of the βR1 gene by IFNβ (82). These results demonstrate the different type I IFNs utilize distinct sites for interaction with the IFNα/β receptor, and that only a complex of IFNAR1 and IFNAR2c is capable of mediating the biological effects of all members of the IFNα/β family (Figure 1).

SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION (STATs)

Identification of IFN-induced RNAs and analysis of the promoters of IFNα/β-stimulated genes led to the identification of an enhancer termed the interferon stimulated response element (ISRE), which proved necessary and sufficient for activation of these genes by IFNα/β (48,49,86,87). Binding of IFNα/β to its receptor activates the latent cytoplasmic transcription factor complex interferon stimulated gene factor 3 (ISGF3) (25,39, 50), whose nuclear translocation and binding to the ISRE is required for the activation of early response genes by type I IFNs. The SH2-domain containing proteins STAT1α (formerly p91), its splice variant STAT1β (formerly p84), and STAT2 (formerly p113) were identified as the regulatory components of the ISGF3 complex (26,27,91). In contrast, IRF9 (formerly p48, ISGF3γ) functions independently of IFNα/β-induced post-translational modification as a DNA adapter molecule (14,50,51). Studies into the activating mechanism revealed that the IFNα/β-induced formation of ISGF3 requires the phosphorylation of Tyr701 in STAT1 and Tyr690 in STAT2, such that they can form heterodimers via their SH2 domains (14,90,95, 96). IFNα/β as well as IFNγ also promote the formation of STAT1 homodimers, which bind the gamma response region (GRR) or IFNγ activation sequence (GAS) (52,71) in genes such as IRF-1 (31). The development of a cell-free system where IFNα/β-stimulated STAT binding to the ISRE or GAS was reenacted in either cell homogenates or partially purified plasma membranes provided evidence that the pre-associated signaling cascade is localized to the plasma membrane (12,14).

The subsequently identified family members STAT3, STAT4, STAT5a, STAT5b, and STAT6 also contain SH2 domains and a conserved tyrosine in their carboxy terminus, which is phosphorylated upon incubation of cells with the appropriate cytokine (44,45). Interestingly, while the tyrosine phosphorylation of STAT1 and STAT2 in response to IFNα/β occurs in all non-transformed cells, the type I IFN mediated tyrosine phosphorylation of STAT3, STAT4, STAT5, and STAT6 takes place in a more cell-type-specific manner (9,23,59,88).

Although tyrosine phosphorylation and an intact SH2 domain are essential for STAT dimer formation and activity (26,28,96), other regions of STAT1 have also been implicated in the regulation of its transcriptional activity. A domain required for STAT1 to bind DNA has been localized between residues 400 and 500 (36). Under circumstances where adjacent DNA binding sites are present in a promoter, STATs can also form multimers (118). Recently the crystal structure of tyrosine phosphorylated STAT1 bound to DNA has been elucidated (7). In addition to Tyr701, the phosphorylation of Ser727, located within the carboxyl terminus of STAT1 in a consensus MAP kinase phosphorylation site is required for robust transcriptional activity (16,116). STAT1β, which lacks the Ser727 containing C-terminal 38 amino acids of STAT1α is unable to completely reconstitute IFN-stimulated STAT1-mediated gene transcription (6).

Although the IFNs have been shown to activate several STAT family members, STAT1 activation is probably the most significant. The importance of STAT1 in interferon signaling has been demonstrated in different systems. First, the development of IFN-resistant cell lines by chemical mutagenesis demonstrated the prerequisite for STAT1 expression to convey the antiproliferative and antiviral effects of IFN (65). Further, STAT1 knockout mice appear to develop normally, but rapidly succumb to opportunistic viral infections due to an inability to respond to the type I and type II IFNs (21,60).

JANUS KINASES

As both the type I and type II IFN receptors lack intrinsic kinase domains, they require the association with a family of non-receptor tyrosine kinases known as the Janus kinases (Jaks) to facilitate the tyrosine phosphorylation of STAT proteins (100). Of the four mammalian Jak kinase family members, which share

highly conserved regions including a pseudokinase domain located adjacent to the tyrosine kinase domain, Jak1, Jak2, and Tyk2, are ubiquitously expressed, whereas Jak3 expression is primarily restricted to hematopoietic cells (38).

