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TRANSCRIPTION FACTORS IN INTERFERON SIGNALING

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Abstract—Interferons (IFNs) comprise a family of polypeptides that exhibit diverse biological effects such as inhibition of cell growth and protection against viral infection. These activities are based mainly on the transcriptional induction of cellular genes by both type I (IFN- α and IFN- β) and type II (IFN- γ) interferons. Several of these IFN-induced early response genes have been cloned and common elements within their promoters defined. Transcription factors, such as interferon-stimulated gene factor-3, IFN- γ activation factor and FcRF γ , that bind to these enhancers subsequently have been isolated and their components identified. This review shall provide an overview of the DNA response elements, the components of the IFN-induced transcription factors and their mechanism of action.

Keywords—Interferon, transcription factor, signal transduction.

CONTENTS

1. Introduction	149
1.1. Interferons	150
1.2. Interferon receptors	150
1.3. Interferon-induced genes	151
2. Transcription Factors in Interferon Signaling	151
2.1.1. DNA binding region	152
2.1.2. Interferon-stimulated gene factors (E-factors)	152
2.1.3. Interferon-stimulated gene factor 3 and its components	152
2.1.4. Mechanism of action	153
2.2. γ -IFN activation factor	154
2.2.1. DNA binding region	154
2.2.2. Components of γ -IFN activation factor and mechanism of action	154
2.3. γ -IFN response region binding factors (FcRF γ s)	155
2.3.1. DNA binding region (GRR) and components of FcRF γ s	155
2.3.2. Components of FcRF γ s and mechanism of action	155
Acknowledgements	157
References	157

1. INTRODUCTION

Interferons (IFNs) were discovered in the early 1950s by Isaacs and Lindenmann (1957) by their ability to interfere with viral replication. This antiviral activity, which led to the name of the protein, serves today as an assay for the specific activity of IFN. Paucker *et al.* (1962) found that IFNs had

Abbreviations—AAF, IFN activation factor; AF, accessory factor; GAF, γ -IFN activation factor; GAS, γ -IFN activation sequence; GBP, guanylate binding protein; GRR, gamma response region; IFN, interferon; IRF, interferon regulatory factor; ISGF, interferon-stimulated gene factor; ISRE, interferon stimulation response element; MHC, major histocompatibility complex; NEM, *N*-ethyl-maleimide; SH, src-homology region.

strong antiproliferative activity. At that time, there were no general rules to predict which cells will be affected in their growth and which viruses in their replication. Empirical results were the only basis for treatment with IFN, as very little was known about their molecular mechanisms of action. Since then, many developments have occurred that provided significant insight into the action of IFNs and how they mediate immune responses. Many of the effects of IFNs are based on the rapid expression of certain genes after IFN binds to its cell-surface receptor and the subsequent synthesis of new proteins. The observed increase in gene expression led to the first demonstration of an early response mechanism, as documented in the rapid activation of several DNA-binding proteins. This review will provide an overview of the transcription factors involved in the transcriptional activation of IFN-induced genes.

1.1. Interferons

The basal level of all IFNs in the blood is usually low, but expression can be strongly induced by most viruses and mycoplasma, bacteria, double-stranded RNA, endotoxins and antigens (Lengyel, 1982; Pestka *et al.*, 1987). Although IFNs are found in all mammalian species, they show species specificity. There are four antigenically different types of IFN: leukocyte or IFN- α , fibroblast or IFN- β , immune or IFN- γ and IFN- ω .

Human IFN- α is composed of a number of various subtypes of glycosylated proteins whose molecular weights range from 16 to 20,000, with about 70% sequence homology (Pestka, 1986; Pestka *et al.*, 1987). In contrast, only one type of human IFN- β , with a molecular weight of approximately 20,000, has been detected, which shows about 29% sequence similarity with human IFN- α (Weissman and Weber, 1986). The purification of human IFN- γ yielded several different isoforms that resulted from a different glycosylation pattern of a single polypeptide species. Natural IFN- γ exists as a dimer with a molecular weight of 45–50,000 (Rinderknecht *et al.*, 1984).

