THE HUMAN INTERFERON SYSTEM: CHARACTERIZATION AND CLASSIFICATION AFTER DISCOVERY OF NOVEL MEMBERS

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Received October 13, 2003; accepted November 13, 2003

Summary. – The human interferon (IFN) system is the best characterized of all animal IFN systems. Until recently it is thought that all IFNs and IFN-related genes and proteins have been discovered. However, in the last three years, the discovery and characterization of IFNs including IFN-epsilon (IFN-ε), IFN-kappa (IFN-κ) and a novel IFN-lambda (IFN-λ) family, in particular, substantially changed this opinion. In this article, we attempt to review recent developments in the field of interferon discovery and present an overview of current classification of the human IFN system. Characterization of the constituent parts of the human IFN system including ligands, receptors and players involved in the signal transduction pathway are discussed.

Key words: cytokine; dsRNA IFN family; IFN gene; IFN ligand; IFN polypeptide; IFN receptor; IFN signaling; IFN subgroup; IFN type; IFNAR; IFNGR; IFNLR; JAK-STAT; signal transduction

Introduction

IFNs are a distinct group of cytokines exhibiting pleiotropic activity generally categorized as antiviral, antiproliferative and immunomodulatory (reviewed by Pestka *et al*., 1987). Originally identified for their ability to induce cellular resistance to viral infection, IFNs are currently known to be potent mediators in the host defense mechanism and homeostasis, modulating both the innate and adaptive immune responses (Biron, 2001; Le Bon and Tough, 2002). IFNs are small, inducible 20–25 K, usually glycosylated proteins that are produced by vertebrate cells in response to various biological stimuli. In addition to viruses, a vast array of biomolecules, including bacteria, protozoa, certain cytokines, mitogens, natural and synthetic double-stranded RNA (dsRNA) and perhaps other known substances (De Maeyer and DeMaeyer-Guignard, 1988), are IFN inducers. Mechanistically, IFNs mediate their biological activities by binding to receptors present on the surface of target cells. Specific ligand-receptor interactions trigger intracellular signaling cascade downstream, resulting in the synthesis of proteins that mediate mentioned pleiotropic activities (reviewed by Pestka *et al*., 1987; Stark *et al*., 1998).

On a broad outline, IFNs are classified into two groups: type I or type II, based on their structure, physicochemical properties and biological activities (reviewed by Kontsek and Kontseková, 1997). In mammals, eight families of type I IFN have been described. These are: IFN-α, IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-λ, IFN-ω and IFN-tau (IFN-τ). Among these families, trophoblast IFN-τ, found only in ruminant ungulates, is not inducible by virus and is produced in the embryonic trophoectoderm at a specific time, early during pregnancy. Its major function is to create conditions for the completion of pregnancy (Roberts *et al*., 1999). IFN-δ (delta), a polypeptide of about 149 amino acids, has been described only in pigs. This IFN is physiologically expressed by trophoblast during the period of implantation in uterus (Lefevre and Bulay, 1993). In mice, a type I IFN-like molecule, limitin, has been detected (Oritani *et al*., 2000). Limitin exhibits an about 30% amino acid identity with murine and human IFNs-α, β, and ω and displays its biological functions (antiviral, antiproliferativre and

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Abbreviations: IFN = interferon; IL = interleukin

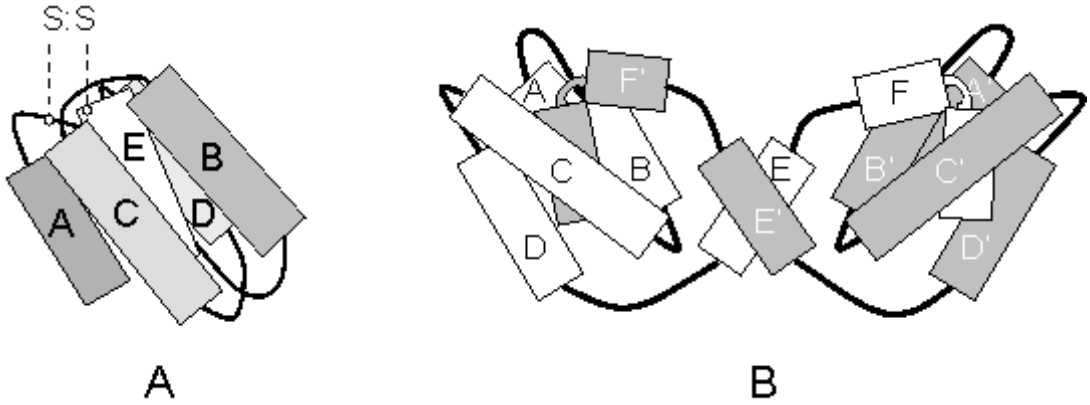

Fig. 1
3D structure of type I and type II IFNs

A. Conformation of type I IFNs formed by a bundle of five long α-helices A–E. The position of the disulfide bond connecting the AB loop with the E helix, a hallmark of type I IFNs, is indicated.
B. Conformation of type II IFNs formed by antiparallel assembly of two subunits, each composed of six short α-helices A-F and A'–F", respectively.

immunomodulatory) through the type I IFN receptor. Homolog (ortholog) of limitin has not been found in other animal species.

The type I IFN likely diverged from a common ancestral gene through mechanisms involving gene duplication (Miyata *et al*., 1985). IFN-γ is the sole representative of type II IFN in mammals. Interestingly, type I IFNs have no significant structural homology at the gene or protein level (reviewed by Epstein, 1984). However, both type I and type II IFNs exert their biological effects through different cellular receptors (Branca and Baglioni, 1981).

Structural and physicochemical differences between type I and type II IFNs

Structurally, type I and type II IFNs represent distinct conformations of α-helical globular proteins (Mitsui *et al*., 1993). At the amino acid level, type I IFNs (except for IFN-λ) show about 25–30% identity. The region of identity determines identical folding topology of their polypeptide chains as shown in the crystal structures of murine IFN-β, human IFN-α2, human IFN-β and ovine IFN-λ (Senda *et al*., 1995; Radhakrishnan *et al*., 1996, 1999; Karpusas *et al*., 1997). Type I IFNs share a common structural framework, which corresponds to a bundle of five long and nearly parallel α-helices (Fig. 1A). The pH 2-stable type I IFNs are biologically active in monomeric forms.

On the other hand, the conformation of bioactive type II IFN is quite different as revealed in X-ray crystallography studies of human IFN-γ (Ealick *et al*., 1991). The polypeptide of IFN-γ consists of six short α-helices. To exert biological activity, two monomers have to associate in an antiparallel fashion to form a homodimer (Fig. 1B). Homodimerization contributes to the labile nature of type II IFN, because the homodimeric forms dissociate upon acidification (Kontsek *et al*., 2000). The overall topology of the helices in IFN-γ and their quaternary rearrangement (homodimer) strongly resemble that of IL-10, and demonstrate the close relationship between these cytokines (Frickenscher *et al*., 2002).

Differences in induction and biological potency between type I and type II IFNs

In general, type I IFNs are induced in all nucleated cells by viruses or ds-RNA, and are the main cytokines involved in innate immune responses during viral infections. In addition type I IFNs are involved in a variety of other physiological responses. They exhibit antiproliferative activity, stimulate cytotoxic activity of natural killer cells, and modulate cellular differentiation and apoptosis. Type I IFNs also modulate the adaptive immune response by stimulating the expression of major histocompatibility complex class I (MHC I) molecules, thereby promoting antigen presentation to cytotoxic T cells (De Maeyer and DeMaeyer-Guignard, 1988; Marrack *et al*., 1999). Apparently, each of the type I IFN species exhibits a different pattern of receptor interactions that determine differences in the spectra of their biological activities (reviewed by Kontsek, 1994).