The selection of cell lines defective in IFNα/β signaling allowed for the reconstitution of IFNα signaling in these lines with cDNAs encoding the defective proteins (72). The first such IFNα signaling defective mutant (U1) was rescued by complementation with a cDNA encoding the protein tyrosine kinase Tyk2 (115). In a similar manner, Jak1 was identified as the second Jak tyrosine kinase that is required for signaling via the type I receptor (66). Subsequent studies revealed that Tyk2 associates with IFNAR1 and mediated its tyrosine phosphorylation, whereas Jak1 performs this function on IFNAR2c (11,20). The tyrosine phosphorylation of the receptor by the preassociated Jak kinases presumably creates the docking sites for the SH2 domains of the STAT proteins. Indeed, SH2 domain-swapping experiments indicate the SH2 domains of the individual STAT molecules determine the specificity in the phosphotyrosine interaction both at the receptor and between the STATs themselves (33). Nevertheless, this simplified model is complicated by the findings that STAT2 and STAT3 bind to IFNAR1 in a ligand- and IFNAR1 tyrosine phosphorylation-dependent manner, whereas the association of STAT1 and STAT2 with IFNAR2c occurs independent of IFN (53,67). Interestingly, STAT1 activation by IFNα/β is dependent on the presence of STAT2, which interacts with IFNAR2c outside its SH2 domain (47,53).

Although several STATs are activated in response to IFNα/β, they seem to be activated by distinct mechanisms. The use of specific tyrosine kinase inhibitors as well as genetic approaches