1.2. Interferon Receptors

It has been well established that IFNs exert their action by binding to specific cell-surface receptors (Aguet, 1980; Branca and Baglioni, 1981). Cells lacking IFN receptors are insensitive towards the effects of IFN. IFN- α and IFN- β seem to share a common receptor, as demonstrated by binding competition assays (Aguet *et al.*, 1984; Joshi *et al.*, 1982). One component of the receptor has been cloned and consists of a protein of 550 amino acids (Uze *et al.*, 1990). The native IFN- α/β receptor has a molecular weight of 95,000 on a reducing SDS–polyacrylamide gel electrophoresis, which is probably due to glycosylation (Schwabe *et al.*, 1988; Vanden Broecke and Pfeffer, 1988). This cloned receptor protein consists of a large extracellular domain, a single transmembrane region and an approximately 100 amino acid intracellular tail (Uze *et al.*, 1990). Interestingly, the C-terminal end shows a sequence highly conserved among species, whereas variations in the extracellular region may account for the species specificity. An absolutely preserved pentameric region is also found in the human, murine and rat IFN- γ receptor (Cook *et al.*, 1992; Farrar *et al.*, 1992), whose intracellular domains are otherwise only 55% identical. Site-directed mutagenesis of this sequence (440-YDKPH-444) revealed that the hydroxyl group of Tyr-440 is of particular importance for signal transduction (Cook *et al.*, 1992; Farrar *et al.*, 1992; Farrar and Schreiber, 1992). The cloned ligand-binding protein with a molecular mass of 90 kDa contains nearly equivalent-sized extra- and intracellular domains and appears to dimerize after binding of IFN- γ (Aguet *et al.*, 1988; Kumar *et al.*, 1988). Receptors on different cells can display mass heterogeneity due to cell-specific differences in glycosylation (Hershey and Schreiber, 1989). A species-specific accessory protein besides the 472 amino acids counting receptor is required to form a functional IFN- γ receptor (Jung *et al.*, 1987, 1988; Hemmi *et al.*, 1992; Hibino *et al.*, 1992). This accessory factor (AF-1) has been cloned recently and shown to be a transmembrane protein required for induction of interferon-stimulated gene factor (ISGF)-3 and γ -IFN activation factor (GAF). AF-1 is a transmembrane protein that interacts with the extracellular and, perhaps, intracellular domain of the receptor (Soh *et al.*, 1993, 1994; Cook *et al.*, 1994; Hemmi *et al.*, 1994).

1.3. Interferon-induced Genes

Research over the last decade has led to the discovery of a variety of genes whose transcription is rapidly activated by IFNs without the necessity of protein synthesis (Friedman *et al.*, 1984; Larner *et al.*, 1984, 1986; Reich *et al.*, 1987). Nevertheless, the knowledge of the function of the proteins that are encoded in these genes is still limited, but already some of them have been shown to play an important role either in the virus defense of the cell or in the regulation of cell proliferation (Koromilas *et al.*, 1992; Meurs *et al.*, 1992; Staeheli *et al.*, 1986). While transcription of some IFN-regulated genes is specifically induced by IFN- α/β or IFN- γ (see Table 1), some genes can be transcriptionally activated by either type of IFN and may be even affected synergistically by a combination of both (Levy *et al.*, 1990). This specificity of transcriptional initiation is based on the activation of distinct transcription factors by the different IFN species, which will then bind to enhancers within the promoters of the various genes. Therefore, the kind of transcription factor activated by a given IFN species, as well as the enhancer sequence found in a distinct gene, will determine its specificity of activation. Whereas a highly conserved sequence has been found in the promoter of all IFN- α -induced early response genes, the Interferon Stimulation Response Element or ISRE, no such preserved region has been found in IFN- γ -induced genes (Cohen *et al.*, 1988; Levy *et al.*, 1988; Porter *et al.*, 1988; Reich *et al.*, 1987). Table 1 provides a short summary of IFN-regulated genes with respect to the specificity of their activation.

