

Review

Interferon Receptor Signaling in Malignancy: A Network of Cellular Pathways Defining Biological Outcomes

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Abstract

IFNs are cytokines with important antiproliferative activity and exhibit key roles in immune surveillance against malignancies. Early work initiated over three decades ago led to the discovery of IFN receptor activated Jak–Stat pathways and provided important insights into mechanisms for transcriptional activation of IFN-stimulated genes (ISG) that mediate IFN biologic responses. Since then, additional evidence has established critical roles for other receptor-activated signaling pathways in the induction of IFN activities. These include MAPK pathways, mTOR cascades, and PKC pathways. In addition, specific miRNAs appear to play a significant role in the regulation of IFN signaling responses. This review focuses on the emerging evidence for a model in which IFNs share signaling elements and pathways with growth factors and tumorigenic signals but engage them in a distinctive manner to mediate antiproliferative and antiviral responses. *Mol Cancer Res*; 12(12); 1691–703. ©2014 AACR.

Introduction

Because of their antineoplastic, antiviral, and immunomodulatory properties, recombinant IFNs have been used extensively in the treatment of various diseases in humans (1). IFNs have clinical activity against several malignancies and are actively used in the treatment of solid tumors such as malignant melanoma and renal cell carcinoma; and hematologic malignancies, such as myeloproliferative neoplasms (MPN; ref. 1). In addition, IFNs play prominent roles in the treatment of viral syndromes, such as hepatitis B and C (2). In contrast to their beneficial therapeutic properties, IFNs have also been implicated in the pathophysiology of certain diseases in humans. In many cases, this involvement reflects abnormal activation of the endogenous IFN system, which has important roles in various physiologic processes. Diseases in which dysregulation of the type I IFN system has been implicated as a pathogenetic mechanism include autoimmune disorders such as systemic lupus erythematosus (3), Sjogren syndrome (3, 4), dermatomyositis (5), and systemic sclerosis (3, 4). In addition, type II IFN (IFN γ) overproduction has been implicated in bone marrow failure syndromes, such

as aplastic anemia (6). There is also recent evidence for opposing actions of distinct IFN subtypes in the pathophysiology of certain diseases. For instance, a recent study demonstrated that there is an inverse association between IFN β and IFN γ gene expression in human leprosy, consistent with opposing functions between type I and II IFNs in the pathophysiology of this disease (7). Thus, differential targeting of components of the IFN system, to either promote or block induction of IFN responses depending on the disease context, may be useful in the therapeutic management of various human illnesses. The emerging evidence for the complex regulation of the IFN system underscores the need for a detailed understanding of the mechanisms of IFN signaling to target IFN responses effectively and selectively.

It took over 35 years from the original discovery of IFNs in 1957 to the discovery of Jak–Stat pathways (8). The identification of the functions of Jaks and Stats dramatically advanced our understanding of the mechanisms of IFN signaling and had a broad impact on the cytokine research field as a whole, as it led to the identification of similar pathways from other cytokine receptors (8). Subsequently, several other IFN receptor (IFNR)-regulated pathways were identified (9). As discussed below, in recent years, there has been accumulating evidence that beyond Stats, non-Stat pathways play important and essential roles in IFN signaling. This has led to an evolution of our understanding of the complexity associated with IFN receptor activation and how interacting signaling networks determine the relevant IFN response.

IFNs and their functions

The IFNs are classified in three major categories, type I (α , β , ω , ϵ , τ , κ , ν); type II (γ), and type III IFNs ($\lambda 1$, $\lambda 2$, $\lambda 3$; refs. 1, 9, 10). The largest *IFN* gene family is the group of

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type I IFNs. This family includes 14 IFN α genes, one of which is a pseudogene, resulting in the expression of 13 IFN α protein subtypes (1, 9). There are 3 distinct IFNRs that are specific for the three different IFN types. All type I IFN subtypes bind to and activate the type I IFNR, while type II and III IFNs bind to and activate the type II and III IFNRs, respectively (9–11). It should be noted that although all the different type I IFNs bind to and activate the type I IFNR, differences in binding to the receptor may account for specific responses and biologic effects (9). For instance, a recent study provided evidence that direct binding of mouse IFN β to the *Ifnar1* subunit, in the absence of *Ifnar2*, regulates engagement of signals that control expression of genes specifically induced by IFN β , but not IFN α (12). This recent discovery followed original observations from the 1990s that revealed differential interactions between the different subunits of the type I IFN receptor in response to IFN β binding as compared with IFN α binding and partially explained observed differences in functional responses between different type I IFNs (9).

A common property of all IFNs, independent of type and subtype, is the induction of antiviral effects *in vitro* and *in vivo* (1). Because of their potent antiviral properties, IFNs constitute an important element of the immune defense against viral infections. There is emerging information indicating that specificity of the antiviral response is cell type-dependent and/or reflects specific tissue expression of certain IFNs. As an example, a recent comparative analysis of the involvement of the type I IFN system as compared with the type III IFN system in antiviral protection against rotavirus infection of intestinal epithelial cells demonstrated an almost exclusive requirement for IFN λ (type III IFN; ref. 13). The antiviral effects of IFN α have led to the introduction of this cytokine in the treatment of hepatitis C and B in humans (2) and different viral genotypes have been associated with response or failure to IFN therapy (14).