The induction of type II IFN (IFN-γ) is mediated by immune (interleukins, antigens, mitogens) and inflammatory stimuli, but not directly by viruses. It is synthesized by T lymphocytes and natural killer cells. However, production

Table 1. Classification and basic characteristics of human IFNs

IFN	Type Ia					Type Ib	Type II
	IFN-α	IFN-β	IFN-ω	IFN-κ	IFN-ε	IFN-λ	FN-γ
Functionalgenes	13	1	1	1	1	3	1
Locus	9p22	9p22	9p22	9p21.2	9p21.2	19q13.13	12q14.1
Exons	1	1	1	1	ND	5(λ1)/6	4
Mature protein	166	166	172	180	187	175	143
(amino acids)	(α2–165)		(174)			(λ1-179)	
Glycosylation	subtypes	yes	yes	no	potential	potential	yes
	α2 (Thr106)	Asn80	Asn78		Asn74	Asn44	Asn25
	α14 (Asn72)				Asn83	(λ1)	Asn97
M_r (predicted)	19.2–19.7 K	20 K	20 K	25.2 K	24 K	22 K	17 K
M_r (natural)	23 K	23 K	24.5 K	ND	ND	ND	20–25 K
Receptor	IFNAR	IFNAR	IFNAR	IFNAR	ND	IFNLR	IFNGR

ND = not determined.

of IFN-γ by macrophages and dendritic cells has been reported recentby (reviewed by Frucht *et al.*, 2001). IFN-γ promotes both innate and acquired mechanisms of host defense against infectious agents and tumors. Like type I IFNs, IFN-γ can protect cells from viral infection and can exert profound antiproliferative effect on cells. However, compared to type I IFNs, IFN-γ seems to be more involved in immunomodulatory functions, including the activation of macrophages and regulation of the production of other cytokines like IL-12 and TNF. IFN-γ is also one of a few natural immunoregulators responsible for upregulating expression of MHC II molecules, thus regulating specific antibody responses. IFN-γ also regulates humoral immune responses by affecting IgG heavy chain switching (reviewed by Farrar and Schreiber, 1993; Billiau, 1996; Boehm *et al*., 1997).

It is well documented that type I and type II IFNs exert their biological activities on target cells through distinct cellular receptors (Branca and Baqlioni, 1981), suggesting that they regulate distinct pathways.

Human IFN system

Basically, the IFN system comprises of ligands (IFNs) and their cellular membrane receptors. Intracellular proteins involved in signaling cascades from activated receptors to the responding genes in the nucleus can be considered components of the IFN system. These proteins include tyrosine kinases of the Janus family (Jak) and signal transducing proteins of the signal transduction and activators of transcription (STAT family). However, these intracellular proteins are also involved in other pathways modulated by other distinct classes of cytokines (reviewed by Darnell *et al*., 1994). At the end of the 20th century it was thought that all members of the human IFN family and their receptors have been discovered, with the corresponding genes mapped. At the dawn of the new millennium, there were new findings about the human IFN system. In *silico* analysis of substantial amounts of data from human genome sequencing led to the identification of new members of type I IFNs, namely IFN-κ and IFN-ε (LaFleur *et al*., 2001; Conklin *et al*., 2002). Perhaps the most interesting was the discovery of a novel family of type I IFN, designated IFN-λ (or IL-28A/B, IL-29), as well as their receptors (Sheppard *et al*., 2003; Kotenko *et al*., 2003). In this review we present an update on the classification of the human IFN system and briefly discuss the characterization of constituent members including ligands, receptor chains and components of signal transduction cascade.

Ligands

In humans, excluding pseudogenes, there are 21 functional non-allelic genes encoding for different IFN species. 20 genes encode type I IFNs: 13 subtypes of IFN-α family, three species of IFN-λ family and single species of IFN-β, ω, ε, κ. With the exception of IFN-λ all genes for type I IFN are clustered on chromosome 9 in the human genome. Genes for IFN-λs are clustered on chromosome 19 (Diaz *et al*., 1994; Kotenko *et al*., 2003). The single gene determining the type II IFN-γ is located on chromosome 12 (Zimonjic *et al*., 1995). Table 1 summarizes the basic characteristics of genes and proteins of all human IFN classes.

The human type I IFNs are placed into six major classes: α, β, ε, κ, λ, and ω. Both IFN-τ and IFN-δ are not found in the human IFN system. The evolutionary conservation of type I IFN genes (except for IFN-λs) is reflected in their common intron-less structure, a rare occurrence in eukaryotic nuclear genes. Moreover, the genes are clustered on the short arm of chromosome 9 (Fig. 2). At the protein level human IFN-α, -β, -ε, -κ, -ω exhibit about 30% amino acid

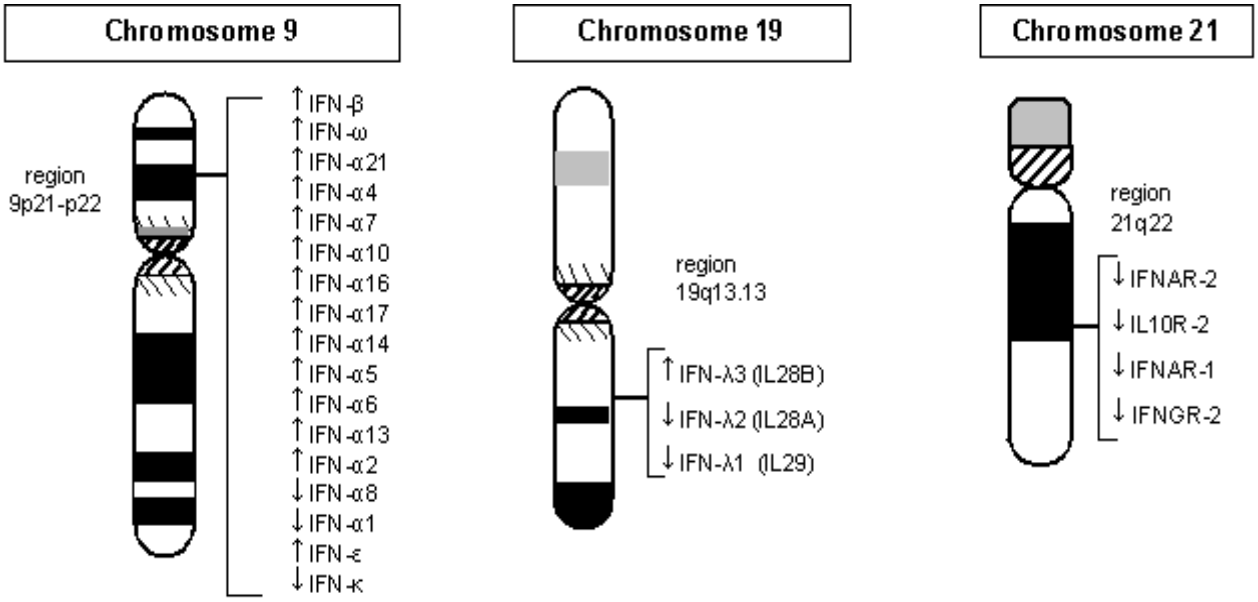

Fig. 2
Chromosomal location of genes for human type I IFNs and their receptors
The direction of transcription is indicated by arrows. The idiograms of human chromosomes were generated from the NCBI database.