2. TRANSCRIPTION FACTORS IN INTERFERON SIGNALING

Three different IFN-induced transcription factors have been characterised that are responsible for the induction of several early response genes. The first IFN-activated transcription factor identified was the ISGF3 (Levy *et al.*, 1988; Pine and Darnell, 1989) or *E-Factor*. Shortly thereafter, the GAF was shown to be activated by IFN- α/β and IFN- γ . Recently, another IFN- α/β - and IFN- γ -activated DNA binding protein was discovered, which binds to the promoter of the high affinity Fc-receptor (Wilson and Finbloom, 1992).

Table 1. Summary of IFN-induced Genes and the Specificity of their Activation

Gene	IFN	Reference
ISG15	IFN- α/β	Reich <i>et al.</i> , 1987
ISG54	IFN- α/β	Larner <i>et al.</i> , 1984
p68-Kinase	IFN- α/β	Meurs <i>et al.</i> , 1990
P1/eIF-2 α -Kinase	IFN- α/β	Roberts <i>et al.</i> , 1976
Metallothionein-II	IFN- α/β	Friedman <i>et al.</i> , 1984
Xanthine oxidase	IFN- α/β	Ghezzi <i>et al.</i> , 1984
Mx-Protein	IFN- α/β	Staeheli <i>et al.</i> , 1984
6-16	IFN- α/β	Kelly <i>et al.</i> , 1986
Indoleamine 2,3- dioxygenase	IFN- $\alpha/\beta/\gamma$	Dai and Gupta, 1990
MHC Class I	IFN- $\alpha/\beta/\gamma$	Shirayoshi <i>et al.</i> , 1988
2'-5'-A-Synthetase	IFN- $\alpha/\beta/\gamma$	Merlin <i>et al.</i> , 1983
GBP	IFN- $\alpha/\beta/\gamma$	Lew <i>et al.</i> , 1989
IRF1 (ISGF2)	IFN- $\alpha/\beta/\gamma$	Miyamoto <i>et al.</i> , 1988
1-8	IFN- $\alpha/\beta/\gamma$	Friedman <i>et al.</i> , 1984
9-27	IFN- $\alpha/\beta/\gamma$	Reid <i>et al.</i> , 1989
Egr-1	IFN- $\alpha/\beta/\gamma$	Cao <i>et al.</i> , 1992
MHC Class II	IFN- γ	Finn <i>et al.</i> , 1990
β 2-Microglobulin	IFN- γ	Wallach <i>et al.</i> , 1982
Fc γ -Receptor	IFN- γ	Pearse <i>et al.</i> , 1991
IP10	IFN- γ	Luster and Ravetch, 1987
IP30	IFN- γ	Luster <i>et al.</i> , 1988
Interferon Consensus Sequence Binding Protein (ICSBP)	IFN- γ	Driggers <i>et al.</i> , 1990
γ .1	IFN- γ	Fan <i>et al.</i> , 1989
GM-CSF-Receptor	IFN- γ	Hallek <i>et al.</i> , 1992

ISG54	→	TAG TTT CAC TTT CCC
ISG15	←	CAG TTT CGG TTT CCC
6-16 a	←	GAG TTT CAT TTT CCC
6-16b	←	CAG TTT CAT TTT CCC
6-16c	←	GAG TTT CTA TTT CTG
202	→	CAG TTT CTC ATT TAC
HLA-A	→	CAG TTT CTT TTC TCC
H-2K	→	CAG TTT CAC TTC TGC
H-2D	→	CAG TTT CAC TTC TGC
H-2L	→	CAG TTT CCC TTT CAG
T1a	→	TAG TTT CAC TTT TTG
Factor B	→	CAG TTT CTG TTT CCT
IP 10	←	AGG TTT CAC TTT CCA
Consensus		YAG TTT C₁Y TTT YCC

Fig. 1. Comparison of ISREs in IFN- α/β -induced genes.

