**Interferon /**

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**Abstract**

Type I Interferons (IFNs) are key cytokines endowed with antiviral and immunomodulatory activities. The human type I IFN family consists of 13 subtypes of IFN, a single IFN subtype, plus IFN, IFN and IFN.

Type I IFNs exert their biological activities via interaction with a heterodimeric receptor complex – a cell surface receptor composed of two subunits, namely IFNR1 and IFNR2. Ligand binding initiates a transcriptional program that leads to the expression of the IFN regulated genes (IRGs) responsible for the multifaceted activity of type I IFNs. Optimal outcomes of these cytokines are achieved through regulation of the nature, strength and duration of interferon production; IFN-receptor interaction; and specific signaling pathways that are modulated in a cell type-specific manner.

When virus-infected cells are exposed to IFN, they develop what is known as an “antiviral state”, regulated by the IRGs, in which the viral life cycle is blocked or impaired. However, viruses have developed an impressive array of tactics to circumvent IFN-mediated antiviral responses. Type I IFNs also induce a broad spectrum of cell activities, including cell proliferation and differentiation, angiogenesis, and immunomodulation, regulated by the release of mediators relevant for the innate and adaptive immune responses. Detailed knowledge about how these pathways are regulated will, in turn, further our understanding of the roles of IFN pathways in the pathogenesis of infectious and inflammatory diseases and cancer.

**Keywords**

Angiogenesis; Antiviral State; Cancer; Cell proliferation; Immunomodulation; Interferon Receptors; Interferon Regulated Genes; Interferons; SOCS; Virus Escape; Virus Restriction Factors

**Glossary**

AIM2: Absent in Melanoma 2

ALRs: AIM2-like Receptors

GAS: Interferon-gamma Activation Site

IFN: Interferons

IFNAR: Receptor for Type I Interferon

IL: Interleukins

IRF: Interferon Regulatory Factors

IRG: Interferon Regulated Genes

ISRE: Interferon-stimulated Response Element

NLR: NOD-like Receptors

NOD: Nucleotide-binding Oligomerization Domain

PAMP: Pathogen-associated Molecular Patterns

PRR: Pattern Recognition Receptors

PYHIN: Pyrin and HIN Domain-containing Proteins

RLR: RIG-1-like Receptors

STING: Stimulator of Interferon Genes

TLR: Toll-like Receptors

**Introduction**

The interferons (IFNs) are a family of cytokines, first discovered as antiviral agents thanks to the viral interference studies performed by Isaacs and Lindenmann (Isaacs and Lindenmann, 1957). Influenza virus-infected chick cells were found to secrete a factor capable of inducing an antiviral state in other cells against homologous and heterologous viruses. A similar phenomenon was reported a year later by Nagano and Kojima (Nagano and Kojima, 1958), thus laying down the foundations for the many subsequent studies that were to come and which have led to the clarification of the IFN system in intricate detail.

IFNs are classified into three major types: Type I, Type II (also known as IFN-), and Type III, which is divided in IFN 1, 2, and 3, or interleukin-29 (IL-29), IL-28A, and IL-28B, respectively, and the last discovered 4 (Donnelly and Kotenko, 2010; Pestka, 2007; Pestka, Krause and Walter, 2004; Prokunina-Olsson *et al.*, 2013). IFNs are distinguished on the basis of their genetic locus, primary amino acid sequence homology, cell binding receptors, inducing stimuli, producing cell type, and biological activities.

**The IFN type I Family**

The genes encoding the type I IFNs lack introns and are located in a cluster on chromosome 9p21 in humans and on the syntenic region on chromosome 4 in mouse (Ivashkiv and Donlin, 2014). The human type I IFN family consists of: 13 subtypes of IFN that share 75-100% amino acid identity; a single IFN subtype that shares 30% amino acid identity with IFN; and a single subtype of IFN, IFNand IFN which share amino acid identity ranging from 15 to 30% with IFN and IFNOne pseudogene named IFNis also present(Table 1). Type I IFNs, with the exception of IFN and IFN, are usually produced in limited groups, never all at once. Their regulatory promoter regions are divergent, containing different regulatory elements that present different modalities of production in response to external stimuli. Thus, in order to fully understand the regulation of type I IFN signaling, it is necessary to consider how and when they are produced. **<Table 1 near here>**