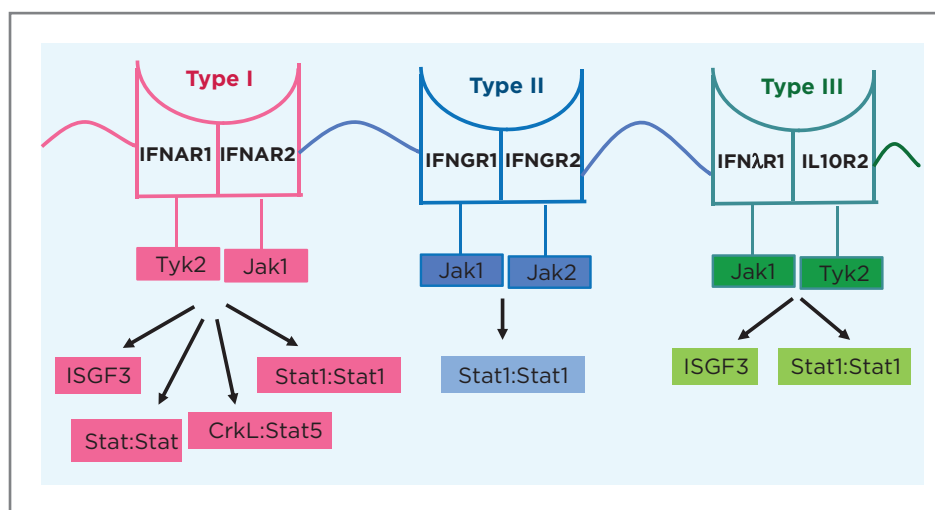
Most importantly, IFNs exhibit important antineoplastic effects, reflecting both direct antiproliferative responses mediated by IFNRs expressed on malignant cells, as well as indirect immunomodulatory effects (15). IFN α and its pegylated form (peg IFN α) have been widely used in the treatment of several neoplastic diseases, such as hairy cell leukemia (HCL), chronic myeloid leukemia (CML), cutaneous T-cell lymphoma (CTCL), renal cell carcinoma, malignant melanoma, and myeloproliferative neoplasms (MPN; refs. 1, 16). Although the emergence of new targeted therapies and more effective agents have minimized the use of IFNs in the treatment of diseases like HCL and CML, IFNs are still used extensively in the treatment of melanoma, CTCL and MPNs (1, 16, 17). Notably, recent studies have provided evidence for long lasting molecular responses in patients with polycythemia vera, essential thrombocytosis and myelofibrosis who were treated with IFN α (16). Beyond their inhibitory properties on malignant hematopoietic progenitors, IFNs are potent regulators of normal hematopoiesis (9) and contribute to the regulation of normal homeostasis in the human bone marrow (18). Related to its effects in the central nervous system, IFN β has clinical

activity in multiple sclerosis and has been used extensively for the treatment of patients with multiple sclerosis (19). The immunoregulatory properties of type I IFNs include key roles in the control of innate and adaptive immune responses, as well as positive and negative effects on the activation of the inflammasome (15). Dysregulation of the type I IFN response is seen in certain autoimmune diseases, such as Aicardi–Goutières syndrome (20). In fact, self-amplifying type I IFN production is a key pathophysiologic mechanism in autoimmune syndromes (21). There is also emerging evidence that IFN λ may contribute to the IFN signature in autoimmune diseases (3).

Jak–stat pathways

Jak kinases and DNA-binding Stat complexes. Tyrosine kinases of the Janus family (Jaks) are associated in unique combinations with different IFNRs and their functions are essential for IFN-inducible biologic responses. Stats are transcriptional activators whose activation depends on tyrosine phosphorylation by Jaks (8, 9). In the case of the type I IFN receptor, Tyk2 and Jak1 are constitutively associated with the IFNAR1 and IFNAR2 subunits, respectively (refs. 8, 9; Fig. 1). For the type II IFN receptor, Jak1 and Jak2 are associated with the IFNGR1 and IFNGR2 receptor subunits, respectively (refs. 8, 9; Fig. 1). Finally, in the case of the type III IFNR, Jak1 and Tyk2 are constitutively associated with the IFN λ R1 and IL10R2 receptor chains, respectively (ref. 10; Fig. 1). Upon engagement of the different IFNRs by the corresponding ligands, the kinase domains of the associated Jaks are activated and phosphorylate tyrosine residues in the intracellular domains of the receptor subunits that serve as recruitment sites for specific Stat proteins. Subsequently, the Jaks phosphorylate Stat proteins that form unique complexes and translocate to the nucleus where they bind to specific sequences in the promoters of IFN-stimulated genes (ISG) to initiate transcription. A major Stat complex in IFN signaling is the IFN-stimulated gene factor 3 (ISGF3) complex. This IFN-inducible complex is composed of Stat1, Stat2, and IRF9 and regulates transcription by binding to IFN-stimulated response elements (ISRE) in the promoters of a large group of ISGs (refs. 8, 9). ISGF3 complexes are induced during engagement of the type I and III IFN receptors, but not in response to activation of type II IFN receptors (refs. 8–10; Table 1). Beyond ISGF3, several other Stat complexes involving different Stat homodimers or heterodimers are activated by IFNs and bind to IFN γ -activated (GAS) sequences in the promoters of groups of ISGs (8, 9). Such GAS-binding complexes are induced by all different IFNs (I, II, and III), although there is variability in the engagement and utilization of different Stats by the different IFN receptors (Table 1). It should also be noted that engagement of certain Stats, such as Stat4 and Stat6, is cell type-specific and may be relevant for tissue-specific functions (9). The significance of different Stat-binding complexes in the induction of type I and II IFN responses was in part addressed in a study in which Stat1 cooperative DNA binding was disrupted by generating knock-in mice

Figure 1. Type I, II, III IFN receptor subunits, associated kinases of the Janus family, and effector Stat pathways. Note: Stat:Stat reflects multiple potential Stat:Stat complexes, as outlined in Table 2.



expressing cooperativity-deficient STAT1 (22). As expected, type II IFN-induced gene transcription and antibacterial responses were essentially lost in these mice, but type I IFN-dependent recruitment of Stat1 to ISRE elements and antiviral responses were not affected (22), demonstrating the existence of important differences in Stat1 cooperative DNA binding between type I and II IFN signaling.