2.1.1. DNA Binding Region

The first IFN-induced genes were cloned in 1986/87 (Kelly *et al.*, 1986; Levy *et al.*, 1986; Reich *et al.*, 1987). Deletions and point mutations revealed an ISRE within the promoters of these genes approximately 100 bp upstream of the cap site. This 15 bp region termed the ISRE is highly conserved, and a similar sequence has been found in all other IFN- α/β -activated early response genes (Levy *et al.*, 1986; Reich *et al.*, 1987). Although the 9 bp core sequence is able to bind ISGF1 (C factor) and ISGF2 (M factor), a larger sequence is necessary to bind ISGF3 efficiently. Binding of ISGF3 to the ISRE has been demonstrated to be necessary and sufficient to induce transcription of these genes by IFN. Figure 1 compares the ISREs found in several IFN- α/β -induced genes.

2.1.2. Interferon-stimulated Gene Factors (E-factors)

Three distinct complexes have been shown to bind the ISRE found in the promoters of several IFN- α/β -induced genes. These factors were named ISGFs by the laboratory of J. E. Darnell, or *E*, *C* and *M*-Factors by the laboratories of G. R. Stark and I. M. Kerr, who first described these DNA-binding proteins in 1988/89 (Dale *et al.*, 1989). ISGF1 (C) was found to be a constitutive factor, whereas ISGF2 (M) demonstrated increased binding in response to IFN- $\alpha/\beta/\gamma$, but the induction required protein synthesis (Kessler *et al.*, 1988; Pine and Darnell, 1989). Pine *et al.* (1990) demonstrated that ISGF2 could also bind to a region within the IFN- β gene promoter, PRD1, which is homologous to the central 9 bp core of the ISRE (Goodbourn and Maniatis, 1988). ISGF2 was shown to be identical with interferon regulatory factor (IRF)1 (Pine *et al.*, 1990), a protein that regulates the transcription of the IFN- β gene (Fujita *et al.*, 1989). Since both ISGF1 and ISGF2 can bind to the 9 bp core region of the ISRE only, and activation of IFN- α/β -induced genes required the entire ISRE and is independent of protein synthesis (Reich and Darnell, 1989), it was deduced that these complexes were not responsible for activation of IFN-stimulated genes. This function was ascribed to ISGF3, which needed the full ISRE sequence for binding (Kessler *et al.*, 1988).

2.1.3. Interferon-stimulated Gene Factor 3 and its Components

The formation of ISGF3 has been shown to parallel the transcriptional activation of all IFN- α/β -induced genes, and it is generally accepted that ISGF3 is the primary activator of IFN-mediated gene expression (Kessler *et al.*, 1988; Reich and Darnell, 1989). Levy *et al.* (1989) demonstrated that ISGF3 consists of at least two components distinguished by their sensitivity towards *N*-ethyl-maleimide (NEM). By reconstituting the DNA-binding activity of ISGF3 after NEM treatment, it was found that the component rapidly activated after IFN bound to its cell-surface receptor was NEM resistant. These polypeptides were named ISGF3 α (Levy *et al.*, 1989). The NEM-sensitive part of the transcription complex was found to be permanently present in the

cytoplasm and nucleus and did not require any further activation. This protein was termed ISGF3 γ because its concentration in the cell could be increased by incubation of cells with IFN- γ (Levy *et al.*, 1990). This effect accounts for the observed synergism of IFN- α and IFN- γ in formation of ISGF3 and gene induction in certain cell lines such as HeLa cells. Purified ISGF3 contains four proteins: ISGF3 γ (the 48-kDa DNA-binding component), which has no ability to initiate transcription, and three ISGF3 α proteins of 84, 91 and 113 kDa, which associate with ISGF3 γ and increase its affinity for the ISRE (Fu *et al.*, 1990). All components of ISGF3 have been purified and the cDNAs have been obtained. Deletion analysis of the cloned ISGF3 γ protein revealed two domains in the protein: an N-terminal region that mediates protein-DNA interaction and a C-terminal region that is required for protein-protein interaction with the ISGF3 α peptides (Veals *et al.*, 1993). The DNA-binding region was identified as the target of alkylation by NEM and shares structural similarity with Interferon Regulatory Factor IRF1, IRF2, IFN consensus sequence binding protein and *c-myc* (Veals *et al.*, 1992). ISGF3 γ , as well as IRF1, require phosphorylation on Ser/Thr residues for their DNA-binding properties, as demonstrated by the loss of DNA-binding activity after treatment with phosphatase (Veals *et al.*, 1993), but the phosphorylation is constitutive and not induced by IFN. After ISGF3 α was cloned, sequence comparison not only revealed that the 84-kDa and the 91-kDa polypeptides were splicing products from the same gene (Schindler *et al.*, 1992a), but they also displayed 42% identity with the 113-kDa component that is clearly derived from a different gene (Fu, 1992). All three proteins contain conserved src-homology region 2 (SH2) and 3 (SH3) domains (Fig. 2) found predominantly in src-related proteins, which indicated the possible involvement of phosphorylation in the association and activation of ISGF3 α (Fu, 1992).

