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The Type I Interferons: Basic Concepts and Clinical Relevance in Immune-mediated Inflammatory Diseases

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Abstract

There is increasing scientific and clinical interest in elucidating the biology of type I Interferons, which began approximately 60 years ago with the concept of "viral interference", a property that reduces the ability of a virus to infect cells. Although our understanding of the multiple cellular and molecular functions of interferons has advanced significantly, much remains to be learned and type I Interferons remain an active and fascinating area of inquiry. In this review, we cover some general aspects of type I interferon genes, with emphasis on interferon-alpha, and various aspects of molecular mechanisms triggered by type I interferons and toll-like receptor signaling by the Janus activated kinase/signal transducer activation of transcription (JAK-STAT) pathway and interferon regulatory factor pathway. We will also describe the role of type I interferons in autoimmune and inflammatory diseases, and its potential use as therapeutic agent.

Keywords

Interferon alpha; Interferon beta; Interferon signature; autoimmune diseases; systemic lupus erythematosus; rheumatoid arthritis; multiple sclerosis; idiopathic inflammatory myopathies

Introduction

The interferons (IFN)s are a family of cytokines with antiviral, antiproliferative, and antitumor activities, as well as immunomodulatory effects on the innate and adaptive immune responses (Lengyel, 1982; Pestka et al., 1987). The awareness that more than one type of IFN existed developed gradually as a result of the molecular cloning of the different IFN genes. Since the first published description of IFN (Isaacs and Lindenmann, 1957,Isaacs et al., 1957), there has been an explosive growth in our understanding of genes encoding the IFNs and their receptors, their complex signaling cascade and regulation, and their

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biological activities (Pestka et al., 2004). Historically, IFNs have been classified into two major types, type I and type II, based on their interactions with the IFN receptor subunits, peptide mapping, and sequencing homology (Pestka et al., 1987, Pestka et al., 2004). Recently, a novel class of cytokines with IFN-like activities has been described and designated as type III IFNs (IFN-λ1-3) (Osterlund et al., 2007). In humans, the type I IFN system consists of a family of IFN proteins encoded by at least 13 IFN alpha (IFNA) subtype genes (IFN-α1, -α2, -α4, -α5, -α6, -α7, -α8, -α10, -α13, -α14, -α16, -α17 and -α21), and one IFN beta gene (IFNB), one IFN-Epsilon gene, one IFN-Kappa gene, and IFN-Omega gene, all of which bind to the type I interferon receptor composed of the IFNAR1 and IFNAR2 chains (Uze et al., 2007). Sequence data indicate the human IFNA gene family shares 70-80% sequence homology within the IFNA subtypes, and about 35% identity with IFNB (Diaz et al., 1994).

This article reviews current understanding of the type I IFN gene family, molecular functions of type I IFNs, and the role of type I IFN in autoimmune disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and idiopathic inflammatory myopathies (IIM). As type I IFNs have been implicated in these human disease processes, therapies are currently being developed targeting this pathway. We have used the nomenclature approved by the Human Genome Mapping Workshop for IFN genes. For example, IFNA designates a gene or locus, whereas IFN-α refers to the protein (Diaz et al., 1996).

Human interferon-alpha gene family

In humans, the genes encoding IFNA are found as a family of 13 intronless genes clustered together within a region spanning ~ 400 kb on the short arm of chromosome 9 (cytogenetic bands 9p22-9p21) (Shows et al., 1982). There are 12 functional human IFNA gene products. All of these IFN-α proteins exhibit high homology in their primary, secondary, and tertiary structures (Karpusas et al., 1997, Mitsui and Senda, 1997, Thomas et al., 2011). They also bind to the same receptor (IFNAR1/IFNAR2) and signal through similar mechanisms eliciting similar biological activity (Pestka et al., 2004; Viscomi, 1997). Currently, there is a small body of experimental data demonstrating differences in the biological activities of human IFN-α subtypes, although some studies suggest that even minor variations in the primary sequences of individual subtypes of human IFNA genes may lead to distinct antiviral and immunoregulatory functions in T cells, B cells, and dendritic cells (DCs) (Pestka et al., 2004, Yanai et al., 2001, Foster et al., 1996, Dipaola et al., 1994, Hilkens et al., 2003, Hibbert and Foster, 1999). Data from the murine IFNA gene family suggests that diverse IFN-α proteins may vary in their affinity for the IFN receptor subunits, resulting in differences in IFN signaling. Interestingly, mouse fibroblasts transfected with different type I IFNA/B transgenes (i.e., IFNA1, IFNA4, IFNA5, IFNA6, Ifna9 and IFNB) showed different degrees of protection against herpes simplex virus type 1 (HSV-1) and HSV-2; suggesting differences in the downstream activation of genes responsible for the antiviral activities of IFN-α subtypes (Harle et al., 2002). Some studies also suggest differences in cell- and ligand-specific expression and different kinetics between IFN-α subtypes, suggesting other mechanisms for diversity in downstream response beyond conformational changes at the type I IFN receptor (Hillyer et al., 2012). The high degree of amino acid