Serine phosphorylation of Stats. The nuclear translocation of Stat proteins occurs after their activation, following phosphorylation on specific sites by Jak kinases (8, 9). It is well established that phosphorylation on tyrosine 701 is required for activation of Stat1 and phosphorylation on tyrosine 705 is required for activation of Stat3 (8, 9). Beyond tyrosine phosphorylation, phosphorylation on serine 727 in the Stat1 and Stat3 transactivation domains is required for full and optimal transcriptional activation of ISGs (8, 9). There is evidence that serine phosphorylation occurs after the phosphorylation of Stat1 on tyrosine 701 and that translocation to the nucleus and recruitment to the chromatin are essential in order for Stat1 to undergo serine 727 phosphorylation (23). Several IFN-dependent serine kinases for Stat1 have been described, raising the possibility that this phosphorylation occurs in a cell type-specific manner. After the original demonstration that protein kinase C (PKC) delta (PKC δ) is a serine

kinase for Stat1 and is required for optimal transcriptional activation in response to IFN α (24), extensive work has confirmed the role of this PKC isoform in the regulation of serine 727 phosphorylation in Stat1 and has been extended to different cellular systems (refs. 25–29; Table 2). In the type II IFN system five different serine kinases for the transactivation domain (TAD) of Stat1/phosphorylation on serine 727 have been demonstrated in different cell systems. These include PKC δ (30, 31), calmodulin-dependent kinase II (CAMKII; ref. 32), PKC ϵ (33), PKC α (34), Erk (35), and cyclin-dependent kinase 8 (CDK8; ref. 36; Table 2). Thus, it appears that in the type I IFN system, PKC δ is the predominant kinase that regulates phosphorylation of Stat1 on serine 727 (Table 2), while in the type II IFN system several serine kinases appear to play roles in different cell types (Table 2). It remains to be determined whether the diversity of serine kinases in the type II IFN system reflects differences in cellular expression patterns or is context-dependent, possibly influenced by parallel signaling events. It should also be noted that it is likely that, beyond phosphorylation on serine 727 in the TAD, phosphorylation on other serine residues in Stats may be important for transcriptional activity and the generation of IFN responses. For instance, phosphorylation of serine 708 in Stat1 by the kinase IKK ϵ is important for transcriptional activation of a subset of ISGs (37). Thus, it appears

Table 1. Different Stat–DNA binding complexes induced by type I, II, and III IFNs

IFN type	Stat complexes
Type I	Stat1: Stat2: IRF9, Stat1:Stat1, Stat1:Stat2, Stat1:Stat3, Stat2:Stat3, Stat3:Stat3, Stat4: Stat4, Stat1:Stat4, Stat1:Stat5, Stat5:Stat5, Stat5:Stat6, CrkL:Stat5
Type II	Stat1:Stat1, Stat1:Stat3, Stat3:3,
Type III	Stat1:Stat2: IRF9, Stat1:1

Table 2. Serine kinases demonstrated to regulate phosphorylation of Stat1 on serine 727 in response to different IFNs

IFN type	Putative kinases for TAD/serine 727
Type I	PKC δ
Type II	PKC δ , PKC ϵ , PKC α , CAMKII, Erk, JNK, CDK8
Type III	Unknown

that our current understanding of the role of serine phosphorylation of Stats is incomplete and future studies may uncover other serine phosphorylation sites and corresponding kinases relevant to Stat activity.

Regulatory effects of phosphatases on Jak–Stat signaling. After undergoing tyrosine phosphorylation by Jaks and translocation to the nucleus to regulate ISG transcription by binding to specific promoter elements, nuclear Stats are deactivated by dephosphorylation. Several phosphatases have been identified as regulators of IFN signaling pathways (Table 3). In the type I IFN system, it has been shown that the tyrosine phosphatase TC-PTP modulates Stat1 activity in BCR-ABL–transformed leukemia cells (38). TC-PTP is involved in dephosphorylation of Stat1 in the type II IFN system and pharmacologic inhibition of its activity has been shown to enhance IFN γ signaling (39). In the type I IFN system, SHP1 is associated with the Tyk2 tyrosine kinase (40), while it has been shown to dephosphorylate IFN γ tyrosine phosphorylated Stat1 in brain microglia and astrocytes (41). In addition, interaction of tyrosine phosphorylated SHP-2 (pY-SHP-2) with cytosolic STAT1 has been shown to prevent recruitment of Stat1 to the type II IFNR and to inhibit Stat1-mediated signaling (42). The protein tyrosine phosphatase PTPN1 has been implicated in both type I (43) and type II (44) IFN signaling. Moreover, there is evidence that PTPN1 and TC-PTP have nonoverlapping roles in type II IFN signaling (44). Finally, recent studies have shown the negative regulator of JAK kinases, phosphatase CD45 exhibits regulatory effects on IFN signaling (45). Thus, the coordinated function of distinct tyrosine phosphatases at different important check points of IFN-activated signaling cascades accounts for control of tyrosine phosphorylation-mediated signaling events and optimal balancing of IFN responses.

Other modifications of Stat activity

There has been accumulating evidence over the last decade that events unrelated to Stat phosphorylation have important regulatory roles on the functions of Stats. IFN-inducible unphosphorylated Stat1 (U-Stat1) appears to increase or maintain the expression of a subset of ISGs independently of tyrosine-phosphorylated Stat1 (46). Remarkably, this regulation can also occur by the formation of a complex with unphosphorylated Stat2 and IRF9, suggesting the existence of an unphosphorylated ISGF3 complex (8). U-Stat2 has also recently been shown to play important regulatory roles in transcriptional activation of a set of ISGs (47). Although the physiologic and pathophysiologic relevance of unphosphorylated Stat functions remain to be precisely defined, it has been suggested that some of the genes regulated by the unphosphorylated ISGF3 complex (8) may be mediators of resistance of tumor cells to DNA damage, to chemotherapy and/or radiation. Other events that appear to modulate IFN-dependent Stat activity include SUMO conjugation (48, 49) and interaction with histone deacetylases (50). A recent study demonstrated that a complex involving the ATP-binding RVB proteins (RVB1 and RVB2) is required for

type I, but not type II, IFN-dependent transcription of ISGs (51). In that study, it was shown that RVB1 and RVB2 interact with the transactivation domain of STAT2 after type I IFN treatment (51), suggesting a mechanism by which their effects occur and underscoring the complexity of events required for optimal ISG transcriptional activation. It should be noted that IFN-inducible Jak–Stat signaling is tightly regulated by additional negative regulators. Beyond the factors described above, suppressors of cytokine signaling (SOCS) and protein inhibitors of activated Stats (PIAS) have been associated with negatively regulating IFN inducible Jak–Stat signaling (reviewed in ref. 52). In addition, the IFN-inducible ubiquitin carboxyterminal hydrolase 18 (USP18)/ubiquitin-specific protease, UBP43, can displace Jak1 from the associated IFNAR2 subunit, thereby affecting Jak–Stat signaling (reviewed in ref. 52).