2.1.4. Mechanism of Action

Early studies on activation of the ISGF3 transcription factor complex not only focused on the classical second messengers such as cAMP, cytosolic Ca²⁺ or phosphoinositols (Hannigan and Williams, 1991; Larner *et al.*, 1984; Lew *et al.*, 1989), but also explored the possibility of protein phosphorylation (Bandyopadhyay and Sen, 1992; Benveniste *et al.*, 1991; Fan *et al.*, 1988; Kessler and Levy, 1991). Unfortunately, these experiments were based mainly on the use of inhibitors whose specificity is somewhat unclear. Therefore, very contradictory results were obtained using the protein kinase C inhibitor, staurosporine, which was able to block formation of ISGF3, leading to the suggestion of a protein kinase C-mediated event (Benveniste *et al.*, 1991; Fan *et al.*, 1988). Nevertheless, even cells that were depleted of protein kinase C by prolonged treatment with phorbol esters could still form ISGF3 in response to IFN (Kessler and Levy, 1991). Using the kinase inhibitors staurosporine and genistein in combination with immunoprecipitation of the proteins of ISGF3, phosphoamino acid analysis and Western blots, it was demonstrated that all three ISGF3 α polypeptides became tyrosine-phosphorylated after IFN treatment of cells (David *et al.*, 1993; Fu, 1992; Gutch *et al.*, 1992; Schindler *et al.*, 1992a). At the same time, the first *in-vitro* system for IFN signaling was developed that allowed activation of ISGF3 in a cell-free environment by adding IFN- α to a cell homogenate (David and Larner, 1992). With this system, fractionation of the cell lysate indicated that a membrane fraction alone was sufficient to activate ISGF3 α . Immunoprecipitations, phosphotyrosine blots and treatment of assembled ISGF3 with a tyrosine phosphatase proved that IFN-induced tyrosine phosphorylation is the mechanism of ISGF3 activation (David *et al.*, 1993; Fu, 1992; Gutch *et al.*, 1992; Schindler *et al.*, 1992b). In addition, it was found that a membrane-associated tyrosine phosphatase is required prior to the tyrosine kinase activity for ISGF3 assembly (David *et al.*, 1993). Interestingly, Velazquez *et al.* (1992) found by complementation of deletion mutants defective in IFN signaling (Pellegrini *et al.*, 1989) that the tyk2 tyrosine kinase was required for ISGF3 activation. Tyk2 contains in the C-terminal domain a sequence that is

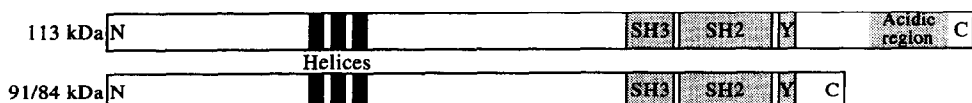


Fig. 2. Structure and functional elements of the ISGF3 α proteins (Fu, 1992).