sequence similarity within the IFN-α proteins suggests a common ancestral gene. Gene clusters such as the IFNA cluster are genomic regions that comprise multiple similar copies in close proximity, and are thought to be generated by local duplication of a common ancestral segment. (Chen et al., 2007, Song et al., 2011). A study published by Woelk and colleagues (Woelk et al., 2007) using gene conversion analysis of 156 IFNA genes from mammalian species (chimpanzee, dog, mouse, rat, and rhesus macaque) in which gene-specific clustering is also evident, identified specific sequences and fragments involved in gene conversion and gene duplication events. This study suggested that both of these evolutionary mechanisms contributed to the evolution of IFNA gene clusters. Other studies have been unable to clarify whether gene conversion or recent duplication play a role for gene-specific clustering of IFNA genes (Hughes, 1995). An evolutionary analysis of human and mouse IFNA genes failed to find evidence of gene conversion in humans but some interlocus recombination was identified among mouse IFNA genes (Hughes, 1995).

Interplay between type I IFN signaling and Toll-like receptor response

Type I IFNs elicit antiviral, antiproliferative and immunomodulatory responses by binding to the type I interferon receptor. The receptor consists of the IFNAR1 and IFNAR2 transmembrane proteins, and two associated cytoplasmic tyrosine kinases, the Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2). The IFNAR2 subunit is considered as the primary binding chain as it binds type I IFNs with relatively high affinity, whereas the IFNAR1 subunit does not bind type I IFNs with detectable affinity but is absolutely required for signal transduction from the heterodimeric IFNAR complex and for type I IFN biological activity (Cohen et al., 1995, Arduini et al., 1999, Uze et al., 2007). Thus, both the IFNAR1 and IFNAR2 subunits are required to mediate the biological effects of all type I IFNs. As shown in Figure 1, the biological effects of IFNs are mediated through the Janus kinase/ signal transducer and activator of transcription (JAK/STAT) pathway. STAT1 and STAT2 mediate the antiviral and inflammatory effects of IFN-α/IFN-β (Aaronson and Horvath, 2002}. Upon IFNAR engagement, IFNs induce tyrosine phosphorylation of STAT1 and STAT2 proteins and, together with IFN-regulatory factor 9 (IRF9) , form the IFN-stimulated gene factor 3 (ISGF3) transcription factor complex (Mowen and David, 1998), which then translocates to the nucleus and binds to IFN-stimulated response elements (ISREs) in the promoters of IFN-regulated genes (IRGs). In addition, canonical type I IFN signalling may activate STAT1 homodimers that bind to interferon-gamma-activating factor (GAF), which translocates to the nucleus and activates transcription of IFN-stimulated genes (David, 2002). In contrast, IFN-α-activated STAT3 is thought to inhibit STAT1-dependent gene activation, thereby down-regulating IFN-α-mediated induction of inflammatory mediators, attenuating the inflammatory properties of type I IFNs (Ho and Ivashkiv, 2006).

The canonical IFN-JAK/STAT signal transduction pathway is not isolated, but communicates extensively with other signal transduction pathways such as the innate pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), RIG-I-like receptors (RLGs), NOD-like receptors, and C-type lectin receptors (Takeuchi and Akira, 2010). The virus-induced expression of IFNA/IFNB genes is primarily controlled at the gene transcription level by the IRFs and IFN-stimulated genes (Honda and Taniguchi, 2006a). Immune complexes (ICs) containing nucleic acids can access intracellular TLRs (TLR3,