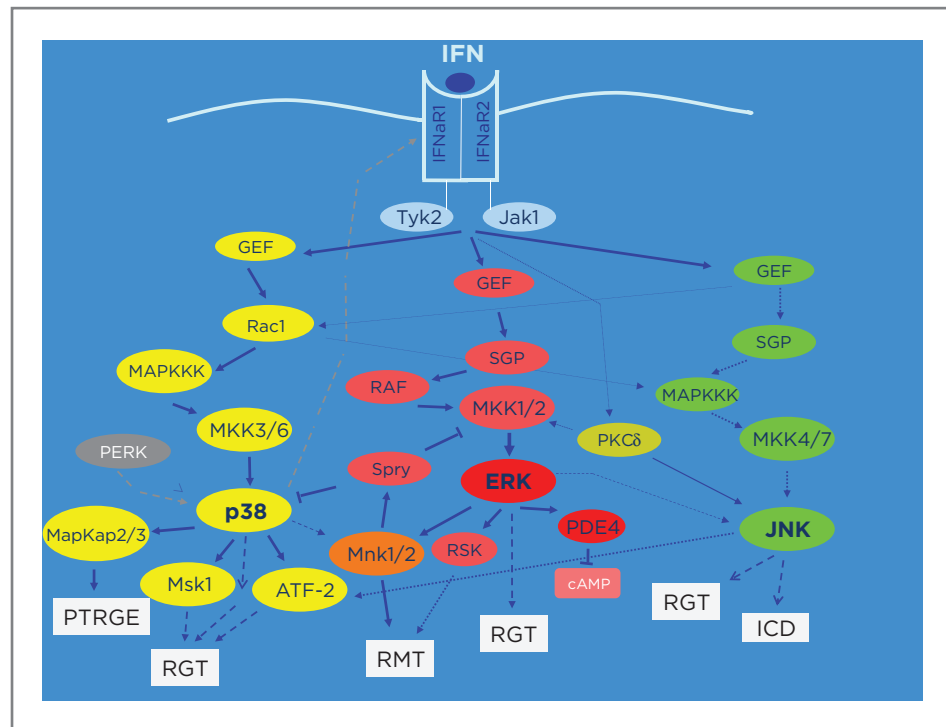
Map kinase pathways

Mitogen activated protein (Map) kinases control key effector pathways in cytokine signaling and play important roles in the control of various important cellular processes (9). Map kinase pathways are involved in the regulation of innate immunity (53) and have important roles in the pathophysiology of malignancies, a fact that makes them attractive therapeutic targets for the treatment of certain tumors (54). All three major classes of Map kinases (p38 MAPK, Erk, and JNK) have been shown to participate in the induction of IFN responses via distinct cellular signaling events, as outlined below.

p38 Map kinase pathways. There is extensive evidence that the p38 Map kinase signaling pathway acts as an auxiliary cascade for Jak–Stat pathways and that its function is required for optimal transcriptional activation of ISGs (9, 18). This pathway has been shown to be engaged by the type I (9, 55–60), type II (60, 61), and type III (62) IFN receptors. The functional relevance of this signaling cascade in the type I IFN system was established some time ago, when it was demonstrated that p38 MAP kinase engagement is essential for type I IFN-dependent suppression of normal and leukemic hematopoiesis (9, 60). There is also recent evidence implicating the p38 MAPK in the induction of type I IFN-dependent antiproliferative and/or proapoptotic responses in T-cell leukemia cells (58) and primary malignant hematopoietic progenitors from patients with polycythemia vera expressing the JAK2-V617F mutation (63). Not surprisingly, as the function of the p38 MAP kinase pathway is required for IFN-inducible expression of ISG protein products, its engagement is essential for IFN responses against different viruses (9, 57, 64). However, there is also evidence for selectivity in the IFN responses controlled by the p38 MAPK, suggesting differential regulation of target genes by p38 signals. For instance, the neuroprotective effect of IFN β against mitochondrial toxicity occurs via modulation of Stat1 activity, but it seems to be p38 MAPK independent (65).

Because of the importance of this pathway in the generation of IFN responses, extensive work has been

Figure 2. Map kinase pathways in type I IFN signaling. GEF, guanine exchange factor; RGT, regulation of gene transcription; RMT, regulation of mRNA translation; PTRGE, posttranscriptional regulation of gene expression.



conducted to identify the mechanisms by which its activation is regulated and to define downstream signaling effectors. The engagement of the p38 MAPK by the type I IFN receptor occurs via activation of an upstream cellular pathway that involves the Vav proto-oncogene and/or other guanine exchange factors, the small G-protein Rac1, and/or other GTPases, a yet to be defined MAPKKK and then MMK3/6 (9) (Fig. 2). Several downstream effectors of the type I IFN-activated p38 MAPK have been identified. These include the kinases MapKapK2/3 (55, 57), the nucleosomal kinase Msk1 (57), and the transcription factor ATF-2 (56). Although the precise mechanisms by which the p38 MAPK pathway regulates gene transcription in the IFN system remain to be identified, it is possible that Msk1 plays a role by modifying nuclear histone phosphorylation (9). It is also possible that the involvement of p38 MAPK in the generation of type I IFN growth inhibitory responses involves transcriptional regulation of members of gene families with growth inhibitory properties, such as *Schlafen* (*Slf*) genes (66). Notably, malignant transformation by BCR-ABL has been shown to involve suppression of type I IFN-dependent gene transcription, via inhibition of both p38 MAPK activity and Stat-activation (67), underscoring the relevance of the p38 MAPK in immune surveillance against cancer. A novel function of the p38 MAPK was recently established by Fuchs and colleagues (68). Evidence was provided for ligand-independent PKR-like endoplasmic reticulum kinase (PERK) - mediated p38 MAPK activation that regulates priming phosphorylation of IFNAR1, facilitating ubiquitination and degradation of this receptor subunit (68).