The innate immune system reacts to the presence of pathogens by recognizing pathogen-associated molecular patterns (PAMPs) that trigger immune effector mechanisms and ultimately lead to the rejection of the invading pathogen. PAMPs are detected by several classes of host pattern recognition receptors (PRRs), including membrane and endosomal Toll-like receptors (TLRs)(Akira and Hemmi, 2003), RIG-I-like receptors (RLRs) (Loo and Gale, 2011), NOD-like receptors (NLRs) (Wen, Miao and Ting, 2013; Williams, Flavell and Eisenbarth, 2010), and the more recent members of the PYHIN family, namely human AIM2 and IFI16 and murine p204 or AIM2-like receptors (ALRs) (Gariano *et al.*, 2012; Gariglio *et al.*, 2011; Johnson, Chikoti and Chandran, 2013; Kerur *et al.*, 2011; Rathinam *et al.*, 2010; Unterholzner *et al.*, 2010). Thus, PRRs sense pathogens and drive the production of type I IFNs, as well as other cytokines and chemokines, as the effectors of the innate inflammatory response (Mogensen, 2009; Unterholzner, 2013). The Toll-like receptors (TLRs), located on both the cell surface and within endosomal compartments, recognize PAMPs, such as bacterial lipopolysaccharide (LPS), as well as danger-associated molecular patterns (DAMPs), including host cell DNA released from damaged cells. LPS recognition by TLR4 specifically triggers IFN(Poltorak *et al.*, 1998; Toshchakov *et al.*, 2002), while TLR3 and TLR7/8 recognize double-stranded RNA and single-stranded RNA, respectively, leading to the production of IFN subtype combinations and IFN during viral infection (Alexopoulou *et al.*, 2001; Diebold *et al.*, 2004; Heil *et al.*, 2004). Similarly, in plasmacytoid dendritic cells, TLR9 recognizes CpG DNA and triggers the production of a mixture of type I IFNs (Takeshita *et al.*, 2004). However, the IFN response to nucleic acids is not exclusively mediated by TLRs. The finding that RNA and DNA can elicit robust induction of type I IFNs in the absence of TLRs during viral and bacterial infection led to the discovery of several cytosolic and nuclear sensors. The DEX(D/H) box RNA helicases RIG-I and MDA5 detect 5’-ppp single-stranded RNA and long double-stranded RNA, respectively (Kato *et al.*, 2006; Loo and Gale, 2011). Other nucleic acid sensors (AIM2, IFI16, cGAS, etc.), located in the cytosol and nucleus, lead to activation of STING and TBK-1-dependent phosphorylation of IRF3 and transcription of type I IFN genes (Barber, 2011; Brunette *et al.*, 2012; Lam, Stein and Falck-Pedersen, 2013; Orzalli, DeLuca and Knipe, 2012; Thompson *et al.*, 2014; Unterholzner *et al.*, 2010).

PAMP recognition by PRRs initiates a series of signal transduction pathways that, through the activation of one or more of the transcription factors belonging to the Interferon Regulatory Factor (IRF) family, lead to type I IFN production. IRF1, 3, 5, and 7 are involved in the stimulation of IFN gene expression (Honda *et al.*, 2005), whereas IRF3, together with NFB, is relevant for the induction of IFN gene expression (Wathelet *et al.*, 1998). Hemopoietic cells and, in particular, plasmacytoid dendritic cells (pDC) produce high levels of type I IFNs (Colonna, Trinchieri and Liu, 2004; McKenna, Beignon and Bhardwaj, 2005). The explanation to this stems from their very high levels of constitutive IRF7 expression compared to the low levels observed in other cell types, where IRF7 expression must be primed by an initial burst of IFN(Honda *et al.*, 2005). Another distinct mechanism involves the IRF3/NFB pathway, which activates pathogen-driven IFN production. IFN can be produced via a pathway that activates the transcription factor AP-1, which binds to cognate sites on IFN(Wathelet *et al.*, 1998). Finally, various other pathways have also been described that lead to type I IFN production, but in general all these studies confirm that IFN production is tightly dependent on the site and the time of stimulation.