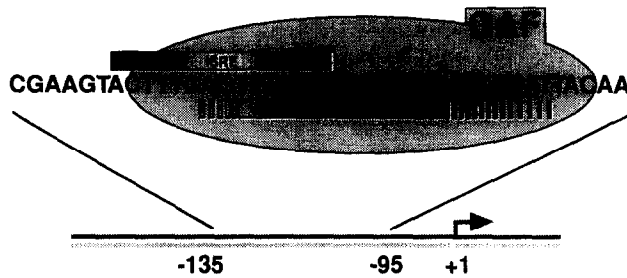


Fig. 3. Structure of the GAF binding region (Decker *et al.*, 1991a).

homologous to *c-src* in the region around tyrosine 527, the regulatory tyrosine phosphorylation site (Firmbach-Kraft *et al.*, 1990). The *tyk2* deletion mutant was also found to possess only low affinity receptors for IFN- α . It is still unclear whether *tyk2* is actually the kinase phosphorylating the ISGF3 α polypeptides or functions to maintain a high affinity receptor (Velazquez *et al.*, 1992).

2.2. γ -IFN Activation Factor

Compared with the fairly detailed understanding of the activation of IFN- α -induced early response genes and the transcription factors involved, much less is known about the IFN- γ -regulated gene expression. The first early response gene whose induction by IFN- γ was described in detail with respect to the responsible transcription factors was the gene encoding the 67-kDa Guanylate Binding Protein or GBP.

2.2.1. DNA Binding Region

Among the genes activated by IFN- γ that show the characteristics of an early response gene is the one encoding a cytoplasmic GBP (Decker *et al.*, 1989; Lew *et al.*, 1989). Activation of the GBP gene by both IFN- α and IFN- γ was first described by Cheng *et al.* (1983, 1986), and the transcriptional regulation investigated in detail by Decker *et al.* (1989, 1991a) with respect to the IFN species responsible for activation. Although the induction of the GBP gene was equally strong, rapid and protein synthesis-independent with both types of IFN, a clear difference was found in the transcriptional rate of decline. After IFN- α stimulation the GBP gene in fibroblasts behaved like the earlier described IFN-stimulated genes, returning to the basal transcription level after approximately 6 hr. However, IFN- γ induction of the gene remained transcriptionally active for more than 24 hr, not affected by the protein synthesis-dependent mechanism that actively shut off transcription after IFN- α stimulation (Decker *et al.*, 1989; Lew *et al.*, 1989). Sequences responsible for the induction of the GBP gene by both types of IFN were mapped to a 25-bp region from -130 to -101 of the GBP promoter (Lew *et al.*, 1991). Sequence comparison displayed an ISRE region from -130 to -116 , deletion of which completely abrogated the inducibility by IFN- α , but still allowed activation by IFN- γ , although to a much lower extent. Further mutational analysis proved the existence of another element between -125 and -101 , termed γ -IFN Activation Sequence or GAS, which is also necessary for full induction by IFN- γ (Fig. 3). Therefore, both the ISRE and the GAF region are required for full response towards IFN- γ (Lew *et al.*, 1991; Strehlow and Decker, 1992).

2.2.2. Components of γ -IFN Activation Factor and Mechanism of Action

Based on the knowledge of the sequence necessary for IFN induction of the GBP gene, Decker *et al.* (1991a) were successful in their search for a DNA-binding protein that specifically associated with this region after treatment of cells with IFN- γ . This DNA binding factor was called GAF for *Gamma Interferon Activation Factor* (Decker *et al.*, 1991a,b). Similar to the formation of ISGF3 through IFN- α , the activation of GAF is rapid and protein synthesis independent, therefore providing a suitable model to investigate the transcriptional regulation of IFN- γ -induced genes (Decker *et al.*, 1991a,b). GAF activation, like ISGF3, is based on ligand-binding to a cell-surface receptor, leading to the rapid modification of a latent precursor in the cell membrane and cytoplasm,

which translocates to the nucleus and binds DNA. Using an *in-vitro* activation system, Igarashi *et al.* (1993a) showed that GAF's binding to DNA, similar to ISGF3, requires a tyrosine kinase, and that a tyrosine phosphatase is needed prior to the kinase activity. It is still unclear whether the kinase is activated by the phosphatase — as *c-src* is — or if another element in the activation cascade, e.g. the receptor, is the substrate to be dephosphorylated. Recently, Shuai *et al.* (1992) demonstrated that the 91-kDa component of ISGF3 α also is activated by IFN- γ , and binds to the GAS enhancer. Phosphopeptide mapping of IFN- γ activation of the 91-kDa protein displayed the same tyrosine phosphorylation pattern as activation by IFN- α . Whether the 91-kDa protein is the only component of GAF requires further exploration, but it seems likely that the GAF transcription factor is also a multi-protein complex, as multiple bands appear to be induced in a band shift assay (Igarashi *et al.*, 1993a).