TLR7/8 and TLR9) after binding to Fc receptors and induce IFN-α production by IRF3, IRF7, and IRF5 (Honda and Taniguchi, 2006a, Honda and Taniguchi, 2006b). Signaling through TLRs can broadly be categorized into two pathways; the MyD88 and the TRIF-dependent pathway. All TLRs, except TLR3, activate through the MyD88-dependent pathway. Only TLR3 and TLR4 activate through the TRIF-dependent pathway (Honda and Taniguchi, 2006b). The MyD88-dependent pathway recruits several effector molecules such as IRAK1/4 and tumor necrosis factor receptor-associated factor 6 (TRAF6) (Kawai and Akira, 2006). These molecules are linked to at least three major downstream pathways: the NF-κB pathway, the pathway involving mitogen-activated protein kinases (MAPKs), and IRF pathways. Depending on the stimulus and the responding cell types, activation of these pathways results in transcription of various cytokines including IFN-α/β (Honda and Taniguchi, 2006b). In human plasmacytoid DCs (pDCs), IRFs such as IRF3, 5, and 7 are activated by TLR7 and TLR9 signaling pathways, enabling type I IFN production (Baccala et al., 2007). In a model of virus-mediated IFNA/IFNB gene induction in fibroblasts, IRF3 and IRF7 were both required for efficient induction of IFNA and IFNB genes, as they cooperate with each other as DNA-binding transcription factors at the promoter (Sato et al., 2000). Studies have suggested that IRF3 is mainly responsible for the initial induction of IFNB, whereas IRF7 is involved in the late phase of both IFNA and IFNB gene induction. Honda et al (Honda et al., 2005) showed a robust induction of IFNA/IFNB mRNA expression upon CpGstimulation (a TLR9 agonist) of splenic-derived pDCs, which was abolished in splenic-derived pDCs from Irf7−/−mice, despite the normal expression of TLR9 mRNA. In contrast, induction of IFNA/IFNB mRNA expression occurred normally in Irf3−/−pDCs. Similar results were obtained upon stimulation with synthetic single-stranded RNA (TLR7 agonist). Their results suggest that IRF7 is essential and IRF3 is dispensable for MyD88-dependent induction of IFNA/IFNB genes via the TLR9 and TLR7 in pDCs in these animal models.

Role of interferon-α in cellular autoimmunity

The induction of IFNA gene expression may represent a finely tuned mechanism by which different cell types within the innate and adaptive immunity systems produce specific IFN-α subtypes in response to different stimuli, and in different physiological and pathological conditions. Although IFN-α and IFN-β are produced by a wide range of cells such as macrophages, fibroblasts, and endothelial cells, plasmacytoid dendritic cells (pDCs) are thought to be the major cell type responsible for producing high levels of IFN-α in response to RNA or DNA viruses. PDCs are thought to produce type I IFN in response to nucleic acid-containing immune complexes through activation of TLRs 7 and 9 (Ronnblom et al., 2003), which is relevant in autoimmune conditions such as SLE in which these types of immune complexes are prevalent. IFN-α has been reported to modulate the number and function of several key immune effector cells such as B cells, T effector cells, and regulatory T cells in autoimmune disease. For instance, type I IFN induced by pDCs significantly stimulated full differentiation of autoreactive B cells into Ig-secreting plasma cells and promote B cell survival in B cells purified from anti-snRNP Ig Tg mice upon TLR7/9 stimulation (Ding et al., 2009). These responses were partially abrogated by neutralization of IFN-α/β and IL-6 (Ding et al., 2009). IFN-α also plays a major role in T cells by inducing immunogenic T cell responses. Ag-specific naïve CD8+ T cells primed in the presence of

IFN-α undergo marked proliferation and acquisition of effector functions (Le Bon et al., 2006). In addition, T cells isolated from the skin of psoriasis patients show an increased and prolonged IFN-α signaling pathway activation when compared with infiltrating T cells from skin of non-psoriatic donors (Eriksen et al., 2005). With regard to Foxp3+ Treg cells, it has been shown that IFN-α mediates the inactivation of human Treg cells by downregulating intracellular cAMP levels and negative regulation of T-cell receptor signaling, and might be responsible for autoimmune dysfunctions associated with IFN-α treatment of hematologic malignancies (Bacher et al., 2013). Similarly, the blockade of Treg cell development by IFN-α-producing antigen-presenting cells has been suggested as a pathogenic factor in untreated active SLE patients (Yan et al., 2008).