Although a functional p38 MAPK is required for type I IFN transcriptional activation via ISRE or GAS elements (55, 57), it does not appear to play a major role in type II IFN-induced Stat-dependent ISG transcription (57). However, the p38 MAPK pathway is activated by the type II IFN receptor and/or plays important roles in the generation of type II IFN biologic responses in several different cell types (34, 60, 61, 69). There is also evidence for what appears to be cell type-specific regulation of expression of genes required for the innate immune response (70). As the p38 MAPK is a mediator of the suppressive effects of IFN γ on normal hematopoiesis (60), its pharmacologic inhibition may be relevant in diseases in which there is overproduction of IFN γ -associated suppressed hematopoiesis. Indeed, there is evidence that inhibition of p38 MAPK activity can enhance hematopoietic progenitor colony formation *in vitro* from bone marrows of patients with aplastic anemia (60), anemia of chronic disease (71), and myelodysplastic syndromes (71, 72).

The roles of the p38 Map kinase in the type III IFN system is less well defined compared with the type I and II IFN systems, primarily because of the relatively recent discovery of the IFN λ family compared with other IFNs. Nevertheless, it has been shown that IFN λ induces activation of the p38 MAPK pathway and that, as is the case for type I IFN signaling, p38 activity is required for ISG transcription (62). Future studies should define the effectors of the p38 MAPK pathway in the type III IFN system and determine whether there are type III IFN-specific effectors or unique type III IFN-dependent engagement of downstream pathways. Viewed altogether, the p38 MAPK

pathway plays a prominent role in signaling for all three different classes of IFNs and its function is central for the biologic effects of IFNs.

Erk kinase pathways. There is considerable evidence that the Mek/Erk kinase pathway is also activated by IFNs. Since the original demonstration that type I IFNs activate Erk (reviewed in 9), a substantial amount of data have defined the relevance of Mek/Erk signaling to the generation of IFN responses. This activation appears to be Jak1-dependent and to involve upstream Raf1 activation (ref. 9; Fig. 2). Recent evidence reveals that type I IFN-dependent activation of Erk occurs in several different cell types, including hepatocytes (73), endometrial epithelial cells (74), gastric carcinoma cells (75) and adrenal chromaffin cells (76). Type I IFN-activated Erk has been shown to regulate phosphorylation of tyrosine hydroxylase on serine 31 (76) and to mediate IFN α -induced apoptosis (77). Importantly, a recent study demonstrated that engagement of the MEK/Erk pathway is critical for IFN α -induced phosphodiesterase 4 (PDE4) activation and repression of cAMP in Treg cells (78). This study provided evidence for a novel type I IFN-induced, Erk-mediated, function, involving inhibition of the suppressive effects of Tregs on CD4⁺ T cells and NK cells (78).

In addition to effects on transcriptional activation of ISGs, the Mek/Erk pathway has an important role in mRNA translation of ISGs via activation of at least two distinct effectors. One pathway involves engagement of the kinase Mnk1 and downstream phosphorylation of the eukaryotic initiation factor 4E (eIF4E; ref. 79). Although Mnk kinases can be activated downstream of either p38 MAPK or Erk in response to stress signals (80), it appears that in the type I IFN system, this activation occurs selectively downstream of the Mek/Erk, but not the p38 MAPK pathway (79). Studies using cells from mice with targeted deletion of *Mnk1* and *Mnk2* have established that the Mnk pathway is essential for mRNA translation of the *Isg15* and *Isg54* genes and that its function is required for the generation of the inhibitory effects of type I IFNs in normal hematopoietic progenitors (79). A recent study (81) showed that the Mnk pathway is an essential mediator of the antineoplastic effects of IFN α on malignant hematopoietic progenitors from patients with myeloproliferative neoplasms. The key role for Mnk in these responses (81) has provided important clues on the mechanisms by which type I IFNs generate their antitumor effects against Jak2V617F malignancies. Other studies have shown that Sprouty (Spry) proteins are stabilized/upregulated downstream of type I IFN-dependent Mnk kinases and exert negative feedback regulatory roles on the activation of the p38 MAPK and Erk kinase pathways (82). These proteins have negative regulatory roles in the generation of antiviral and antileukemic effects of type I IFNs (82). Another effector of the MEK/Erk pathway in the type I IFN system is the kinase RSK1 (83). This kinase regulates type I IFN-dependent eIF4B phosphorylation in hematopoietic cells and is required for induction of type I IFN-dependent antileukemic responses (83).

The Mek/Erk pathway is also activated during engagement of the type II IFN receptor (35, 70, 84, 85) and is

required for optimal gene transcription via IFN γ -activated site (GAS) elements (35) and IFN γ -activated transcriptional elements (GATE; ref. 86). Effectors of the pathway, such as Mnk1, are also engaged downstream of MEK/Erk activation by the type I IFN receptor (87). The MEK/Erk pathway has been shown to mediate diverse responses following engagement of the type II IFN receptor, including suppressive effects on normal hematopoiesis (87), IFN γ -dependent death of oligodendroglial progenitor cells (84), and bacterial internalization by gut epithelia (85). There is also evidence that the MEK/Erk pathway is activated by the type III IFN receptor and mediates IFN λ -dependent activation of the kinase RSK1 and downstream upregulation of p21^{WAF1/CIP1}, suggesting a mechanism for the generation of IFN λ -inducible growth inhibitory responses (88).