**Type I IFN Receptors and Signal Transduction Pathways**

All type I IFN subtypes exert their biological activities via interaction with the type I IFN heterodimeric receptor complex composed of IFNR1 and IFNR2 (Table 1). The IFNR1 chain of the receptor is responsible for signal transduction following ligand binding to the high affinity binding chain, IFNR2. Several studies have demonstrated the importance of cysteine residues in the ligand that influence binding to the receptor subunits (Nisbet *et al.*, 1985). Moreover, conserved hydrophilic residues, such as Arg33 and Tyr123, appear to be critical for the activity of these cytokines (Tymms *et al.*, 1989), consistent with the observations that differences in the amino acid sequence between different type I IFNs account for different degrees of binding affinity to the cognate receptor and the potency of their biological activity (Jaks *et al.*, 2007). The interaction of type I IFNs with the extracellular domains of IFNR1 and IFNR2 was definitively clarified when X-ray crystallography analysis of the ternary complex demonstrated that IFN subtypes differently interact with the receptor components and transduce signals depending on the interacting residues of the three proteins (the ligand and the two receptor subunits) (Thomas *et al.*, 2011).

Type I IFN engagement with the extracellular domain of IFNR1 and IFNR2 triggers a conformation change that brings the intracellular domains of the receptors into proximity and activates the receptor-associated proteins Tyk2 (with IFNR1) and JAK1 (with IFNR2) of the Janus kinase (Just Another Kinase) family (Domanski *et al.*, 1997; Yan *et al.*, 1996). JAK phosphorylation, in turn, leads to tyrosine phosphorylation of receptor residues that act as docking sites for Signal Transducers and Activator of Transcription (STAT) proteins (Stark and Darnell, 2012). Once phosphorylated by JAKs, receptor-docked STATs dissociate from the receptor and form a ternary complex called IFN Stimulated Gene Factor 3 (ISGF3), composed of STAT1, STAT2, and IRF9 (also called ISGF3 or p48). This complex translocates into the nucleus where it binds to cognate DNA elements known as IFN-stimulated Response Elements (ISREs) that span the promoter regions of ISGs – the actual mediators of the antiviral response. Type I IFNs also activate STAT3 and STAT1 to homo- and hetero-dimerize, thereby forming complexes that can bind to other responsive elements, the so-called GAS (IFN-gamma-activated sites), located on the promoters of other cytokines, including IFN- and IL6 (Levy and Darnell, 2002) (Figure 1). **<Figure 1 near here>**

Type I IFNs have also been reported to activate other STATs (4, 5, and 6), but their binding to the cognate receptor chains and the signaling pathways activated are presently poorly characterized (Platanias, 2005; van Boxel-Dezaire, Rani and Stark, 2006). Finally, it should be mentioned that type I IFNs, in addition to the JAK-STAT pathways, may trigger other signaling pathways to ensure the optimal transcriptional activation of ISGs and the subsequent biological responses, including the MAPK (p38 and ERK), NFB, and P13/AKT pathways (Goh, Haque and Williams, 1999; Joshi *et al.*, 2009; Yang *et al.*, 2001).

**The Interferon Regulated Genes**

IFN binding to cognate receptors and the ensuing activation of signaling transduction pathways can stimulate or repress the expression of hundreds of different Interferon Regulated Genes (IRGs). Upon IFN exposure, virus-infected cells develop an “antiviral state” regulated by the IRGs, the products of which are the actual mediators of the biological IFN response – which may consist of protection against viral infection, inhibition of cell proliferation, and modulation of the immune response (Schneider, Chevillotte and Rice, 2014). Microarray analysis of gene modulation in different cell types has led to the detection of more than 2000 genes with altered expression following IFN exposure. Indeed, the microarray experiments performed over the last 15 years have identified sets of genes involved in: antiviral activity, cell cycle regulation, the immune response, and cell survival (Der *et al.*, 1998; de Veer *et al.*, 2001; Hilkens, Schlaak and Kerr, 2003; Holko and Williams, 2006; Indraccolo *et al.*, 2007; Samarajiwa *et al.*, 2009; Sanda *et al.*, 2006). One important aspect that emerges from these analyses is that the IFN response is extremely fine-tuned, involving the induction of a specific set of genes, and that all the IFN-stimulated genes are never stimulated together. Thus, it is reasonable to suppose that the specific nature, duration, cell context, activation or repression of these pathways all contribute toward determining the ultimate type of response.