Type I Interferon in systemic lupus erythematosus

Increased serum IFN-α and IFN-α-induced gene expression are frequently observed in systemic lupus erythematosus (SLE) patients, suggesting that type I IFNs are important in the molecular pathogenesis of the disease (Ytterberg and Schnitzer, 1982, Crow et al., 2003, Baechler et al., 2003). High circulating levels of type I IFN are frequent in SLE patients, and correlate with SLE disease severity, as well as with the presence of SLE-associated autoantibodies (Baechler et al., 2003; Ronnblom et al., 2003; Feng et al., 2006; Niewold, 2008; Weckerle et al., 2012). In addition, healthy first degree relatives of SLE patients frequently have higher serum IFN-α levels compared to healthy unrelated individuals (Mavragani et al., 2007; Niewold et al., 2008a), suggesting that high serum IFN-α is a heritable risk factor for SLE. It is likely that the high concentrations of circulating IFN-α is produced by excessive pDC activation. Aberrant activation of endosomal TLR within pDCs via ICs is one of the mechanisms behind the activation of pDCs in SLE (Alexopoulou et al., 2001). In support of this model, in vitro studies have shown that DNA-containing ICs purified from serum of active SLE patients, but not protein-containing ICs from other autoimmune rheumatic diseases, induces pDCs to produce IFN-α, and other pro-inflammatory cytokines and chemokines, known to contribute directly to the pathogenesis of SLE (Means et al., 2005; Ronnblom et al., 2003; Lovgren et al., 2004).

Recent studies have shown that both anti-double-stranded DNA (ds-DNA) and anti-RNA binding protein autoantibodies can trigger IFN-α production in in vitro systems (Ronnblom et al., 2003; Lovgren et al., 2006; Rekvig and Nossent, 2003). These ICs are associated with high IFN in SLE patients, but are not sufficient to cause high levels of circulating IFN in humans (Niewold et al., 2008c). These data would suggest that underlying genetic susceptibility, possibly resulting in a hyperactive TLR system, may also be required for the ICs to result in systemic increases in IFN-α. This hypothesis has been supported by emerging data demonstrating genetic associations between variants in the IRF pathways with both SLE susceptibility and increased circulating IFN-α in SLE patients. For instance, single nucleotide polymorphisms (SNPs) in the IFN-regulatory factor 5 (IRF5)and tyrosine kinase 2 (TYK2) genes have been associated with SLE susceptibility in several populations (Sigurdsson et al., 2005, Graham et al., 2006, Kawasaki et al., 2008, Feng et al., 2010). In addition to the association of SNPs in IRF5 with SLE susceptibility, we have shown an association of the IRF5 risk haplotype with higher serum IFN-α activity in SLE patients (Niewold et al., 2008b). Also, we have observed associations between genetic variations in

IRF genes and SLE-associated autoantibody profiles. For example, the same genetic variants in IRF5 which are associated with increased IFN-α are also associated with autoantibody formation, and these effects are independent (Niewold et al., 2012, Cherian et al., 2012). This suggests a feed-forward mechanism, in which the same genetic variant predisposes the patient to autoantibody formation (possibly via TLR pathway stimulation in B cells), and then the autoantibodies result in increased IFN-α production by pDCs in the setting of the same genetic variants downstream of TLRs (Jensen and Niewold, 2015). IRF-7 is considered a master regulator of type I IFN induction and IFN-stimulated gene expression (Honda et al., 2005). Similar to IRF5, SLE-associated genetic variants in IRF7 are associated with both increased circulating IFN-α as well as autoantibody formation (Salloum et al., 2010). This parallel pattern observed with both IRF5 and IRF7 variations supports the idea that genetic variants downstream of TLRs follow a similar feed-forward mechanism with respect to IFN-α (Salloum and Niewold, 2011). It seems that the autoantibody ICs are important for high circulating IFN-α in SLE patients, suggesting an induced model in which the upstream stimulus acts upon overactive variants in the downstream signaling pathway. A recent gene expression microarray study showed that this was particularly important in African-American SLE patients, as activation of IFN-related pathways was dependent on the presence of RNA-binding proteins (anti-RBP) antibodies in this ethnic background, while evidence for IFN pathway activation was observed in some European-American SLE patients who lacked these antibodies (Ko et al., 2013). STAT4 is a transcription factor belonging to the STAT protein family, and a genetic variant of STAT4 has been associated with the risk of SLE (Remmers et al., 2007). This risk allele is also correlated with presence of SLE-associated anti-ds-DNA autoantibodies (Sigurdsson et al., 2008). STAT4 is required for optimal IFN transcription downstream of IFNAR activation, as well as for the transcription of IFN-α induced genes (Tyler et al., 2007). We find that the SLE-associated STAT4 allele is associated with increased sensitivity to IFN-α in SLE patients, being associated with an increased amount of IFN-induced gene expression for a given amount of IFN-α in circulation (Kariuki et al., 2009). A similar phenomenon was observed with the SLE-risk allele of the interferon induced with helicase C domain 1 (IFIH1) gene (Robinson et al., 2011), supporting the idea that genetic variants can tune the IFN pathway by both modulating IFN-α production and sensitivity to IFN-α.