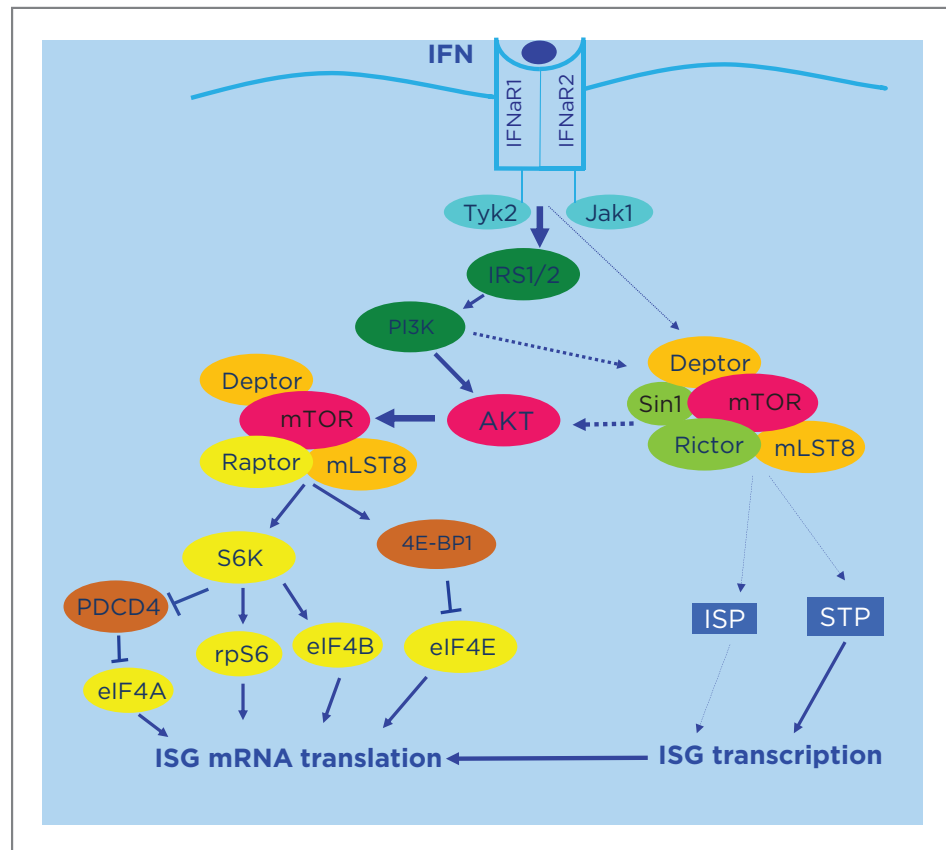
JNK kinase pathways. The JNK family of Map kinases is composed of three distinct isoforms (JNK1, JNK2, and JNK3) (53). In recent years, there has been accumulating evidence that the members of this family participate directly in IFN signaling and mediate IFN biological responses. Type I IFNs have been reported to activate JNK1 (27, 56, 77), although this activation appears to be weaker than the activation of other MAPK pathways by the type I IFNR. Two reports (27, 77) have suggested a unique mechanism of activation of the JNK pathway by the type I IFN receptor, involving PKC δ -dependent activation of JNK1 (Fig. 2). This sequential activation was found to be essential for type I IFN-induced apoptosis of malignant cells (27, 77). Other studies have shown that sequential IFN α -dependent activation of PKC δ and JNK is required for IFN-induced expression of IFIT4 (89) and induction of phospholipid scramblase 1 (PLSCR1) which promotes proapoptotic and antiviral activities (26).

The JNK kinase pathway is also activated during engagement of the type II IFN receptor (70, 90, 91) and mediates important biologic and biochemical responses, including transcriptional activation of genes involved in antigen presentation (70), differentiation of neural progenitor cells (91), upregulation of B7-DC, and antitumor immunity (90). Similarly, the JNK pathway is engaged by the type III IFN receptor, albeit in a cell type-restricted manner, and appears to participate in type III IFN gene induction (62).

mTOR pathways

The ability of the mTOR pathway to regulate initiation of mRNA translation is critical for important functions in normal cells, including cell proliferation and survival, cell division and motility, lipid synthesis, glycolysis, and autophagy (92). Because of these roles in important cellular functions, dysregulation of the mTOR pathway has been implicated in the pathogenesis and/or pathophysiology of diverse diseases and syndromes, including malignancies, obesity, diabetes, neurodegenerative diseases, cognitive defects, and depression (92). As dysregulation of mTOR signaling is particularly important in promoting malignant transformation and neoplastic cell proliferation, there has been an intense interest leading to extensive efforts to target mTOR pathways for the treatment of cancer (93).

Figure 3. mTOR pathways in type I IFN signaling. ISP, signals regulating transcription independent of Stat pathways; STP, Stat pathways.



mTOR exists in at least two distinct complexes with unique elements and downstream effectors, namely mTORC1 and mTORC2 (92, 93). mTORC1 is a protein complex of mTOR with Deptor, mLST8, and Raptor, whereas the mTORC2 complex includes Deptor, mLST8, Sin1, and Rictor (refs. 92, 93; Fig. 3). mTORC1 signals are important for the initiation of mRNA translation, whereas mTORC2 is critical for the activation of survival cellular pathways via engagement of the AGC family of kinases, which include AKT, SGK, and PKC α (92, 93). mTOR pathways are activated during engagement of the type I and II IFN receptors and play important roles in mRNA translation of ISGs (9). The first evidence implicating mTOR in IFN signaling emerged about 10 years ago, when it was demonstrated that type I IFN treatment of cells results in phosphorylation/activation of the p70 S6 kinase and its downstream effector, S6 ribosomal protein, as well as the translational repressor, 4E-BP1 (94). At that time it was also shown that engagement of mTORC1-dependent signals is defective in cells with targeted disruption of the p85 α and p85 β regulatory subunits of the PI3K (94). In subsequent studies, evidence was also provided that mTOR pathways are activated during engagement of the type I IFN (IFN γ) receptor (95). Later studies identified upstream effectors and regulators of the mTOR pathway in the IFN system as the PI3K (96) and the AKT kinase (97). These kinases are sequentially activated in an IFN-dependent manner and act as positive upstream effectors of mTORC1 activity (96, 97)