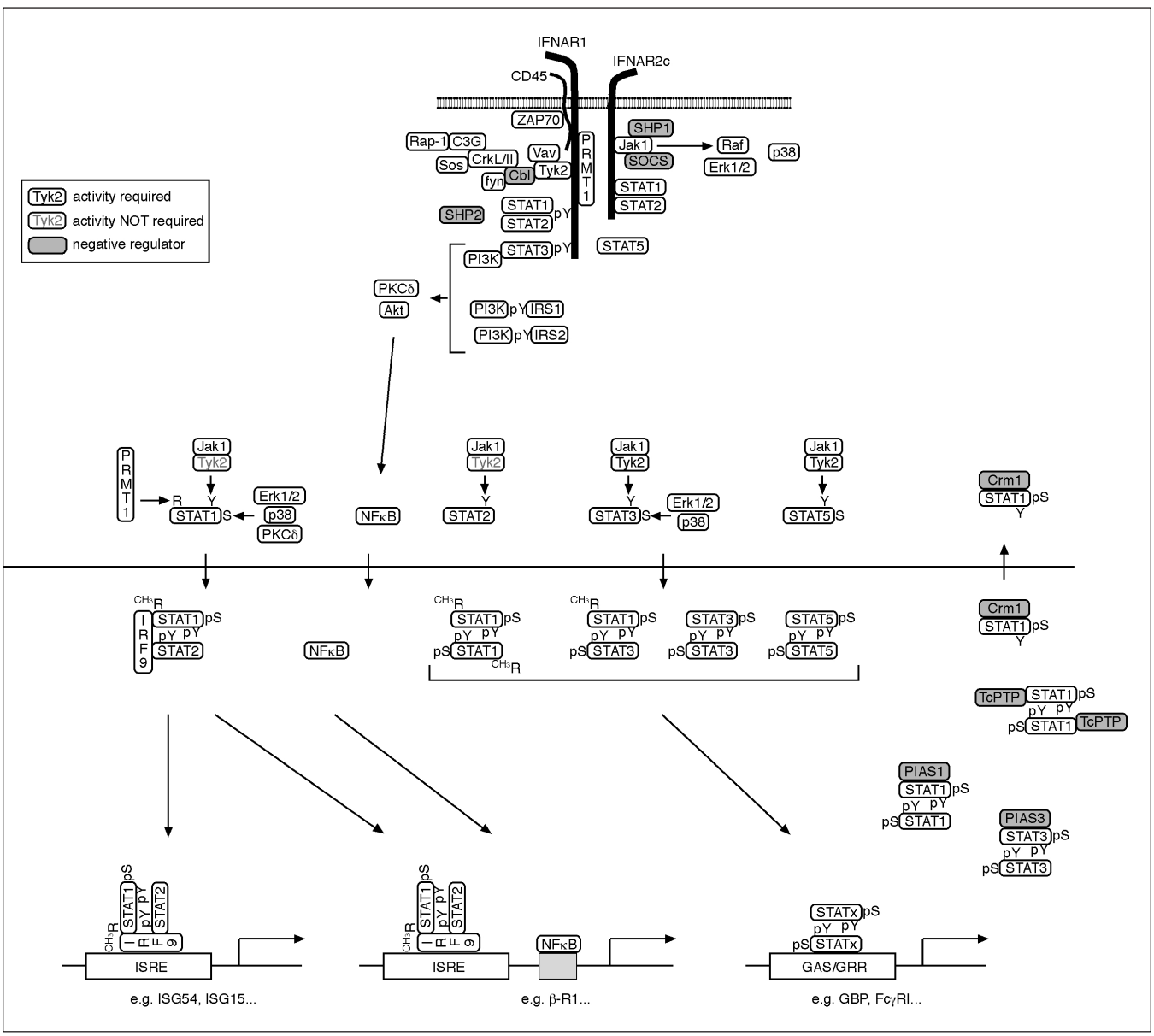

Figure 1. Signaling pathways activated by the type I interferon receptor.

demonstrated that IFNα/β-mediated tyrosine phosphorylation of STAT3 and STAT5 requires the kinase activity of Tyk2, while the presence of an inactive Tyk2 protein suffices to achieve tyrosine phosphorylation of STAT1 and STAT2 and subsequent gene induction (83,101).

ATTENUATION OF JAK/STAT SIGNALING

Of equal importance to the activation of a signaling pathway is its spatially and temporally coordinated attenuation. Several independent mechanisms are responsible for the negative regulatory control over the Jak/STAT pathway. The two SH2-domain containing tyrosine phosphatases SHP-1 and SHP-2 are at least in part responsible for modulating the IFNα/β activation of the Jak/Stat pathway. SHP1 is associated with IFNAR1 and suppresses activation of the IFNα/β-induced Jak1 kinase (15). Contradicting reports exist on the role of SHP2 in IFNα/β mediated STAT activation. Expression of dominant-negative SHP2 mutants inhibits IFNα-mediated gene induction (17), whereas the absence of SHP2 in gene-targeted animals leads to an enhanced interferon response (121).

The existence of a nuclear tyrosine phosphatase that inactivates STAT1 has been described by several labs (13,32). This crucial attenuator of the interferon response was recently identified as the nuclear 45-kDa isoform of TcPTP (105).

The SH2-domain containing suppressor of cytokine signaling (SOCS, also known as CIS) proteins have been identified as a family of seven cytokine-inducible inhibitors of the Jak/STAT pathway (8,34). These proteins bind to either tyrosine phosphorylated receptors or activated Jak kinases and mediate their ubiquitin-dependent degradation (40), thereby inactivating these essential signaling components in a classical negative feedback loop. A ubiquitin-proteosomal degradation pathway for STAT1 has also been suggested as an attenuation mechanism of the IFN activated Jak/STAT pathway (41).

In contrast to the cytokine-inducible SOCS proteins, the constitutively expressed PIAS proteins do not prevent the phosphorylation of STAT proteins, but exert their negative regulatory role by association with tyrosine phosphorylated STAT dimers and preventing them from binding DNA (10,54). Recently, PIAS proteins have been shown to perform additional functions by acting as SUMO E3-ligases for c-jun and p53 (43,92).