Currently, a number of anti-IFN-α monoclonal antibodies are in clinical trials for SLE, and thus far the proof of concept data is encouraging. Preliminary data from a phase I clinical trial of the anti-IFN-α monoclonal antibody MEDI-545 in SLE patients suggested possible disease activity improvement among SLE patients (Wallace et al., 2007). Furthermore, in another phase I clinical study, the authors reported a dose-dependent inhibition of IFN-α/β-inducible genes in both peripheral blood and skin biopsies in SLE patients treated with a single dose of an anti-IFN monoclonal antibody, as well as a possible reduction in clinical disease activity (Yao et al., 2009). Further data from phase II and phase III trials will be needed to assess the clinical efficacy of anti-IFN-α agents in SLE.

Type I interferon in autoimmune myositis

Similar to SLE, studies in the last several years have documented marked over-expression of type I IFN-inducible genes and IFN-regulated proteins in the peripheral blood and inflamed

muscle tissues of patients with autoimmune myositis, with pDCs infiltrating inflamed tissues (Tezak et al., 2002, Zhou et al., 2004, Greenberg et al., 2005, Baechler et al., 2007, Lopez de Padilla et al., 2007, Niewold et al., 2009, Shrestha et al., 2010, Higgs et al., 2011). Many of these IFN-induced genes are similar to those which are upregulated in SLE. Also, studies have suggested a genetic or heritable component to the high type I IFN levels observed in this disease, similar to seen in SLE (Niewold et al., 2010, Niewold et al., 2011). The expression of the type I IFN-inducible genes in dermatomyositis (DM) also correlates positively with disease activity and with titers of anti-Jo1 and anti-Ro autoantibodies, which can be observed in this disease (Baechler et al., 2007, Niewold et al., 2009). As a result of these observations, great interest has been directed toward the role of type I IFNs in the pathogenesis of DM. Recent studies suggest that the engagement of endosomal TLRs by ICs containing anti-Jo-1 or anti-Ro 60 autoantibodies and self-antigens may activate endogenous IFN-α production in myositis patients (Eloranta et al., 2007, Balboni et al., 2013). In line with these findings, a study published by Cappelletti and colleagues showed that TLR3 mRNA transcript and protein were upregulated in muscle tissue from DM patients compared to controls, and were uniquely found to be associated with muscle type I IFN-dependent transcripts (Cappelletti et al., 2011). More recently, the endoplasmic reticulum stress response pathway (unfolded protein response) has been suggested to contribute to skeletal muscle damage and dysfunction in autoimmune myositis. Proposed mechanisms by which the unfolded protein response contributes to muscle pathology include induction of MHC class I expression in immature myoblast precursors, and augmented type I IFN production by muscle cells as well as by the infiltrating pDCs in the inflamed muscle tissue (Nagaraju et al., 2005, Tournadre et al., 2010, Vitadello et al., 2010, Tournadre et al., 2012).

Type I interferon in Multiple sclerosis

Multiple sclerosis (MS) is a disorder of the central nervous system characterized by inflammation, demyelination, and neurodegeneration with presumed autoimmune origin. The pathological lesion of MS consists of multiple focal demyelinated plaques within the central nervous system with variable degree of inflammation and gliosis (Frohman et al., 2006). The inflammatory infiltrates in acute and relapsing-remitting MS lesions are composed mainly of activated macrophages and CD8+ cytotoxic T lymphocytes, which are predominantly clustered in the perivascular white matter (Noseworthy et al., 2000; Frohman et al., 2006, Popescu et al., 2013). In contrast to other autoimmune diseases, MS patients have lower levels of circulating type I IFN than controls (Hertzog et al., 1991, Reder and Feng, 2013, Feng et al., 2012). Additionally, the mRNA expression levels of IFNα/βregulated antiviral proteins 2′,5′-OAS and MxA are significantly lower in peripheral mononuclear cells from untreated MS patients with exacerbations or rapid disease progression compared to MS patients with stable disease (Feng et al., 2002). And while type I IFNs are thought to induce some autoimmune conditions such as SLE as noted above, MS is effectively treated by administering recombinant human IFN-β. In MS, treatment with IFN-β abrogates the development of new inflammatory lesions as detected using MRI, reduces relapses in many patients with relapsing-remitting MS, and slows disease progression (Jacobs et al., 1996). In contrast, IFN gamma (type II IFN) appears to exacerbate the disease (Panitch et al., 1987).