**The Negative Regulation of IFN Signaling**

In order to prevent toxicity resulting from an over-production of IFN, negative regulation mechanisms exist for every step of the process, starting with ligand production, receptor binding, TF activation and IRG induction, post-transcriptional and post-translational modification; endogenous inhibitors of the proteins encoded by the IRGs also exist and can be expressed when required.

A truncated transmembrane isoform of the IFNR2, the primary binding chain, can be generated by alternative splicing or produced by protease cleavage. This truncated, soluble form of the receptor inhibits IFN signaling, as has been shown in some cytokine systems; it can also bind directly to the signal-transducing chain, IFNR1, as in the case of gp130 for IL6, resulting in the transduction of specific signals (Hardy *et al.*, 2001; Lutfalla *et al.*, 1995; Owczarek *et al.*, 1997). Negative regulation of IFN type I signaling can also be attained via the SOCS (Suppressors Of Cytokine Signaling proteins) family of proteins, which comprises 7 members, composed of three key domains: KIR, SH2 and SOCS BOX (Linossi *et al.*, 2013; Mansell and Jenkins, 2013). The important role of these suppressor proteins in IFN type I signaling is supported by the finding that SOCS1-/- mice die pre-weaning as a consequence of multi-organ inflammation (Alexander *et al.*, 1999). *In vitro* co-precipitation experiments directed at clarifying the function of SOCS in type I IFN signaling have demonstrated SOCS1 to associate with Tyk2 kinase, which interacts with the justa-membrane region of the intracellular domain of IFNR1 (Fenner *et al.*, 2006; Piganis *et al.*, 2011). Negative regulation of type I IFN also takes place at the transcription factor level, via the interaction of TFs with negative regulator proteins, including protein inhibitors of activated STATs (PIAS) (Shuai and Liu, 2005), TRIM proteins (binding to the retinoic acid receptor, RAR) ((Tisserand *et al.*, 2011), and several members of the IRF family (Yoshida *et al.*, 2005). The negative regulation of type I IFN signaling can also be achieved via the up-regulation of Sprouty (Spry) protein expression, which results in the suppression of the IFN-activated p38 MAK kinase (MAPK) and the consequent suppression of IRG transcription (Sharma *et al.*, 2012).

**A global view of the type I IFN response**

*The antiviral state*

Upon IFN exposure, infected cells develop an “antiviral state” that is regulated by the IRGs. Usually, IRGs do not have virus-specificity, thus the actions of a defined set of IRGs are able to inhibit the replication of an array of viruses. Investigations into the antiviral functions of IRGs have included overexpression studies using infected cell cultures, microarray analysis, gene knock-out mouse models, and the identification of virus-encoded inhibitors. Over the last thirty years, the proteins responsible for the antiviral state have been characterized and many aspects of their activities clarified.

The dsRNA-activated protein kinase, PKR, is induced by interferon, although in many cell types, it is constitutively expressed at low levels (Hovanessian, 2007). After binding to dsRNA of viral or cellular origin, it dimerizes and undergoes autophosphorylation accompanied by the phosphorylation of translation initiation factor 2a (eIF2a), resulting in both cellular and viral translation inhibition (McAllister, Taghavi and Samuel, 2012). In response to cellular stress, PKR can also be activated by the direct binding of PACT (a protein activator of PKR), stimulating apoptosis (Marques *et al.*, 2008; Peters *et al.*, 2001). The replication of several RNA viruses, such as Vesicular stomatitis virus (VSV) (Baltzis *et al.*, 2004), Encephalomyocarditis virus (EMCV) (Yeung *et al.*, 1999), West Nile virus (WNV) (Samuel *et al.*, 2006), hepatitis C virus (HCV) (Dabo and Meurs, 2012), and DNA viruses, such as herpes simplex virus 1 (HSV-1) (Al-Khatib *et al.*, 2002), is inhibited by activated PKR (Sen and Peters, 2007).