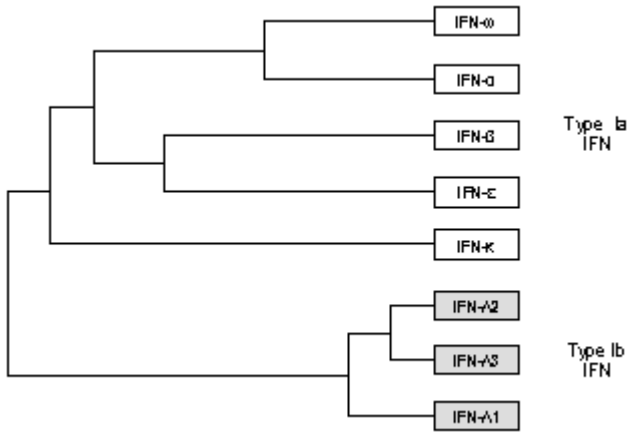

Fig. 3
A phylogenetic tree of human type I IFNs
Adapted from Kotenko *et al*. (2003).

identity. These human type I IFNs recognize the same receptor and utilize the same signal transducing pathway.

IFN-λ is structurally and evolutionarily less related to other type I IFNs. Unlike the genes encoding other type I IFNs, the genes encoding IFN-λ contain introns and are located on chromosome 19. Mature proteins of IFN-λ family exhibit only about 17% amino acid identity with other IFN type I species. Predictive methods indicate that IFN-λs are helical proteins but their conformation has not been resolved. Another distinguishing feature of IFN-λ from other type I IFN is the utilization of a distinct cellular receptor different from that used by other type I IFNs. Therefore we suggest a division of type I IFNs into subgroups designated Ia (comprising families α, β, ε, κ, ω) and Ib (IFN-λ family). A predicted phylogenetic evolution (Fig. 3) suggests evolutionary relatedness among classes of human type I IFN.

IFN-α family

The human IFN-α family is represented by a group of related subtypes, encoded by a multigene family comprising 13 genes (Fig. 2). Two of these genes, IFN-A1 and IFN-A13, have identical coding sequences and produce a single protein species (Weissmann and Weber, 1986) designated IFN-α1 or IFN-α13. Mature proteins of the IFN-α family are made of 166 amino acids, except for subtype α2 which lacks an amino acid at position 44 (Fig. 4). At the protein level, there is 79–95% identity in the primary structure of human IFN-α species (Kontsek, 1994).

Among the 13 non-allelic IFN-α genes, a total of 28 different sequence variants have been described (Diaz *et al*., 1996). Known variants of subtypes IFN-α1, α2, α4, α7, α8, α10, α14, α17 and α21 differ from each other in one to four amino acid positions (Table 2) (Allen and Diaz, 1996). So far only variants 2b and 2c of subtype IFN-α2 have been shown to be allelic variants, 2b being the predominant allele and 2c

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                    10         20         30         40
IFNα1a/α13 CDLPETHSLD NRRTLMLLAQ MSRISPSSCL MDRHDFGFPQ EEFDGNQFQK
IFNα2b     CDLPQTHSLG SRRTLMLLAQ MRRISLFSCL KDRHDFGFPQ EEF.GNQFQK
IFNα4b     CDLPQTHSLG NRRALILLAQ MGRISHFSCL KDRHDFGFPE EEFDGHQFQK
IFNα5      CDLPQTHSLS NRRTLMIMAQ MGRISPFSCL KDRHDFGFPQ EEFDGNQFQK
IFNα6      CDLPQTHSLG HRRTMMLLAQ MRRISLFSCL KDRHDFRFPQ EEFDGNQFQK
IFNα7a     CDLPQTHSLR NRRALILLAQ MGRISPFSCL KDRHEFRFPE EEFDGHQFQK
IFNα8b     CDLPQTHSLG NRRALILLAQ MRRISPFSCL KDRHDFEFPQ EEFDDKQFQK
IFNα10a    CDLPQTHSLG NRRALILLGQ MGRISPFSCL KDRHDFRIPQ EEFDGNQFQK
IFNα14c    CNLSQTHSLN NRRTLMLMAQ MRRISPFSCL KDRHDFEFPQ EEFDGNQFQK
IFNα16     CDLPQTHSLG NRRALILLAQ MGRISHFSCL KDRYDFGFPQ EVFDGNQFQK
IFNα17b    CDLPQTHSLG NRRALILLAQ MGRISPFSCL KDRHDFGLPQ EEFDGNQFQK
IFNα21b    CDLPQTHSLG NRRALILLAQ MGRISPFSCL KDRHDFGFPQ EEFDGNQFQK
                   60         70         80         90        100
IFNα1a/α13 APAISVLHEL IQQIFNLFTT KDSSAAWDED LLDKFCTELY QQLNDLEACV
IFNα2b     AETIPVLHEM IQQIFNLFST KDSSAAWDET LLDKFYTELY QQLNDLEACV
IFNα4b     TQAISVLHEM IQQTFNLFST EDSSAAWEQS LLEKFSTELY QQLNDLEACV
IFNα5      AQAISVLHEM IQQTFNLFST KDSSATWDET LLDKFYTELY QQLNDLEACM
IFNα6      AEAISVLHEV IQQTFNLFST KDSSVAWDER LLDKLYTELY QQLNDLEACV
IFNα7a     TQAISVLHEM IQQTFNLFST EDSSAAWEQS LLEKFSTELY QQLNDLEACV
IFNα8b     AQAISVLHEM IQQTFNLFST KDSSAALDET LLDEFYIELD QQLNDLESCV
IFNα10a    AQAISVLHEM IQQTFNLFST EDSSAAWEQS LLEKFSTELY QQLNDLEACV
IFNα14c    AQAISVLHEM MQQTFNLFST KNSSAAWDET LLEKFYIELF QQMNDLEACV
IFNα16     AQAISAFHEM IQQTFNLFST KDSSAAWDET LLDKFYIELF QQLNDLEACV
IFNα17b    TQAISVLHEM IQQTFNLFST EDSSAAWEQS LLEKFSTELY QQLNNLEACV
IFNα21b    AQAISVLHEM IQQTFNLFST KDSSATWEQS LLEKFSTELN QQLNDLEACV
                  110        120        130        140        150
IFNα1a/α13 MQEERVGETP LMNADSILAV KKYFRRITLY LTEKKYSPCA WEVVRAEIMR
IFNα2b     IQGVGVTETP LMKEDSILAV RKYFQRITLY LKEKKYSPCA WEVVRAEIMR
IFNα4b     IQEVGVEETP LMNVDSILAV RKYFQRITLY LTEKKYSPCA WEVVRAEIMR
IFNα5      MQEVGVEDTP LMNVDSILTV RKYFQRITLY LTEKKYSPCA WEVVRAEIMR
IFNα6      MQEVWVGGTP LMNEDSILAV RKYFQRITLY LTEKKYSPCA WEVVRAEIMR
IFNα7a     IQEVGVEETP LMNEDFILAV RKYFQRITLY LMEKKYSPCA WEVVRAEIMR
IFNα8b     MQEVGVIESP LMYEDSILAV RKYFQRITLY LTEKKYSSCA WEVVRAEIMR
IFNα10a    IQEVGVEETP LMNEDSILAV RKYFQRITLY LIERKYSPCA WEVVRAEIMR
IFNα14c    IQEVGVEETP LMNEDSILAV KKYFQRITLY LMEKKYSPCA WEVVRAEIMR
IFNα16     TQEVGVEEIA LMNEDSILAV RKYFQRITLY LMGKKYSPCA WEVVRAEIMR
IFNα17b    IQEVGMEETP LMNEDSILAV RKYFQRITLY LTEKKYSPCA WEVVRAEIMR
IFNα21b    IQEVGVEETP LMNVDSILAV KKYFQRITLY LTEKKYSPCA WEVVRAEIMR
                  160
IFNα1a/α13 SLSLSTNLQE RLRRKE
IFNα2b     SFSLSTNLQE SLRSKE
IFNα4b     SLSFSTNLQK RLRRKD
IFNα5      SFSLSANLQE RLRRKE
IFNα6      SFSSSRNLQE RLRRKE
IFNα7a     SFSFSTNLKK GLRRKD
IFNα8b     SFSLSINLQK RLKSKE
IFNα10a    SLSFSTNLQK RLRRKD
IFNα14c    SLSFSTNLQK RLRRKD
IFNα16     SFSFSTNLQK GLRRKD
IFNα17b    SLSFSTNLQK ILRRKD
IFNα21b    SFSLSKIFQE RLRRKE
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Fig. 4
Primary structure of mature proteins of human IFN-α family
Amino acid sequences from the Swiss-Prot database.