The mechanistic basis for low IFN expression in MS is not well-understood, but some evidence suggests that IFN signal transduction is defective in MS patients. In the above-mentioned study in untreated relapsing-remitting MS patients (Feng et al., 2002), blood mononuclear cells also showed downregulation of IRF1 and IRF2 genes, two key transcription factors that regulate many type I IFN-regulated genes and IFN-α-induced expression of the antiviral proteins 2′,5′-OAS and MxA. Nevertheless, the IRF1 and IRF2 expression levels only increased slightly above the baseline levels in response to IFN-β-1b therapy (Feng et al., 2002), suggesting that MS patients may have a defect in IFN signaling which is only partially reversed by therapy. Although most MS patients display low levels of type I IFN-regulated genes, a subset of MS patients has a high IFN signature as well as more clinical and MRI disease activity before therapy, and these patients often do not respond to IFN-β treatment (Comabella et al., 2009, Hundeshagen et al., 2012, Matas et al., 2014), suggesting that MS immunopathogenesis may differ between patients. The heterogeneity among MS patients with respect to IFN induction and expression of IFN-induced genes, may, in part, explain the varied clinical response to IFN-β treatment observed in a MS population. Additionally, the MS-like illness neuromyelitis optica is associated with higher circulating IFN levels, and similarly does not respond well to IFN-β treatment (Feng et al., 2012).

Type I IFN in rheumatoid arthritis

Several observations suggest that type I IFN is involved in the pathogenesis of rheumatoid arthritis (RA). First, IFN immunotherapy has been reported to induce RA (Passos de Souza et al., 2001; Ionescu et al., 2008; Cacopardo et al., 2013). Second, type I IFN has been reported in the circulation and synovial tissues of a subset of RA patients (Olsen et al., 2004, Mavragani et al., 2010). A recent study reported by van der Pouw Kraan and colleagues showed that many IFN-inducible transcripts up-regulated in RA patients were very similar to those up-regulated in SLE patients, including G1P2/ISG15 (interferon-induced protein 15), MX1 (Myxovirus resistance 1), IFIT1 (interferon-induced with tetratricopeptide repeats 1), IFIT2, IRF7, and IFRG28 (28 kDa interferon responsive protein) (van der Pouw Kraan et al., 2007). In this study, RA patients with higher IFN-response gene expression in peripheral blood had increased activity of complement, coagulation cascades, and fatty acid metabolism pathways compared to patients with low IFN-induced gene expression in peripheral blood cells. In addition, phenotypic analysis has shown prominent expression of IFN-β protein by macrophages, DCs, and fibroblast-like synoviocytes in rheumatoid synovium compared with controls (van Holten et al., 2005). Fibroblast-like synoviocytes play a major role in the initiation and perpetuation of synovial inflammation, suggesting that type I IFN might be involved in chronic inflammation and joint destruction in RA.

While the relevance of the IFN signature to RA disease activity and progression remains unclear, some studies suggest that type I IFN in circulation may predict response to immunotherapy in RA (Mavragani et al., 2010, Thurlings et al., 2010). Thurlings and colleagues recently showed that RA patients with a low IFN signature had a better clinical response to rituximab compared with patients with a high IFN high signature (Thurlings et al., 2010). Similarly, Sekiguchi and colleagues also showed that in RA patients treated with infliximab (anti-TNF-alpha antibody) and that had a high IFN signature at baseline, disease

activity was higher as measured using the disease activity of 28 joints (DAS28) score (Sekiguchi et al., 2008). Furthermore, they showed that changes in IFN-regulated gene expression during infliximab treatment correlated with changes in DAS28 score and individual clinical parameters, more prominently in responders. Interestingly, an increase in the IFN-regulated gene levels was associated with disease activity flare after 2 weeks in the non-responders. Mavragani et al examined pre-treatment serum from RA patients who were to receive anti-TNF-α, and found that the ratio of IFN-β/IFN-α in circulation provided some ability to predict those patients who would respond to anti-TNF-α treatment (Mavragani et al., 2010). Thus, type I IFN might be a feasible biomarker for predicting or monitoring response to biologic agents in RA.