Another group of IFN-induced enzymes, activated upon their binding to dsRNA, is the 2'-5'-oligoadenylate synthetases, which generate unique 2'-5'-linked AMP-oligomers (2-5A) from ATP. In turn, the 2-5As oligomers activate the latent RNase L enzyme, which undergoes dimerization and then cleaves cellular and viral ssRNA, thereby inhibiting protein synthesis (Hovanessian, 2007; Kristiansen *et al.*, 2011; Sen and Peters, 2007). The viruses most sensitive to the antiviral activity of the OAS/RNase L system include picornaviruses (EMCV) and influenza A virus along with other RNA viruses. Depending on the nature of the virus, its genomic RNA or viral mRNAs are cleaved (Banerjee *et al.*, 2014; Chebath *et al.*, 1987; Silverman, 2007). Furthermore, RNase L-cleaved cellular RNAs can amplify interferon induction by serving as ligands for RIG-I (Malathi *et al.*, 2007; Rehwinkel *et al.*, 2010).

Virus RNAs are also targets of other IFN-inducible genes. For example, ISG20 encodes a 3’-exoribonuclease that triggers nonspecific ssRNA cleavage, leading to the inhibition of RNA viruses, including VSV (Espert *et al.*, 2003). Similarly, inhibition of HCV replication is obtained by the ISG56/IFIT family proteins P56 and P54 via their binding to eIF3, providing a non-enzymatic mechanism of translation inhibition (Raychoudhuri *et al.*, 2011).

The Mx dynamin-like GTPases (MxA, MxB) are antiviral effector proteins inducible by both type I and type III IFNs (Haller *et al.*, 2015). The cytoplasmic human MxA protein is able to inhibit a broad set of viruses, including Influenza A virus (FLUAV), Thogoto virus (THOV), VSV, Measles virus, and Bunyaviruses (Frese *et al.*, 1996, 1995; Haller, Staeheli and Kochs, 2009; Schnorr *et al.*, 1993; Staeheli and Pavlovic, 1991). The nucleocapsids (vRNPs, viral Ribonucleoprotein complexes) of FLUAV and THOV consist of genomic RNA segments associated with the viral nucleoprotein and RNA polymerase. Human MxA blocks nuclear translocation of incoming vRNPs and inhibits transcription and replication of virus genomes by interfering with synthesis and nuclear import of newly synthesized viral components. The long form of human MxB localizes to the cytoplasmic face of nuclear pores and inhibits HIV uncoating, thus the import of the pre-integration complex into the nucleus, in turn, preventing chromosomal integration of proviral DNA (Liu *et al.*, 2013).

ISG15 is conjugated to target proteins by interferon-inducible conjugases/ligases, a process similar to ubiquitin conjugation; however, although the effects of ISG15 conjugation remain unclear, they are known to contribute to HSV-1 and influenza virus resistance (Morales and Lenschow, 2013; Zhao *et al.*, 2013). Viperin (CIG5) might interfere with viral budding of enveloped viruses, such as human Cytomegalovirus (HCMV), HCV, and influenza virus, by disrupting lipid rafts within membranes; however its mode of action remains to be determined (Helbig and Beard, 2013; Seo, Yaneva and Cresswell, 2011). The nucleic acid-editing enzymes APOBEC3G and -3F, representing deoxycytidine deaminases, inhibit retroviruses; they act by introducing C to U mutations in viral reverse transcribed DNA or by directly interfering with reverse transcription (Harris *et al.*, 2003; Huthoff and Towers, 2008; Mangeat *et al.*, 2003).