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                    10         20         30         40         50
IFNα2b      CDLPQTHSLG SR-RTLMLLA QMRRISLFSC LKDRHDFGFP QEEF-GNQFQ
IFNω   (LG) CDLPQNHGLL SR-NTLVLLH QMRRISPFLC LKDRRDFRFP QEMVKGSQLQ
IFNβ    MS  YNLLGFLQRS SNFQCQKLLW QLNGRLEY-C LKDRMNFDIP EEIKQLQQFQ
IFNε    LD  LKLIIFQQRQ VNQESLKLLN KLQTLSIQQC LPHRKNFLLP QKSLSPQQYQ
IFNκ    LD  CNLLNVHLRR VTWQNLRHLS SMSNSFPVEC LRENIAFELP QEFLQYTQPM

                    60         70         80         90         100
IFNα2b      KAETIPVLHE MIQQIFNLFS TKDSSAAWDE TLLDKFYTEL YQQLNDLEAC
IFNω        KAHVMSVLHE MLQQIFSLFH TERSSAAWNM TLLDQLHTGL HQQLQHLETC
IFNβ        KEDAALTIYE MLQNIFAIFR QDSSSTGWNE TIVENLLANV YHQINHLKTV
IFNε        KGHTLAILHE MLQQIFSLFR ANISLDGWEE NHTEKFLIQL HQQLEYLEAL
IFNκ        KRDIKKAFYE MSLQAFNIFS Q-HTFKYWKE RHLKQIQIGL DQQAEYLNQC

                    110        120        130        140        150
IFNα2b      VIQGVGVTET PLMKE----- ---------- DSILAVRKYF QRITLYLKEK
IFNω        LLQVVGEGES AGAIS----- ---------- SPALTLRRYF QGIRVYLKEK
IFNβ        LEEKLEKEDF TRGKL----- ---------- MSSLHLKRYY GRILHYLKAK
IFNε        MGLEAEKLSG TLGSD----- ---------- NLRLQVKMYF RRIHDYLENQ
IFNκ        LEEDENENED --MKEMKENE MKPSEARVPQ LSSLELRRYF HRIDNFLKEK

                    160        170        180        190        200
IFNα2b      KYSPCAWEVV RAEIMRSFSL STNLQESLRS KE
IFNω        KYSDCAWEVV RMEIMKSLFL STNMQERLRS KDRDLGSS
IFNβ        EYSHCAWTIV RVEILRNFYF INRLTGYLRN
IFNε        DYSTCAWAIV QVEISRCLFF VFSLTEKLSK QGRPLNDMKQ ELTTEFRSPR
IFNκ        KYSDCAWEIV RVEIRRCLYY FYKFTA-LFR RK
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Fig. 5
Primary structure of human type Ia IFNs

Amino acid sequences from the Swiss-Prot database, the sequence of IFN-ε from Conklin *et al*. (2003). Two variants of IFN-ω differ in the presence or absence of the first two N-terminal amino acids LG.

Table 2. Protein variants of human IFN-α subtypes

Gene	Protein variant	
	Major species	Minor species (difference from major species)
IFNA1	IFN-α1a	1b (A114V)
IFNA2	IFN-α2b	2c (R23K)/2a(H34R)
IFNA4	IFN-α4b	4a (T51A, V114E
IFNA5	IFN-α5	single species
IFNA6	IFN-α6	single species
IFNA7	IFN-α7a	7b (K159Q, G1513), 7c (M132T)
IFNA8	IFN-α8b	8a (98SCVM101–98VLCD101)
		8c (R161D Δ162–166)
IFNA10	IFN-α10a	10b (S8T, L89I)
IFNA13	IFN-α13	single species identical to IFN-α1a
IFNA14	IFN-α14c	14a (L152F), 14b (L152F, Q159K, R161G)
IFNA16	IFN-α16	single species
IFNA17	IFN-α17b	17a (H34P), 17c (I161R), 17d (S55P, I161R)
IFNA21'	IFN-α21b	21a (L96M)

only a minor (less than 0.1 %) allelic variant (Lee *et al*., 1995). Other reported variants of α-subtypes represent most probably non-polymorphic rare mutants that may have arisen in tumor cell lines and not present in normal human genome (Di Paola *et al*., 1994; Hussain *et al*., 1996; Nyman *et al*., 1998).

Two of the IFN-α subtypes, IFN-α2 and IFN-α14 are glycosylated. IFN-α2 is O-glycosylated at position Thr106 (Adolf *et al*., 1991). No other α-subtype contains threonine at this position. IFN-α14 is the only subtype, which is N-glycosylated at position Asn72 (Nyman *et al*., 1998).

The main natural producers of IFN-α are virus-induced peripheral blood leukocytes and hematopoetic cell lines. In particular, immature plasmatic cells were identified as a major source of IFN-α (Siegal *et al*., 1999). However, IFN-α genes are not regulated as a cohesive block, rather they show differential, subtype-specific patterns of expression. The major species produced by virus-induced leucocytes are IFN-α1/13, IFN-α2 and IFN-α8 (Nyman *et al*., 1998). At

the level of transcription, mRNAs for subtypes α1/13, α2 and α4 are most abundant (Hiscott *et al*., 1984).

The physiological significance of the large number of IFN-α subtypes remains obscure. However, individual subtypes show quantitatively distinct patterns of antiviral, antiproliferative and NK cell stimulatory activities (Pestka, 1983). In particular, subtypes α1/13 have a 20-fold to 100-fold lower specific antiviral activity, although they are one of the major IFN species produced by virally-induced blood leukocytes and lymphoblastoid cells.

Natural IFN-α and recombinant IFN-α2 are currently the human proteins most widely used for therapeutic purposes, having been approved for the treatment of various types of cancer and viral diseases (hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic myelogenous leukemia, and hepatitis B and C).

IFN-β

Human IFN-β is encoded by a single gene. The mature protein consists of 166 amino acids and shares about 30% amino acid identity with other type Ia proteins (Fig. 5). In contrast to other type Ia IFNs, IFN-β lacks a disulfide bond connecting helix A to helix C in its structure. It is N-glycosylated at a single site (Asn80) located at the C end of helix C (Karpusas *et al*., 1998). Fibroblasts induced by viruses or dsRNA molecules are the known natural producers of IFN-β. IFN-β appears to be more species-specific then IFN-α (DeMaeyer and DeMaeyer-Guignard, 1988), probably due to the carbohydrate moiety. Moreover, IFN-β can trigger the transcription of some unique genes, while IFN-α subtypes do not (Rani *et al*., 1996).

Recombinant IFN-β is used for the treatment of relapsing/remitting multiple sclerosis. The molecular mechanism underlying its therapeutic efficiency in this particular disease is unknown.

IFN-ω

There are several genes encoding members of the IFN-ω family in the human genome. To date, only one of the genes is known to express IFN-ω (Adolf *et al*., 1990).