Type I IFNs and Tumor Necrosis Factor Alpha Cross-Regulation

TNF-α is a pleiotropic cytokine with potent proinflammatory effects, and is elevated in inflammatory diseases such as RA and inflammatory bowel disease (Feldmann and Maini, 2001). TNF-α is a recognized and relevant therapeutic target to attenuate the chronic inflammation in those diseases. As TNF-α inhibitors have gained wider clinical use for inflammatory diseases such as RA, psoriatic arthritis, juvenile idiopathic arthritis, and inflammatory bowel disease, they have been associated with the new onset of cutaneous and systemic autoimmune disorders such as the paradoxical development of psoriasis and psoriasiform eruptions, leukocytoclastic vasculitis, and anti-TNF-induced lupus in patients receiving anti-TNF-α therapy for Crohn's disease or RA (Sfikakis et al., 2005, Flendrie et al., 2005, Williams et al., 2009, Sokumbi et al., 2012, Denadai et al., 2013). These manifestations can occur with any of the available TNF inhibitors and withdrawal of anti-TNF-α therapy usually leads to resolution of symptoms. Moreover, a subset of SLE patients treated with anti-TNF-α therapy has shown increased titers of anti-dsDNA antibodies (Aringer et al., 2004). The immune mechanisms underlying the development of new onset features of other immune disorders distinct from the primary rheumatologic disease remain unclear. Although it has been reported that the monocyte-gene expression profile in SLE is predominantly IFN-driven, while the RA cytokine profile is mainly TNFα-driven, both types of responses are present in SLE and RA (Smiljanovic et al., 2012, Weckerle et al., 2012), and these cytokines are hypothesized to counteract each other. Accumulating evidence suggests that the inhibition of TNF-α might cause disequilibrium in the balance of serum cytokine profiles, potentially skewing the immune system towards activated IFN-α signaling pathway. The immunostimulatory effects of IFN-α can then lead to pathological activation of T cells and DCs and a subsequent inflammatory response (Palucka et al., 2005, Fiorentino, 2007, Aringer and Crow, 2008, Asarch et al., 2009). A study in Sjogren's syndrome patients supports this idea, as TNF-α inhibition resulted in increased type I IFN-induced gene expression in peripheral blood immune cells (Mavragani et al., 2007). Similarly, TNF-α blockade in inflammatory myositis patients resulted in an increase of pre-existing high IFN-induced gene expression, and TNF-α blockade was associated with clinical worsening (Dastmalchi et al., 2008).

Conclusions

Type I IFNs exert many effects on the immune system including antiviral, control of proliferation, apoptosis, antitumor activity, and immune modulation. We could not review all of these effects, but have summarized current data regarding type I IFNs in a range of autoimmune diseases. The fact that type I IFNs can be both beneficial and detrimental in autoimmune diseases illustrates both the central nature of type I IFN in human immunity and tolerance, as well as the complexity inherent in the system. The cellular and molecular mechanisms underlying the pathogenic role of IFN-α and IFN-β in autoimmunity are not well understood, and this represents an active area of investigation in immunology and translational research. Such studies may lead to a better understanding of the involvement of these pleiotropic cytokines in chronic inflammation and immunity, and targeting IFN transduction pathways could potentially enable new therapeutic avenues.

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Abbreviations

IFN	interferon
IFNA	interferon alpha gene
IFN-α	interferon α protein
IFNB	interferon beta gene
IFN-β	interferon β protein
SLE	systemic lupus erythematosus
IIM	idiopathic inflammatory myopathies
DC	dendritic cells
JAK	Janus kinase
STAT	signal transducer and activator of transcription
TYK2	tyrosine kinase 2
IRF	IFN-regulatory factor
PDCs	plasmacytoid dendritic cells
ICs	immune complexes
SNP	single nucleotide polymorphism
IFNAR	Type I interferon receptor

TLR	toll-like receptor
ICs	Immune complexes
MS	multiple sclerosis
RA	rheumatoid arthritis

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Highlights

- The interferon-alpha (IFNA) gene cluster consists of at 13 IFNA homologous genes
- The type I IFN genes exhibit diverse biological functions in cellular immunity
- IFN-α plays a role in several autoimmune diseases, including lupus and myositis
- Clinical trials with anti-IFN-α antibodies are underway in autoimmune disease
- In contrast, IFN-β is an effective treatment for multiple sclerosis