(Fig. 3). On the other hand, TSC1/2 act as negative upstream effectors of IFN-activated mTORC1 (98). Several of the downstream effectors of the mTOR pathway during engagement of the IFN receptors have been identified and their functions defined. The translational repressor 4E-BP1 is phosphorylated on multiple sites by IFN-activated mTOR, resulting in its dissociation from the eukaryotic initiation factor 4E (eIF4E), to allow for initiation of cap-dependent mRNA translation (94, 98). Induction of expression of type I and II IFN-inducible proteins and IFN antiviral responses are enhanced in cells with targeted disruption of the *4e-bp1* gene (98). Other studies have shown a key role for the S6K effector, eIF4B, in the generation of IFN responses (83). IFN-dependent phosphorylation of eIF4B promotes the interaction of the protein with eIF3A (p170/eIF3A) and results in increased associated ATPase activity (83). In addition, the IFN-activated form of S6K was shown to phosphorylate the tumor suppressor protein, programmed cell death 4 (PDCD4), on Ser67, resulting in the interaction of PDCD4 with the ubiquitin ligase β -TRCP (β -transducin repeat-containing protein) and its subsequent degradation (99). This degradation of PDCD4 results in increased IFN-induced eukaryotic translation initiation factor 4A (eIF4A) activity and binding to translation initiation factor eIF4G and increased cap-dependent translation (99). Other studies have shown that mTORC2 complexes are engaged by the type I IFN receptor and regulate expression of ISGs (100). Remarkably, these complexes appear to

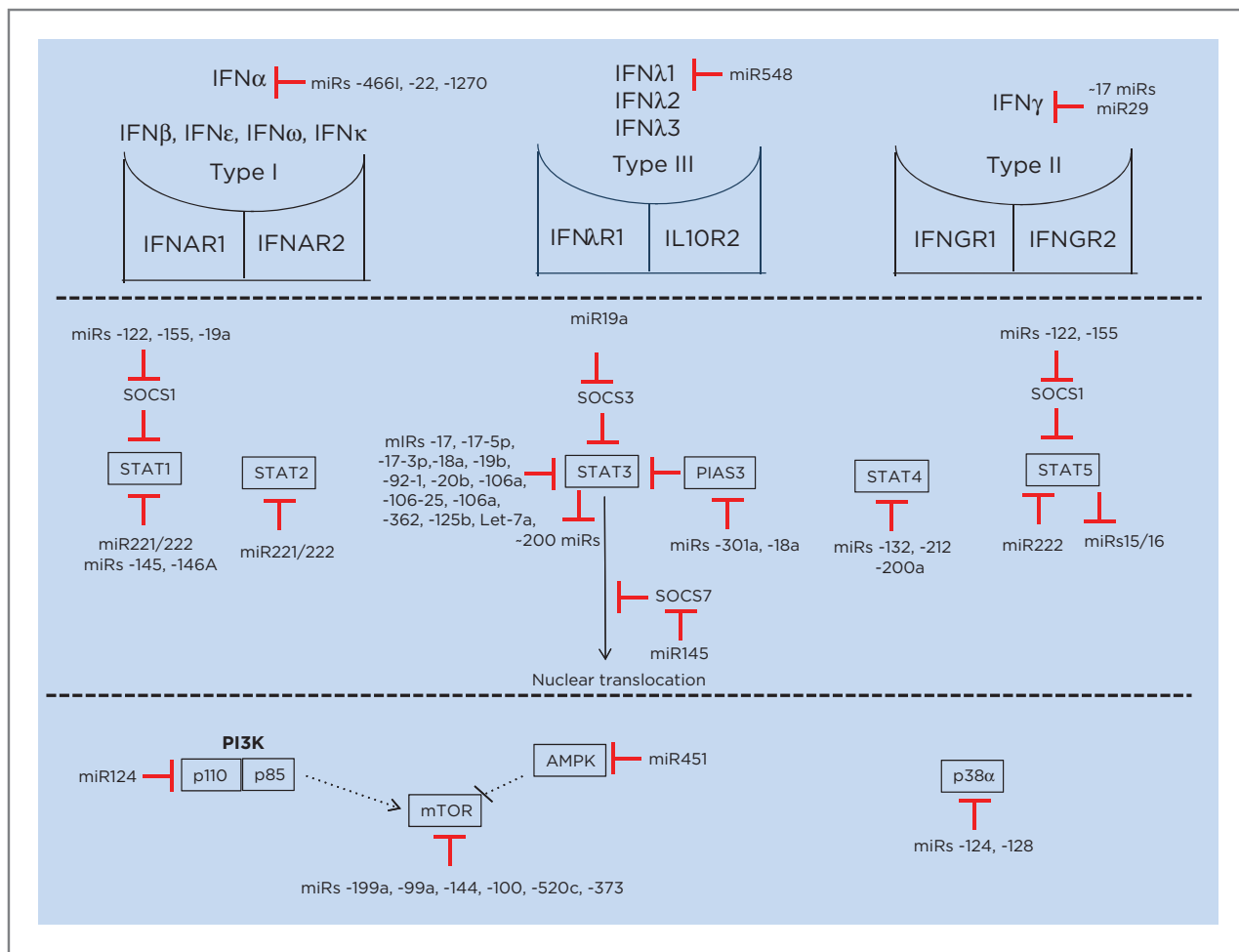


Figure 4. Targeting and regulation of various proteins known to be involved in IFN signaling by different miRNAs.

selectively regulate an Akt/mTORC1 axis in response to engagement by the type I IFN receptor, but not in response to growth factor receptors or oncogenic signals, suggesting the existence of an IFN-specific mTORC2/mTORC1 modification and function (100). Altogether, the mTOR pathway exerts important roles in type I IFN-dependent responses (96–98, 101, 102) and antineoplastic effects (77). Importantly, the mTOR pathway is also required for type I IFN production by plasmacytoid dendritic cells (103), suggesting the existence of a positive feedback regulatory loop for the induction of IFN responses. There is also some evidence for engagement of mTOR by the type III IFN receptor (10), suggesting important roles for this signaling cascade in responses to each of the IFN types.