The mature IFN-ω consists of 172 amino acids, carrying additional six amino acids at the C-terminus, compared to other type I IFNs (Fig. 5). A relatively less abundant form of IFN-ω protein resulting from an alternative cleavage of the signal peptide (23 or 21 amino acids long) and containing 174 amino acids has been described (Adolf *et al*., 1990). Natural IFN-ω is N-glycosylated at Asn79, corresponding to the glycosylated Asn80 in IFN-β. Inspite of this similarity to IFN-β in glycosylation, IFN-ω appears to be more structurally related to IFN-α2, with which it shares 61% amino acid identity (Kontsek, 1994).

IFN-ω is the major species produced by virus-induced leukocytes, and responsible for 10–15% of antiviral activity of IFNs produced by virus-induced leukocytes (Adolf *et al*., 1990).

IFN-ω is the major species produced by virus-induced leukocytes, and responsible for 10–15% of antiviral activity of IFNs produced by virus-induced leukocytes (Adolf *et al*., 1990). IFN-ω is predominantly secreted in the same cell types as IFN-alpha (blood leukocytes) as IFN-α and both have similar biological activity (Kubeš *et al*., 1994). Recombinant IFN-ω, being antigenicaly different from IFN-α2, can be used as an alternative therapeutic drug in patients showing humoral response to treatment with recombinant IFN-α2.

IFN-κ

High throughput cDNA sequencing led to the identification of IFN-κ, a new member of human type I IFN (LaFleur *et al*., 2001). The chromosomal location of the IFN-κ gene suggests that IFN-κ evolved separately from the other type Ia IFNs. The gene for IFN-κ is located on the short arm of chromosome 9, adjacent to the other type I IFN gene cluster (Fig. 2). In contrast to intronless genes for type Ia IFNs, IFN-κ gene contains an intron, although not in the coding sequence. The polypeptide of IFN-κ contains 180 amino acids and shares a 30–32% identity with other human type Ia IFNs. The most significant structural difference of IFN-κ is the length of the loop between the C and D helices where IFN-κ has an insertion of 13 amino acids (Fig. 5). IFN-κ does not contain a consensus sequence for N-linked glycosylation.

The gene for IFN-κ is selectively expressed in epidermal keratinocytes. The expression is enhanced upon viral infection or upon exposure to double-stranded RNA (dsRNA). IFN-κ has antiviral activity, however and may have other biological activities that are not yet known (LaFleur *et al*., 2001).

IFN-ε

There is only a single member of IFN-ε in human, which appears more structurally related to IFN-β (Conklin *et al*., 2002). The mature IFN-ε polypeptide contains 187 amino acids and it is the largest human type Ia IFN species. An allelic variant of IFN-ε has been identified which carries a substitution of alanine at position 56 for threonine. In comparison to other type Ia proteins, IFN-ε has an extended C-terminus. A predicted disulfide bond (Cys32-Cys140) in IFN-ε located at the top of the AB loop and at the top of helix E, respectively, is a hallmark of all human type Ia IFNs. IFN-ε lacks a disulfide bond connecting helices A and C. There are two potential N-linked glycosylation sites in IFN-ε located at Asn74 and Asn83 in the short connecting loop

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                      10         20         30         ↓          50
IFNλ1(IL29)   VPTSK---PT TTGKGCHIGR FKSLSPQELA SFKKARDALE ESLKLKNWSC
IFNλ2(IL28)   VPVARLHGAL PDARGCHIAQ FKSLSPQELQ AFKRAKDALE ESLLLKDCRC
IFNλ3(IL28B)  VPVARLRGAL PDARGCHIAQ FKSLSPQELQ AFKRAKDALE ESLLLKDCKC
IFNα2b                     CDLP- -----QTHSL GSRRTLMLLA QMRRISLFSC

                      60        ↓70         80         90         100
IFNλ1(IL29)   --SSPVFPGN WDLRLL-QVR ERP-VALEAE LALTLKVLEA AA---GPALE
IFNλ2(IL28)   --HSRLFPRT WDLRQL-QVR ERP-MALEAE LALTLKVLEA TAD-TDPALV
IFNλ3(IL28B)  --RSRLFPRT WDLRQL-QVR ERP-VALEAE LALTLKVLEA TAD-TDPALG
IFNα2b        LKDRHDFGFP QEEF-GNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWDE

                    110        120↓        130        140        150
IFNλ1(IL29)   DVLDQPLHTL HHILSQLQAC IQP-----QP TA-GPRPRGR LHHWLHRLQE
IFNλ2(IL28)   DVLDQPLHTL HHILSQFRAC IQP-----QP TA-GPRARGR LHHWLYRLQE
IFNλ3(IL28)   DVLDQPLHTL HHILSQLRAC IQP-----QP TA-GPRTRGR LHHWLYRLQE
IFNα2b        TLLDKFYTEL YQQLNDLEAC VIQGVGVTET PLMKEDSILA VRKYFQRITL

                   ↓ 160        170         180        190
IFNλ1(IL29)   APK--KESAG CLEASVTFNLF RLLTRDLKYV ADGNLCLRTS THPEST
IFNλ2(IL28)   APK--KESPG CLEASVTFNLF RLLTRDLNCV ASGDLCV
IFNλ3(IL28)   APK--KESPG CLEASVTFNLF RLLTRDLNCV ASGDLCV
IFNα2b        YLKEKKYSP- CAWEVVRAEIM RSFSLSTNLQ ESLRSKE
```

Fig. 6
Alignment of amino acid sequences of mature human IFN-λ family (the Swiss-Prot database) with human IFN-α2 (Sheppard *et al.*, 2003)
Position of introns in IFN-λs is indicated by arrows.

between helices B and C. Human IFN-β and IFN-ω have a single glycosylation site in this region.

Expression of human IFN-ε can be stimulated by typical IFN inducers such as polyinosinic -polycytidylic (polyI:C) acid (dsRNA), and also by proinflammatory cytokines like TNF and IL-1β. IFN-ε is strongly expressed in placental tissue and its expression appears to be constitutive in human coronary artery smooth muscle cells, human microvascular endothelial cells, and normal human bronchial epithelial cells (Conklin *et al*., 2002). IFN-ε exhibits antiviral and antiproliferative activities. A more detailed characterization of other biological activities of this IFN is necessary to understand its physiological relevance. The receptor for IFN-ε was has not been identified, but may be similar to the receptor for other type I IFNs.

IFN-λ family

This is a recently discovered IFN family. Three members designated IFN-λ1 (IL-29), IFN-λ2 (IL28A) and IFN-λ3 (IL-28B) have been identified (Sheppard *et al*., 2003; Kotenko *et al*., 2003). The genes encoding three non-allelic members of this family are clustered on chromosome 19 (Fig. 2) and are composed of exons, in contrast to the type Ia IFNs, which are encoded in a single exon. Kotenko *et al*. (2003) have reported that all genes of IFN-λ family have 5 exons, whereas Sheppard *et al*. (2003) have described 6 exons in the coding sequences for IFN-λ2/λ3. At the protein level there is low sequence homology to type Ia IFNs (15–19% amino acid identity) (Fig. 6). This sequence similarity is significant but lower than among even the most distant members of the type Ia IFN family. IFN-λ1 and IFN-λ2 are paralogous proteins with 81% amino acid identity. IFN-λ2 and IFN-λ3 are virtually identical, with 96% amino acid identity. IFN-λ1 contains a potential N-glycosylation site at Asn43 that is not present in IFN-λ2 or IFN-λ3 (Sheppard *et al.,* 2003; Kotenko *et al*., 2003).

The IFN-λ family represents an evolutionary link between the type I IFNs and the IL-10 family (Sheppard *et al*., 2003). At the protein level, IFN-λs are more closely related to type I IFNs than IL-10, but their genomic structure is more similar to members of the IL-10 gene family.

IFN-λs are transcribed in a wide range of human tissues (blood, brain, lung, placenta) and are induced by viruses or