Additionally, Decker *et al.* suggested the existence of another, IFN- α -induced DNA-binding protein they termed α -IFN Activation Factor or AAF, which required the GAS sequence element in combination with the ISRE for DNA binding and, therefore, is different from ISGF3. The distinction between GAF and AAF was based mainly on the different sensitivity of their activation towards a variety of kinase inhibitors (Decker *et al.*, 1991a). No further information on AAF has been presented.

2.3. γ -IFN Response Region Binding Factors (FcRF γ s)

2.3.1. DNA Binding Region (GRR) and Components of FcRF γ s

One of the early response genes that is rapidly activated in cells of the myelomonocytic lineage upon IFN- γ treatment encodes the high affinity Fc γ receptor that binds the conserved Fc-region of immunoglobulin G (Cassatella *et al.*, 1991). IFN- γ inducibility of the high affinity Fc receptor was first described by Perussia *et al.* (1983). Pearse *et al.* (1991) reported the genomic organization of the gene, including the characterization of a *cis*-acting element within the promoter region responsible for IFN- γ induction. This 39-bp region, termed the Gamma Response Region or GRR, was found to be necessary for IFN- γ induction of the gene. The GRR contains several elements named X-box, H-box and γ -IFN response element (Fig. 4), which were initially found in the promoter region of the major histocompatibility complex (MHC) class II gene (Benech *et al.*, 1992; Pearse *et al.*, 1991). Notably, the 9-bp core region of the GRR contains sequence homology to the GAS elements of the GBP and monokine induced by IFN- γ gene, suggesting a common element that confers IFN- γ inducibility (Pearse *et al.*, 1991).

An overview of the IFN receptor-signal pathways is shown in Fig. 5.

Another regulatory domain in the Fc receptor gene is located within the promoter 25-bp downstream of the GRR named myeloid-activating transcription element (Perez *et al.*, 1993). This region seems to account for the restricted, tissue-specific induction of the Fc receptor by binding a protein complex that is constitutively expressed only in cells of myelomonocytic origin.

2.3.2. Components of FcRF γ s and Mechanism of Action

Using the GRR as a probe in electrophoretic mobility shift assays, Wilson and Finbloom (1992) demonstrated that new DNA-binding protein complexes were formed after treatment of peripheral blood monocytes with IFN- γ . These DNA-binding factors, termed FcRF γ 1 and FcRF γ 2, were

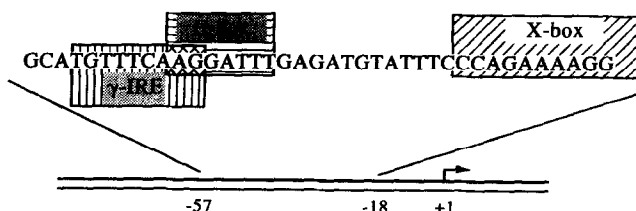


Fig. 4. Structure of the FcRF γ binding region (Pearse *et al.*, 1991).