*Virus escape of the IFN system*

Viruses have developed an impressive diversity of tactics to circumvent IFN responses. Evasion strategies can involve preventing initial virus detection via the disruption of the Toll-like receptors or the retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), or by avoiding the initial production of the viral ligands recognized by these receptors. For instance, several viruses have been found to disrupt TLR signaling by interfering with TLR adaptor proteins, including TRIF and the TIR-containing proteins MAL and TRAM, thus impeding their interactions with down-stream signaling molecules (Ahmad *et al.*, 2011; Lang, 2005; Lei *et al.*, 2011; Qu *et al.*, 2011). Like TLRs, RLRs are hindered by viruses. The N protein from human respiratory syncytial virus (RSV) inhibits MDA5 and MAVS (Lifland *et al.*, 2012), whereas the HIV protease decreases cytoplasmic RIG-I levels by targeting the sensor to the lysosome (Solis *et al.*, 2011). An alternative approach is to preclude IFN production by disarming or degrading the transcription factors involved in the expression of IFN, such as IRF3/IRF7 (Doehle *et al.*, 2012; Ning, Pagano and Barber, 2011; Okumura *et al.*, 2008; Unterholzner *et al.*, 2011; Vandevenne *et al.*, 2011), NFB (Schuhmann, Pfaller and Conzelmann, 2011), or ATF-2/c-jun (Halfmann, Neumann and Kawaoka, 2011), or by inducing a general block on host cell transcription (Verbruggen *et al.*, 2011). Viruses also oppose IFN signaling by both disturbing the type I IFN receptor and by impeding JAK/STAT signal transduction upon IFN receptor engagement (Gauzzi *et al.*, 1997; Hong, Mehta and Laimins, 2011; Leang *et al.*, 2011; Liu *et al.*, 2009; Ren *et al.*, 2011; Sohn and Hearing, 2011). In addition, the global expression of IRGs can be obstructed via interference with epigenetic signaling (Fonseca *et al.*, 2012; Marazzi *et al.*, 2012), and specific IRGs can also be selectively targeted for inhibition (Bhanja Chowdhury *et al.*, 2012; Kim *et al.*, 2011). Finally, some viruses hamper IFN responses by co-opting negative regulatory systems (Funaoka *et al.*, 2011; Strebovsky, Walker and Dalpke, 2012), whereas others use the antiviral mechanisms activated to their own benefit (Frias *et al.*, 2012; Seo, Yaneva and Cresswell, 2011).

*The Immunomodulatory activity*

Immunomodulatory effects include increased expression of surface molecules belonging to the major histocompatibility complex (MHC) and of several immune cell surface receptors, and the activation and functional differentiation of the immune system’s effector cells, including monocytes/macrophages, dendritic cells (DCs), natural killer cells, and T- and B-lymphocytes (Table 2). For example, Type I IFNs up-regulate the expression of class I MHC and co-stimulatory molecules by immune cells (such as DCs) that differentiate into efficient antigen-presenting cells driving the activation of quiescent reactive T helper cells (González-Navajas *et al.*, 2012; Padovan *et al.*, 2002; Tough, 2012). Similarly, type I IFN can up-regulate the expression of class II MHC molecules, leading to the activation of reactive DCs and T- and B-lymphocytes (Simmons *et al.*, 2012). Thus, type I IFNs function at the interface of both innate and adaptive immune systems by inducing chemokines and cytokines and stimulating the functional differentiation of CD4+ helper T cells and CD8+ cytotoxic T cells. Yet, type I IFN has been shown to trigger the differentiation of B lymphocytes, to increase the production of antibodies, and favor the switching of immunoglobulin (Ig) isotypes (Jego *et al.*, 2003; Le Bon *et al.*, 2001). Finally, indirect involvement of type I IFN has been demonstrated during bacterial and parasitic infection. In these cases, type I IFN does not exert direct cytotoxic activity, rather it recruits cytotoxic NK cells and enhances the differentiation of cytotoxic CD8+ T lymphocytes (Welsh *et al.*, 2012). Several in vivo studies in both mouse and human models have confirmed how type I IFN can interact with host cells to induce protective immunity. Mice lacking the type I IFN receptor in DCs are unable to reject highly immunogenic tumor cells (Diamond *et al.*, 2011). Likewise, type I IFN receptor or STAT1 have been shown to be required in the hematopoietic compartment at the level of host antigen presenting cells and for intratumoral infiltration of CD8a+ DCs (Fuertes *et al.*, 2013). Consistent with these findings generated in mouse models, data in human models have been accumulated over the last years showing the importance of type I IFN in the modulation of protective immunity which may lead to novel strategies of cancer immunotherapy. **<Table 2 near here>**

*Activities unrelated to the antiviral effect*

Considering the number of genes activated upon IFN type I exposure, it is possible that, in addition to inducing an antiviral state, these cytokines also affect cellular functions; indeed, broader effects of interferons include immunomodulatory functions, antiproliferative activity, and cell differentiation.