```
1           11  ↓       21          31      ↓   41
QDPYVKEAEN LKKYFNAGHS DVADNGTLFL GILKNWKEES DRKIMQSQIV

51          61          71          81           91      ↓
SFYFKLFKNF KDDQSIQKSV ETIKEDMNVK FFNSNKKKRD DFEKLTNYSV

101         111         121         131         141
TDLNVQRKAI HELIQVMAEL SPAAKTGKRK RSQMLFRGRR ASQ
```

Fig. 7
Amino acid sequence of mature human IFN-γ (the Swiss-Prot database)
The location of the three introns are indicated by arrows.

polyIC (dsRNA). Like other type I IFNs, IFN-λs induce an antiviral state in cells and enhance MHC class I antigen expression, but do not display antiproliferative activity. Like other type I IFNs, IFN-λs are biologically active as monomers. However, IFN-λs exert biological effects through a receptor that is different from the receptor used by other type I IFNs.

IFN-γ

IFN-γ, the only member of human type II IFN, is structurally unrelated to type I IFNs and the mechanisms that regulate its production are also different. The IFN-γ gene is located on the long arm of chromosome 12 and contains three introns and codes for a polypeptide that is shorter than type I IFNs (Fig. 7). Polymorphic variants of IFN-γ gene carry a substitution of lysine for glutamine at position 6 (Lys6Gln) or arginine for glutamine at position 137 (Arg137Gln) (Swiss-Prot, P01579, variants 004017 and 004018, respectively). The functional unit of IFN-γ is a homodimer, in contrast to the monomeric active unit of type I IFNs. IFN-γ s acid-labile and can be rapidly inactivated at pH 2 during few minutes (reviewed by Epstein, 1984). The mature protein was originally predicted to contain 146 amino acids. However, the sequencing of natural IFN-γ revealed only 143 amino acids, lacking a predicted Cys-Tyr-Cys at the N-terminus (Devos *et al.*, 1982; Rinderknecht *et al.*, 1984). IFN-γ is N-glycosylated at two positions, Asn25 and Asn97. The carbohydrate moiety could be attached to the single or to both sites, resulting in heterogeneity of natural IFN-γ with molecular mass ranging from 17 K to 25 K (Rinderknecht *et al.*, 1984).

Whereas the production of type I IFN is most efficiently induced in many types of cells upon viral infection, IFN-γ is produced during immune responses in hemopoetic cells of lymphoid origin – T cells, NKT cells or natural killer cells – upon stimulation by specific antigens, mitogens or cytokines (IL-18), respectively. The effect of IFN-γ is highly species-specific and is mediated via the type II IFN receptor.

Receptors

IFNs trigger their biological effects after binding to their cognate receptors expressed on surfaces of target cells. All IFN receptors belong to class II cytokine receptor (CR II) family, which also contains receptors that are used for signaling by IL-10-related proteins (Bazan, 1990a). The extracellular segments of CR II class share a common

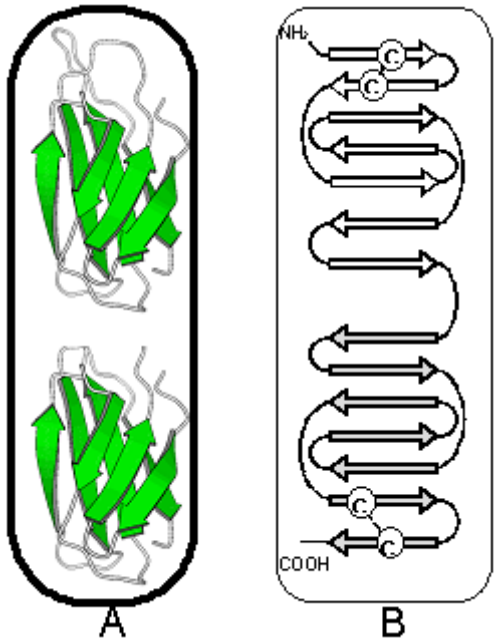

Fig. 8
Structure of a common binding domain of the class II cytokine receptors
A. The binding domain composed of two duplicated subdomains of the fibronectin III-type.
B. The folding topology of β strands in the common binding domain with indicated position of four conserved cysteins forming disulfide bonds (adapted from Bazan, 1990b).

Table 3. Basic characteristics of human IFN receptors

Ligand	Type I IFN				Type II IFN	
	IFN-α,-β,-ε,-κ,-ω		IFN-λ		IFN-γ	
Receptor	IFNAR		IFNLR		FNGR	
Chains	IFNAR-1	IFNAR-2c	IFNLR-1	IL-10R2	IFNGR-1	IFNGR-2
Locus	21Q22.11	21q22.11	1p36.11	21q22.11	6q23.3	21q22.11
Exons	11	9	7	7	7	7
Mature protein	530 aa	489 aa	502 aa	306 aa	472 aa	310 aa
Glycosylation	yes	yes	yes	yes	yes	yes
M_r (natural)	135 K	115 K	ND	60 K	90 K	61–67 K
Function	signal.	binding	binding	signal.	binding	signal.
Associated Jack	Tyk2	Jak1	ND	Tyk2	Jak1	Jak2

binding domain of about 210 amino acids with four conserved cysteins, forming disulfide bridges at both N and C termini. Within the binding domain are duplicated subdomains, which are structurally related to about 90 amino acids of fibronectin type III domain (Fig. 8). This domain consists of seven beta strands forming an antiparallel β-sandwich with a topology analogous to an immunoglobulin constant domain (Bazan, 1990b).

Human IFNs exploit three different receptors. Type I IFNs α-, β-, ω-, ε-, and κ- (designated type Ia in this review) bind to a common receptor IFNAR (Mogensen *et al*., 1999). IFN-λs (type Ib) exploit a different receptor designated here as IFNLR (Kotenko *et al*., 2003) and IFN-γ utilize a distinct receptor, IFNGR (Bach *et al*., 1997). Functional receptors are heterodimeric complexes composed of two transmembrane polypeptide chains, R1 and R2, with distinct complementary functions (Table 3). In general, one subunit has ligand-binding properties and the other has a signal-transducing role. The genes encoding components of IFN receptors contain several introns. Most of the genes for IFN receptor chains are clustered on chromosome 21 (Fig. 2). The mature IFN receptor chains have extracellular domains with about 20% amino acid identity, a transmembrane portion and a cytoplasmic segment. There is no obvious structural homology within the IFN-receptor family (Fig. 10). The evolutionary relatedness deduced from the homology of extracellular domains of IFN receptor subunits is presented in Fig. 9.

All three IFN receptor types are ubiquitously expressed across a broad range of cell types and tissues. Similar to other cytokine receptors, IFN receptors display a high degree of species specificity in ligand recognition (Pestka *et al*., 1987).

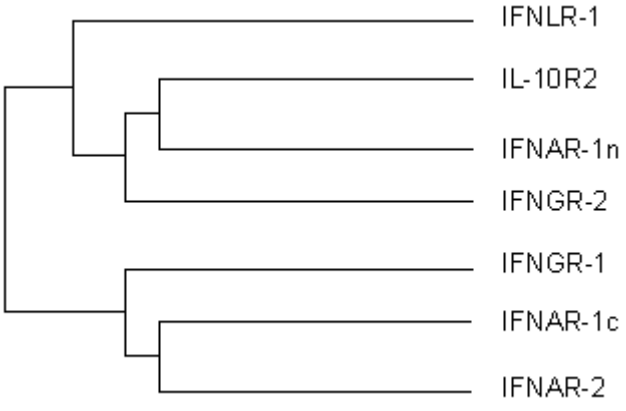

Fig. 9
Evolutionary relatedness of human IFN receptors