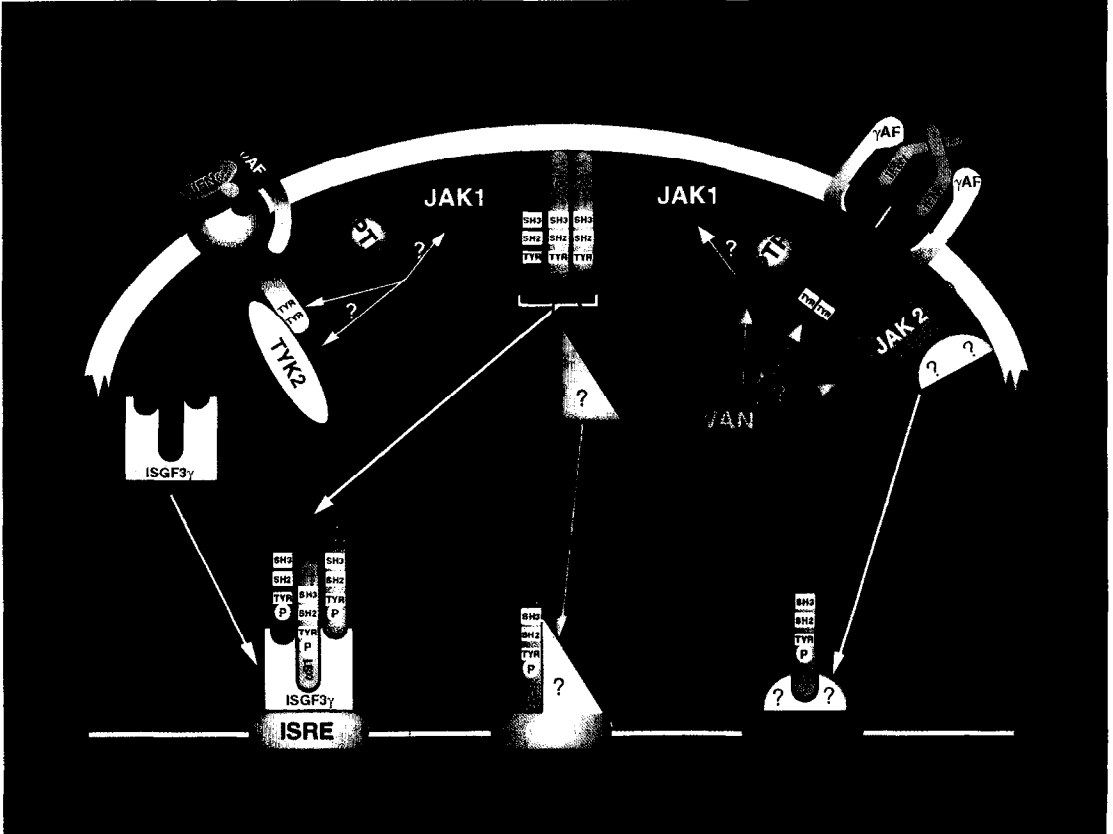


Fig. 5. Summary of activation and common elements of IFN-induced transcription factors.

rapidly induced in the presence of protein synthesis inhibitors and are resistant to treatment with NEM. Inhibition of activation by the kinase inhibitor staurosporine suggested phosphorylation of at least one of the components to be the activating step (Wilson and Finbloom, 1992). Interestingly, DNA binding of these proteins can be induced in a variety of cells, even if they do not transcribe Fc RNA and express the Fc receptor protein (Perez *et al.*, 1993; Wilson and Finbloom, 1992). Furthermore, one of these binding proteins can also be activated in response to IFN- α (Igarashi *et al.*, 1993b; Pearse *et al.*, 1993), although this cytokine does not induce transcription of the Fc receptor gene (Cassatella *et al.*, 1991). Experiments performed to elucidate possible involvement of proteins known to be part of other IFN induced transcription factors revealed that the 91-kDa protein present in ISGF3 and GAF also participates in the formation of these GRR-binding complexes (Igarashi *et al.*, 1993b; Pearse *et al.*, 1993; Perez *et al.*, 1993). In addition, Igarashi *et al.* (1993b) could show that tyrosine phosphorylation is required for DNA binding of FcRF γ 1/2 and that only a membrane fraction is required for activation of DNA binding. Interestingly, the tyrosine phosphatase inhibitor ortho-vanadate was found to activate FcRF γ 1/2 directly without the necessity of IFN binding to its receptor (Igarashi *et al.*, 1993b). It is still unclear what other proteins participate in the formation of the FcRF γ 1/2 complexes, although DNA-protein cross-linking indicated the presence of a 43-kDa DNA-binding component (Igarashi *et al.*, 1993b).

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