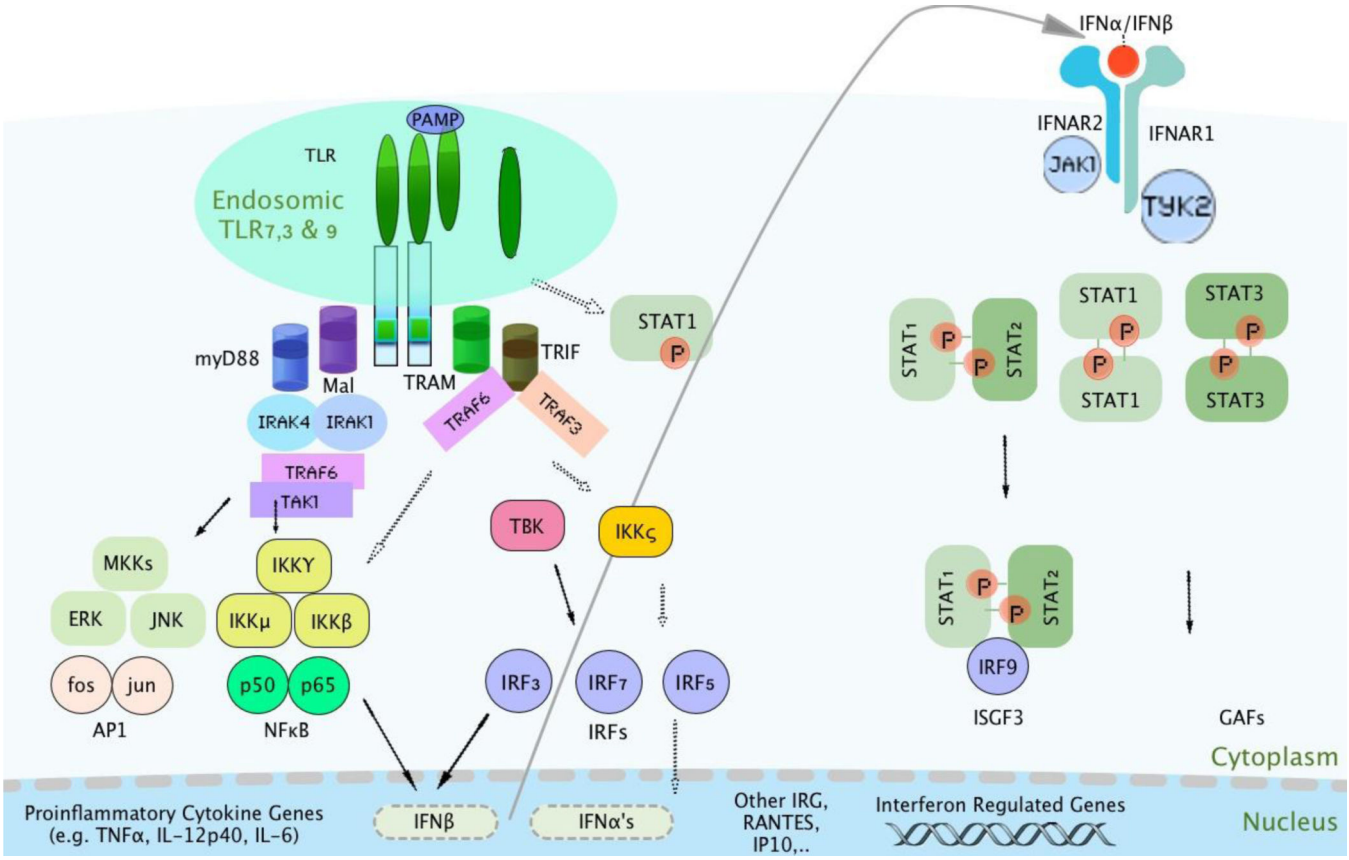

Figure 1.

Schematic diagram shows major signaling pathways stimulated by IFN-α/β (mediated by the type I IFN receptor) and viral pathogen-associated molecular patterns (PAMPs) and/or ICs-containing nucleic acids (mediated by endosomal TLRs). PAMPs or their mimics are detected by TLRs and RNA helicases. The signaling pathways finally lead to the induction of IFN-α/β as well as several IFN-inducible genes. IFN-α/β is then secreted and signals through the type I IFN receptor and the JAK/STAT pathway to regulate the expression of IFN-inducible genes, thereby generating antiviral, anti-proliferative, and immunomodulatory effects.