Phylogenetic tree generated by alignment of amino acid sequences of the extracellular receptor chain domains (adapted from Renauld, 2003). As the common class II cytokine binding domain is duplicated in IFNAR-1, the sequence of this chain is split into N-terminal IFNAR-1n (farther from the cell membrane) and C-terminal IFNAR-1c (closer to the membrane) domains.

IFNAR

The human IFNAR is used by IFN-α, -β, -ω, -κ and most probably also by IFN-ε. The receptor consists of two subunits, IFNAR-1 and IFNAR-2, which associate to form a heterodimer upon IFN binding (rewieved by Mogensen *et al*., 1999). The subunits are encoded by distinct genes located on chromosome 21 (reviewed by Pestka, 1997).

The IFNAR-1 has an apparent molecular mass 110–130 K. In comparison to other IFN receptor chains, the protein has a larger extracellular domain, resulting from duplication of the common CRII binding domain (Fig. 10). The 409 amino acids long extracellular region is composed of repeated homologous domains of about 200 amino acids (23% identical). IFNAR-1 has a short intracellular region (100 amino acids). IFNAR-1 has a very low affinity for IFNs and alone only bind one species of IFN-α (α8), but is required for signaling by all type Ia. IFNs. It enhances binding only when accompanied by its companion receptor chain

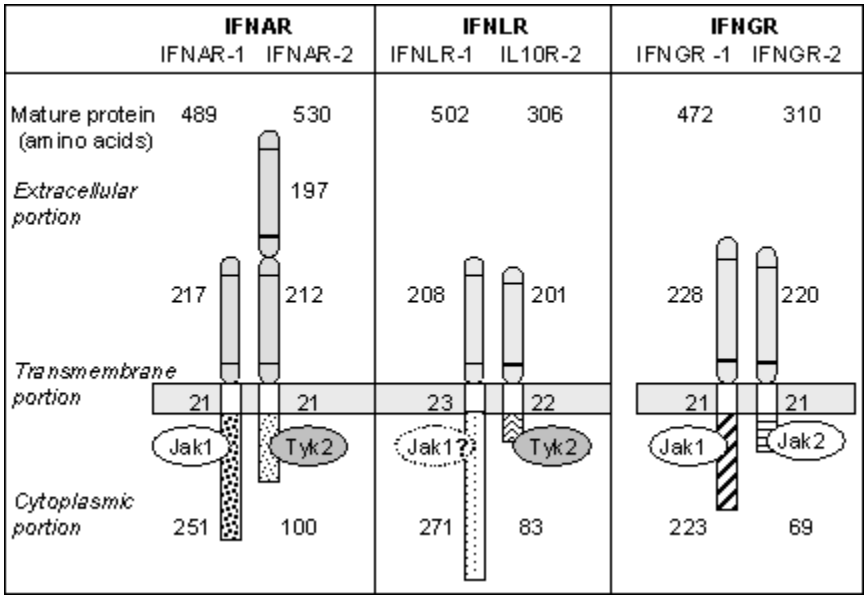

Fig. 10
Human IFN-receptors

Length of mature proteins, extracellular, transmembrane and cytoplasmic portions from the Swiss-Prot database.

(IFNAR-2). A short splice variant, IFNAR-1s, lacks the extracellular portion (Mogensen *et al*., 1999).

The second component IFNAR-2 is a transmembrane protein with a molecular mass of 55–95 K The protein alone displays a relatively high affinity for binding of IFNs and is the major ligand-binding receptor subunit (Novick *et al*., 1994). IFNAR-2 exists in three splice variant forms depending on the length of the transmembrane and intracellular region, namely IFNAR-2a (short), IFNAR-2b (soluble) and IFNAR-2c (long). The long 115 K IFNAR-2c complexes with IFNAR-1 to form a fully functional type I IFN receptor. In contrast, cytoplasmic truncated form, IFNAR-2b is unable to form a functional receptor. The soluble form of IFNAR-2b lacks a transmembrane domainand a portion of cytoplasmic domains, but has ligand binding affinity.

Some orthopoxviruses (large DNA viruses) encode functional and structural homologs of type I IFN receptor called viroceptors, which are secreted from infected cells (reviewed by Smith, 1996). For example, Vaccinia virus (WR strain) encodes a 68 K protein, B18R, composed of 574 amino acids. The C-terminal half of B18R shows low but significant homology (16% amino acid identity) with the extracellular domains of human IFNAR-1 and IFNAR-2, respectively. In contrast to species specificity of human IFNAR, viroceptor B18R is able to bind type Ia IFNs of different mammalian species with high affinity (Symmons *et al*., 1995).

IFNLR

A functional receptor complex for the IFN-λ family comprises of subunit IFNLR-1 (or CRF2-12) and IL-10R2 (CRF2-4) (Kotenko *et al*., 2003; Sheppard *et al*., 2003). IFNLR-1 (ligand-binding subunits) is specific for the lambda family, whereas the second subunit IL-10R2 is shared within the IL-10 and IL-22 receptor complexes (Kotenko, 2002). The IFNLR-1 gene is located on chromosome 1 (1p36.11), close to the gene encoding IL-22R, while the IL-10R2 gene is located on chromosome 21. The length of the IFNLR-1-intracellular domain suggests that this receptor chain represents an R1-type subunit, which associates with tyrosine kinase Jak1. A splice variant of IFNLR-1, carrying deletions of the transmembrane and intracellular domains, is a soluble form of IFNLR-1. Evolutionary relatedness of IFNLR chains with other IFN receptor chains is shown in Fig. 11.

IFNGR

The receptor for IFN-γ consists of two transmembrane chains, IFNGR-1 and IFNGR-2, encoded by genes mapped to chromosomes 21 and 6, respectively (reviewed by Bach *et al*., 1997). The IFNGR-1 chain binds the ligand, whereas the IFNGR-2 chains serve to complete the complex for signal transduction. The interaction of IFN-γ with the IFNGR-1 chain is highly species-specific.

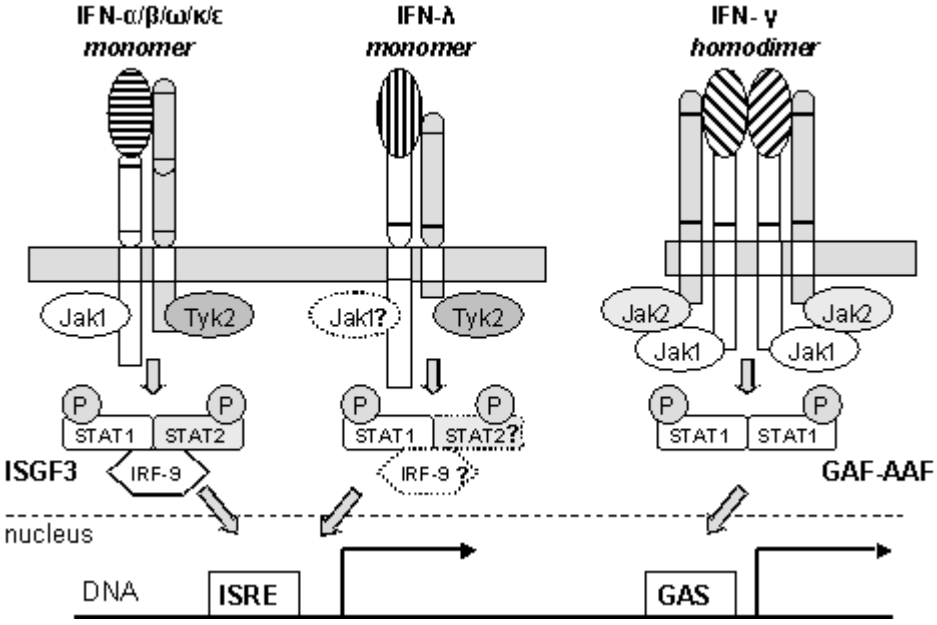

Fig. 11
Signaling pathways activated by IFNs

Binding of type I IFNs to heterodimeric receptors activates two receptor-associated tyrosine kinases Jak-1 and Tyk-2. This is followed by tyrosine phosphorylation of the STAT1 and STAT2 proteins which heterodimerize and assemble with the DNA-binding subunit IRF9 to form the ISGF-3 complex. Upon translocation to the nucleus ISGF-3 binds with high affinity to the ISRE found in promoters of IFN-stimulated genes. The signaling pathway used by IFN-γs is not fully understood, but overlaps (at least in part) with the transducing cascade utilized by other type I IFNs. Binding of IFN-γ homodimer to its receptor complex leads to the tyrosine phosphorylation of the Jak-1 and Jak-2 tyrosine kinases, resulting in phosphorylation of STAT1. The phosphorylated STAT1 homodimerizes to form the GAF-AAF. The latter translocates to the nucleus and binds to GAS elements present in promoters of IFN-γ-inducible genes. However, type I IFNs (α/β) can also induce formation of STAT1 homodimers (GAF-AAF), but in much less extent than type II IFNs.

Poxviruses also encode functional and structural homologs of type II IFN receptors (reviewed by Smith, 1996). For example, Vaccinia virus encodes a 226 amino acid long viroceptor (B8R), which is secreted as a 43 K soluble glycoprotein from infected cells, early during infection. B8R shares a 23% amino acid identity with the extracellular domain of IFNGR-1 chain (ALIGN, Pearson *et al*., 1997), and in contrast to strict species-specificity of IFNGR, is able to bind human, cow, rabbit and rat IFN-γ.

The signal transduction system (Jak-STAT)