Cell growth inhibition by human type I IFN involves direct and indirect activities. Direct activity occurs through cancer cell growth inhibition by cell cycle arrest, apoptosis, or differentiation. Indirect activity occurs through the activation of immune cells, such as T cells and natural killer cells, the inhibition of vascularization, and the induction of cytokines. For a long time, it was thought that the direct inhibitory effects on tumor cell growth were the most effective mechanisms responsible for the antitumor response in IFN-treated patients (Stark *et al.*, 1998). Type I IFN can indeed inhibit the proliferation of tumor cells, both *in vivo* and *in vitro*, through mechanisms that include the down-regulation of oncogene expression, the induction of tumor suppressor genes that regulate cell growth arrest, and the induction of apoptosis through caspase activation (Asmana Ningrum, 2014; Bekisz *et al.*, 2010; Chawla-Sarkar *et al.*, 2003; Fuertes *et al.*, 2013; Pokrovskaja, Panaretakis and Grandér, 2005; Wang, Rahbar and Fish, 2011). In addition to the direct effects on tumor cells, type I IFN exerts a number of effects on host immune cells that can play a central role in the overall antitumor response (Belardelli *et al.*, 2002; Belardelli and Gresser, 1996). An enhancement of the immune response also occurs as a consequence of the increase in MHC I expression, which can enhance immune recognition (Brassard, Grace and Bordens, 2002; Pfeffer *et al.*, 1998).

The type I IFN-induced mechanisms of antiproliferation occurring through apoptosis are triggered via the activation of two main pathways: IFN receptor signal transduction through tumor necrosis factor alpha (TNF-) (Bekisz *et al.*, 2010; Tagliaferri *et al.*, 2005); and the release of cytochrome c by mitochondria (Bekisz *et al.*, 2010). Both of these pathways activate the caspase signaling cascade, resulting in DNA fragmentation and cell death. hIFN2b contributes to an increase in the p53 protein response to stress signaling and the activation of p38, which plays a role in cell death. Additionally, hIFN2b can activate PKR, which has a variety of protein substrates, such as eukaryotic initiation factor 2 (eIF2), NFKB, IRF-1, p53, and STATs.

The direct antiproliferative effects of type I IFN, which include the inhibition of cell growth by promoting arrest in the G1 phase of the cell cycle (Tanabe *et al.*, 2000), are often assumed to be the primary mechanism involved in their efficacy as anti-cancer agents. However, IFNs may also impair tumor growth by affecting angiogenesis involved in tumor vascularization (Indraccolo, 2010; Yıldırım *et al.*, 2015). Their anti-angiogenic properties appear to be mediated in part by their ability to down-regulate the expression of tumor-induced proangiogenic factors, including bFGF (Slaton *et al.*, 1999), VEGF (Aguayo, 2014; von Marschall *et al.*, 2003), and MMP-9 (Slaton *et al.*, 2001; Zhao *et al.*, 2007). Clinical experience has indeed confirmed the anti-angiogenic potential of type I IFN in the treatment of a variety of pediatric vascular neoplasms, including hemangiomas, malignant hemangiopericytoma, and pulmonary hemangiomatosis (Ezekowitz, Mulliken and Folkman, 1992). In addition, IFNis currently the most common cytokine used in human patients (Belardelli *et al.*, 2002), where it is used in the adjuvant therapy of metastatic melanoma (Di Trolio *et al.*, 2014) and renal cell cancer (Ravaud and Dilhuydy, 2005).

Finally, cell differentiation appears to be profoundly affected by IFNs. Both erythropoiesis and adipogenesis have been demonstrated to be stimulated or inhibited by type I and type II IFNs. In addition, normal thyrocytes, when exposed to type I IFN differentially modulate cell surface molecules, such as integrins, and signaling pathways activated by adhesion to fibronectin (Capobianchi *et al.*, 2014).