miRNAs and the IFN response

IFN-inducible JAK–STAT, MAPK, and mTOR signaling cascades are also regulated potentially by microRNAs (miRs). miRs are important regulators of post-transcriptional events, leading to inhibition of mRNA translation or mRNA degradation (104). In recent years, it has become apparent that the direct regulation of STAT activity by miRs has profound

effects on consequent gene expression, specifically in the context of cytokine-inducible events (105). Pertinent for this review of IFN-inducible STAT activation, miR145, miR146A, and miR221/222 target STAT1 and miR221/222 target STAT2 (105). Numerous studies describe different miRs that target STAT3: miR17, miR17-5p, miR17-3p, miR18a, miR19b, miR92-1, miR20b, Let7a, miR106a, miR106-25, miR106a-362, and miR125b (ref. 105; Fig. 4). miR132, miR212, and miR200a have been implicated in negatively regulating STAT4 expression in human NK cells (106) and miR222 has been shown to regulate STAT5 expression (107). In addition, JAK–STAT signaling is affected by miR targeting of suppressors of cytokine signaling (SOCS) proteins. miR122 and miR155 targeting of SOCS1 releases the inhibition of STAT1 (and STAT5a/b; refs. 108–110), and miR19a regulation of SOCS1 and SOCS3 effectively prolongs activation of both STAT1 and STAT3 (111). There is also evidence that miR155 targets the inositol phosphatase SHIP1, effectively prolonging/inducing IFN γ expression (112). Much of the evidence associated with miRs prolonging JAK–STAT activation relates to cancer studies, where tumor-secreted miRs promote cell migration and angiogenesis by prolonging

Table 3. Protein tyrosine phosphatases with regulatory effects on Jak–Stat pathways in IFN signaling

IFN type	Tyrosine phosphatases
Type I	TC-PTP, PTPN1, SHP1, CD45
Type II	TC-PTP, PTPN1, SHP1, SHP2
Type III	Not known

JAK–STAT activation (113). miR145 targeting of SOCS7 affects nuclear translocation of STAT3 and has been associated with enhanced IFN β production (114). Beyond inhibition of SOCS proteins, miRs may influence the expression of other inhibitory factors associated with JAK–STAT signaling, and miR301a and miR18a have been shown to inhibit PIAS3, a negative regulator of STAT3 activation (115). There is also the potential for STATs to directly regulate miR gene expression. STAT5 suppresses expression of miR15/16 (116) and there is evidence that there are potential STAT3 binding sites in the promoters of about 200 miRs (117). Viewed altogether, there is compelling evidence for miR–STAT interactions, yet few studies have considered the contributions of miRs to IFN-inducible JAK–STAT signaling.

Given the accumulating evidence for a miR network that regulates JAK–STAT activation, additional miR networks that directly contribute to signaling output and biologic responses induced by the different IFNs, associated with the other IFN signaling cascades, must operate. Analogous to miR networks that may affect IFN-inducible JAK–STAT signaling, there is a paucity of direct data linking miRs to IFN-inducible mTOR or MAPK signaling cascades. As above, we will identify miRs that potentially may interact with IFN-inducible signaling effectors. A number of studies have focused on miR inhibition of PI3K/mTOR signaling. Similar to investigations related to miR interactions with STATs, the majority of the miR–PI3K/mTOR studies have been conducted in the context of cancers. The catalytic subunit of PI3K, p110, is the target of miR124 (118). mTOR is a direct target for miR199a, miR99a, miR144, miR100, miR520c, and miR373 (refs. 119–122; Fig. 4). When considering MAPK signaling, studies reveal that miR124 targets and miR128 suppress p38a transcripts (123). Moreover, there is some evidence that IFN- β inducible miR431 targets intermediates in the MAPK pathway in cells sensitive to its growth inhibitory effects (124).

Not surprisingly, miRs have been identified that target IFNs and IFN-inducible genes. The expression of multiple IFN α species can be directly inhibited by miR4661, through their 3' untranslated region (125). miR22, associated with the transition from cell quiescence to proliferation, suppresses type I IFN gene expression by targeting high mobility group

box-1 and IRF5, preventing IRF3 and NF κ B activation (126). This effectively blocks the antiproliferative response of type I IFNs. miR203, an IFN-inducible miR, targets IFIT1, effectively providing an inhibitory feedback loop following IFN gene activation (127). miR548 targets the 3' untranslated region of IFN λ 1, affecting IFN λ 1 expression and the expression of a number of ISGs, including the human MxA protein and 2'5'-oligoadenylate synthetase-1 (OAS1; ref. 128). SOCS1 targeting by miR122 in liver Huh7 cells significantly increases type I IFN expression (108). miR29 targets IFN γ mRNA and the transcription factors T-bet and Eomes, inhibiting IFN γ production (129, 130). In addition, using miR databases, at least 17 miRs have been identified that potentially target IFN γ , including miR29 (131). Undeniably, the contributions of miRs to an IFN response are profound, contextual, and involve a network of interactions, affecting both the production of IFNs and the sustainability of the signaling responses they invoke.

Evolution of our understanding of IFN signals and future perspectives

A substantial amount of knowledge has accumulated since the original discovery of the Jak–Stat pathway in the early 1990s. It is now clear that several key signaling cascades are essential for the induction of type I, II, and III IFN responses. The original view that IFN signals can be transmitted from the cell surface to the nucleus in two simple steps involving tyrosine phosphorylation of Stat proteins (8) now appears somewhat simplistic, as it has been established that modifications of Jak–Stat signals by other pathways and/or simultaneous engagement of other essential complementary cellular cascades is essential for induction of ISG transcriptional activation, mRNA translation, protein expression, and subsequent induction of IFN responses. Such pathways include PKC and MAP kinase pathways and mTORC1 and mTORC2-dependent signaling cascades.

Over the next decade, our understanding of the mechanisms by which IFN signals are induced will likely continue to evolve, with the anticipated outcome that it will be possible to exploit this new knowledge for translational therapeutic purposes. For instance, selective targeting of kinase elements of the IFN pathway with kinase inhibitors may be useful in the treatment of autoimmune diseases where dysregulated/excessive type I IFN production contributes to the pathophysiology of disease. On the other hand, efforts to promote the induction of specific IFN signals, may lead to novel, less toxic, therapeutic interventions for a variety of viral infectious diseases and neoplastic disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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