All IFNs involved in the activation of specific gene receptors are linked to Jak-STAT transduction pathway (reviewed by Darnell *et al*., 1994). This transduction pathway is based on cooperation between cytoplasmic tyrosine kinases of the Jak, constitutively associated with IFN receptor chains, and proteins called *signal transduction and activators of transcription* (STAT). The chromosomal location of genes encoding components of the Jak-STAT system is summarized in Table 4. The CRII subunits with long intracellular domains associate with Jak-1, and the short domain subunits associate with Tyk-2 or Jak-2 (Fig. 10) (reviewed by Mogensen *et al*., 1999). To trigger the signaling cascade, receptor chains R1 and R2 have to associate, upon ligand binding. Heterodimerization of receptor subunits stimulates the Jak-STAT signal transduction cascade, leading to transcription of IFN target genes in response to IFN stimulation. Once activated by formation of a ligand-receptor

Table 4. Chromosomal location of genes encoding cytosolic components of Jak-STAT system (the Swiss-Prot database)

Protein	M_r	Chromosome
Janus kinase 1	Jak-1 132 K	1p31.3
Janus kinase 2	Jak-2 131 K	9p24
Tyrosine kinase 2	Tyk-2 134 K	19p13.2
Signal transducer and activator of transcription 1	STAT1 87 K	2q31.2
Signal transducer and activator of transcription 2	STAT2 98 K	17q11.1-q22
IFN regulatory factor 9	IRF9 44 K	14q11.2

complex, the Jak kinases phosphorylate each other, and also phosphorylate the two receptor chains to create a binding site for STATs, which are activated (phosphorylated) by Jaks, following receptor binding.

Jaks and STATs can be shared by several cytokines in their signaling pathways (Bach *et al*., 1997).

Signaling through IFNAR

Signal transduction through the IFNAR receptor complex is illustrated in Fig. 11 (reviewed by David, 2002). Binding of type Ia IFN initiates dimerization of the receptor subunits, IFNAR-1 and IFNAR-2. Tyk-2, which preassociated with IFNAR-1 is phosphorylated by Jak-1 upon ligand stimulation. Jak-1 binds to IFNAR-2 during this process.

The activated Tyk-2 in turn phosphorylates Jak-1. The activated Tyk-2 and Jak-1 are responsible for the subsequent phosphorylation of IFNAR-1 and IFNAR-2 at specific tyrosine positions. However, IFN-β is capable of some residual signaling even in the absence of Tyk-2 (Pellegrini and Schindler, 1993). STAT2 binds to specific phosphorylated amino acids on IFNAR-1. Upon docking, STAT2 is tyrosine-phosphorylated by the Jak kinases, thereby creating an additional docking port for STAT1, which is also subsequently phosphorylated. The phosphorylated STATs dissociate from the receptor heterodimer and bind to DNA-binding subunit IRF9 (p48), a member of the IFN regulatory factor (IRF) family. Association of the phosphorylated STAT proteins with IRF9 forms the IFN stimulated gene factor 3 (ISGF3), which translocates to the nucleus and binds to specific regulatory DNA sequences (ISRE, IFN stimulated response elements) found upstream of IFN-inducible genes, and initiates transcription of these genes.

During this process, homodimers of phosphorylated STAT1 are also formed. These homodimers are capable of driving the expression of a minority of IFN-stimulated genes, independently of IRF9. In this case, they bind to different DNA regulatory sequences called GAS (gamma activated sequence), which are usually found in the promoters of IFN-γ-stimulated genes (reviewed by Taniguchi and Takaoka, 2001).

Signaling through IFNLR

The mechanism of signaling through IFNLR is not fully understood. It is known that the cytoplasmic region of IL-10R2 and the signal chain of IFNLR associate with Tyk-2, but the kinase associated with the long chain of IFNLR-1 has not been identified. Based on analogy with other "long" chains of CRII class proteins, it could be deduced that LR-1 associates with Jak-1. Signal transduction from IFNLR and IFNAR signaling pathway overlaps, at least in part (Fig. 11). IFN-λ-induced receptor heterodimerization results in engagement of the Jak-STAT signal transduction pathway, including the phosphorylation of STAT2 and activation of the ISGF3 transcription complex (Kotenko *et al*., 2003; Sheppard *et al*., 2003).

Signaling through IFNGR

Addition of biologically active IFN-γ homodimer to target cells induces a rapid dimerization of receptor GR1 chains followed by GR2 subunits (reviewed by Bach *et al*., 1997). The ligand induces assembly of the complete receptor complex containing two GR1 and two GR2 subunits (Fig. 11). In this complex Jak-1 and Jak-2 transactivate each other by tyrosine phosphorylation and then phosphorylate GR-1 subunit, which serves as the recruitment site for two STAT1 molecules. The two STAT1 molecules are phosphorylated by activated Jak kinases and released to form homodimeric complexes that constitute the active transciption factor for IFN-γ. This transcription factor was initially termed IFN-γ-activated factor (GAF) but recently renamed IFN-γ-activated factor (GAF-AAF), since it is now recognized that IFN-α/β signaling can also lead to its formation. Activated GAF-AAF complex translocates to the nucleus, binds to the IFN-γ sequence in the promoter region and activates the transcription of IFN-stimulated genes.

Conclusions

A detailed molecular characterization of genes and proteins of newly identified members of the human IFN family and their receptors is now available. Nevertheless, additional studies will be necessary to understand the full spectrum of their biological activities and the physiological significance of these novel cytokines.

Acknowledgement. This work was supported in part by the grant No. 2/1041/21 from the Scientific Grant Agency of Ministry of Education of the Slovak Republic and Slovak Academy of Sciences.

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