**Concluding remarks**

Type I IFNs are potent antiviral cytokines that exert their activity by modulating the induction or suppression of more than 1000 genes in signature sets encoding important effector proteins in target cells. Therefore, viruses have evolved multiple evasion strategies to counteract IFN induction and signaling and the activity of IFN-induced effector molecules.

The last few decades of research has revealed type I IFNs to display an extensive array of biological activities in addition to their antiviral actions. Moreover, seemingly opposing effects of IFN have been observed, unsurprising considering the multitude of IRGs, which depend on in situ production, timing and concentration. Thus, type I IFNs may have both beneficial and detrimental effects. It thus follows that the balance between a protective or a harmful response is controlled at every level, from the machinery that stimulates IFN production to its interaction with cognate receptors and transducing signals in the responding cells. Ultimately, intricate knowledge of the fine tuning of a cell’s response to IFNs will pave the way to new clinical approaches to diagnosing diseases and therapeutic applications. This knowledge will also play a central role in tailoring personalized treatments to individual patients presenting aberrant IFN responses.

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**Cross references**

02001. Pathogen associated molecular patterns

02002. Danger associated molecular patterns

02003. TLR (toll-like R)

02004. NLR (NOD like R)

02005. RLR (Rig-like R) (RNA sensors)

02006. ALR (Aim-like R)

08015. T cell/APC interaction, focus on DC, types of activation

09017. Cytokine regulation of B cell activation and differentiation

09018. Cytokine-producing effector B cells

10006. Interferon γ

10007. New Interferons

10018. Viral Anti-Cytokine Strategies

10020. Inflammasome

11012. Nuclear receptors in immune function

11015. JAK-STAT signaling pathways

11018. Structural Biology of JAK/STAT cytokines and their receptors

13028. Overview: Infectious Disease Immunology

14001. Sensors of Viral Infections

14002. Dendritic Cells in Viral Infection

14004. Intrinsic Cellular Defenses (TRIMS) in Modulating Viral Infection and Immunity

14005. Cytokine Responses and Functions

14006. NK Cells in Antiviral Defense

14010. Viral Immune Evasion

14014. Viral Modulation of Cell Intrinsic Immunity

14025. Immunity to Oncogenic Viruses

15002. Autoimmune thyroid disease

15003. Systemic Lupus Erythematosus (SLE)

15004 Rheumatoid arthritis

17001. Tumor immunosurveillance/tumor editing

17002. Inflammation and cancer

17004. Tumor antigens - viral origin

17016. Positive and negative regulators of anti-tumor immunity

17017. Cytokines and chemokines in the tumor microenvironment

**Figure Legend**

**FIGURE 1. Activation of type I IFNs by viral infections.** (1) Cells sense pathogens by membrane-bound, cytosolic and/or nuclear viral sensors belonging to different families of Pattern Recognition Receptors (PRRs). Engagement of these receptors leads to the induction of different transduction pathways resulting in the activation and nuclear translocation of transcription factors including NF-B, IRF3/7, and AP1, ultimately resulting in transcriptional activation of type I IFN genes (2). After being activated, type I IFNs are released in the extracellular milieu, and bind their specific dimeric receptor (IFNR1/IFNR2) on the same producing or surrounding cells (3). Type I IFN/IFNR binding leads to JAK-STAT phosphorylation and assembly of the ISGF3 transcription factor (4). Eventually, in the nuclear compartment, ISGF3 binds to the ISRE element of various IFN regulated genes (IRGs), some of which in turn behave as PRRs. See text for details. Abbreviations: ALRs, AIM2-like Receptors; AP-1, Activator Protein-1; GAS, Interferon*-*gamma Activation Site; IRF3/7, Interferon Regulatory Factors 3/7; ISGF3, Interferon-stimulated Gene Factor 3; ISRE, Interferon*-*stimulated Response Element; NF-B, Nuclear Factor of kappa light Polypeptide Gene Enhancer in B-cells; NLRs, NOD-like Receptors; RLRs, RIG-1-like Receptors; STAT, Signal Transducer and Activator of Transcription; TLRs, Toll-like Receptors.