STAT NUCLEAR TRANSLOCATION

Signal-induced movement of STAT1 into the nucleus is clearly necessary for its function as a transcription factor. Ligand-induced tyrosine phosphorylation as well as an intact SH2-domain are necessary for nuclear import (62), and tyrosine phosphorylated STAT1 rapidly accumulates in the nucleus within 30 minutes of initial receptor activation. Sekimoto et al. demonstrated that microinjected anti-Ran antibodies, as well as the expression of mutant Ran proteins inhibit nuclear import of tyrosine phosphorylated STAT1 even though STAT1 contains no recognizable classical NLS motif (93). The importin-α homologue NPI-1 interacts with tyrosine phosphorylated STAT1, but does so via a region distinct from its classical NLS binding site. These observations indicate STAT1 nuclear import is an energy-dependent process that relies on induced recognition of STAT1 by nuclear import factors (94).

Additionally, several labs demonstrated relocalization of nuclear STAT1 molecules to the cytoplasm following interferon treatment, indicating the existence of a nuclear export mechanism. Indeed, three leucine-rich nuclear export sequences (NES), which are recognized by the export receptor Crm1, were mapped in STAT1 (4,57,63), and nuclear export of STAT1 appears to be regulated in a Jak1-dependent manner, albeit independent of STAT1 tyrosine phosphorylation (63).

STAT INTERACTIONS

Using the IFNAR1 cytoplasmic domain as bait in a yeast two hybrid screen, Abramovich et al. demonstrated the association of a protein arginine methyl-transferase (PRMT1) with the IFNα/β receptor (1). Using antisense oligos to quench endogenous PRMT1 expression, it was shown that the loss of PRMT1 expression led to an inability to respond to the antiproliferative effects of IFNα/β. Further experiments implicated PRMT1 in the antiviral effects of IFNα/β, while similar experiments demonstrated no effect on IFNγ activity, suggesting a specificity for PRMT1 in type I IFNs but not in type II IFN signaling (2). PRMT1 is a type I arginine methyltransferase that catalyzes the formation of N^G-monomethylarginine and asymmetric N^G,N^G-dimethylarginine. Type II arginine methyltransferases catalyze the formation of N^G-monomethylarginine and symmetric N^G,N'^G-dimethylarginine.

Recently, the NH2-terminal domain of STAT1 was identified as the target for PRMT1-catalyzed protein methylation (64). Arg31, which is highly conserved between all mammalian STAT proteins, requires methylation to support IFNα/β-mediated gene transcription. Inhibition of STAT1 arginine methylation promotes its association with PIAS1, thereby preventing STAT1 from binding ISRE or GRR elements. Additional evidence for arginine methylation in IFN signaling is the recent cloning of Jak binding protein (JBP1) isolated in a yeast two-hybrid screen with Jak2 (81). Capable of binding all mammalian Jaks, JBP1 has homology to the conserved regions of protein arginine methyltransferases and is the first identified type II arginine methyltransferase (81).

Interaction with the replication factor MCM5 is enhanced with Ser727 phosphorylation, and transient expression of MCM5 augments STAT1-induced transcription in a Ser727-dependent manner (122). STAT1 also interacts with the transcriptional coactivator Creb binding protein (CBP). Interaction with CBP enhances STAT1 transcriptional activity. The STAT1 NH2-terminus interacts with the Creb binding domain (KIX) of CBP, while the STAT1 COOH-terminus associates with the C/H3 domain, the same region of CBP that binds the E1a adenovirus protein (35). As such, competition for CBP interaction provides a mechanism for adenoviral suppression of STAT1 function (55). The coiled-coil domain of STAT1 was found to associate with an N-Myc interactor (Nmi) and this interaction was found to enhance CBP coactivator binding to STAT1 and, thus, augment STAT1 mediated transcription (123).

ADDITIONAL SIGNALING CASCADES IN THE TYPE I IFN RESPONSE

Several reports indicate that IFNs can activate many signaling cascades that are distinct from the Jak/Stat pathway. Numerous proteins undergo rapid tyrosine phosphorylation following exposure of cells to IFNα/β. Two members of the insulin receptor substrate (IRS) family of adapter proteins, IRS-1 and IRS-2, become tyrosine phosphorylated in response to type I IFNs, allowing for the SH2-domain mediated binding of the p85 regulatory subunit of PI-3 kinase (79,107). Interestingly, PI-3 kinase association with the IFN receptor can presumably also occur in a STAT3-facilitated manner (76). While the resulting activation of PI-3 kinase promotes the activity of the proto-oncogene Akt (PKB) (69,112) and PKCδ (113), the biological consequences of these events are still unclear. Although PI-3 kinase activity is not required for ISGF3 formation or induction of ISRE-controlled genes, both STAT3 and PI-3 kinase have been proposed to be essential for the antiproliferative effects of IFNα/β (119). These findings, however, are contradicted by the observation that deletion of the STAT3/PI-3 kinase interaction domain of IFNAR1 yields a receptor with enhanced biological activity (29).

Two additional adapter proteins, both of which associate constitutively with Tyk2, undergo rapid tyrosine phosphorylation after IFNα/β stimulation and alter the IFN response. In hematopoietic cells, disrupted expression of the guanine nucleotide exchange factor Vav abrogates the growth inhibitory effects of IFNα (61,77,110). The proto-oncogene c-Cbl modulates IFN signaling in two distinct ways. In unstimulated cells, c-Cbl was reported to regulate the basal expression levels of STAT1 (5). As a target for IFN-mediated tyrosine phosphorylation (108), c-Cbl provides docking sites for the src family kinase fyn (109) as well as the adapters CrkL and CrkII (3,18,85). These SH2 and SH3 domain containing proteins link c-Cbl to Sos and C3G, a guanine nucleotide exchange factor for Rap-1 (97,102). CrkL can associate with STAT5 and form a GAS-binding complex (24), and expression of CrkL and CrkII is essential for the antiproliferative effects of IFNα/β (80). The importance of two components of the T cell receptor complex in IFNα/β signaling was illustrated by the finding that T cells deficient in either ZAP70 or CD45 fail to produce a growth inhibition after exposure to IFNα/β, despite appropriate activation of the Jak/STAT pathway (75).

Another signaling cascade regulated by IFNs is the MAP kinase pathway (16). IFNα/β activates Raf-1 as well as B-Raf, two serine kinases ultimately responsible for the activation of p42MAP kinase, in a Jak1-kinase and STAT1-dependent manner (89,98,99). Likewise, it has also been reported that the p38 SAPK is activated by IFNα/β (30,111). Ser 727 of Stat1, which is conserved in Stat3 and Stat4, is positioned within a consensus phosphorylation site for proline-directed serine kinases such as MAP kinases (116). However, as other IFNα/β activated kinases, such as PKCδ (113) or the IFNγ-activated CamKII (68), also have the ability to phosphorylate Ser727 of STAT1 in vitro, it remains unclear which kinase is ultimately responsible for the phosphorylation of STAT1 Ser727 in vivo.

The exact consequences of IFNα/β treatment with regards to nuclear translocation and DNA binding of NFκB are still unclear. A recent study proposed a specific requirement for NFκB activation in the IFNβ-mediated induction of the βR1 gene (84). However, Yang et al. reported NFκB activation and concomitant cell survival through both IFNα and IFNβ (120). Thus, it appears that NFκB activation by IFNs occurs in a cell-type-specific manner or that additional factors account for the IFNβ-specific activation of the βR1 gene.

Since its discovery, the Jak/STAT pathway has been the center of attention for investigations into the biological effects of type I IFNs. Significant advances in the field over the past decade have led to a broad, albeit incomplete, picture of this signaling cascade. More recent work has now, once again, aimed to characterize Jak/STAT-independent or cooperative IFN-induced signal transduction pathways. A thorough understanding of the intracellular events that govern the IFN response will lay the foundation to identify the mechanisms that alter these effects during viral infection or malignant transformation.

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