

REVIEW

Type I IFN and TNF α cross-regulation in immune-mediated inflammatory disease: basic concepts and clinical relevance

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Abstract

A cross-regulation between type I IFN and TNF α has been proposed recently, where both cytokines are hypothesized to counteract each other. According to this model, different autoimmune diseases can be viewed as disequilibrium between both cytokines. As this model may have important clinical implications, the present review summarizes and discusses the currently available clinical evidence arguing for or against the proposed cross-regulation between TNF α and type I IFN. In addition, we review how this cross-regulation works at the cellular and molecular levels. Finally, we discuss the clinical relevance of this proposed cross-regulation for biological therapies such as type I IFN or anti-TNF α treatment.

Type I IFN and TNF α : cytokines with pleiotropic functions

The family of type I IFN consists of multiple subtypes of IFN α , a single IFN β and some less characterized family members, such as IFN ϵ , IFN κ and IFN ω . The difference in biological function between the multiple subtypes of type I IFN is unclear, especially since the induced genes downstream of the different types of IFN (the IFN response program) are highly similar between, for example, IFN α and IFN β . In peripheral blood, plasmacytoid dendritic cells (pDC) are the main producers of type I IFN. All nucleated cells, however, can produce type I IFN upon activation by, for example, viral infections that trigger cytoplasmic nucleic acid sensors such as TLR-7 and MDA-5.

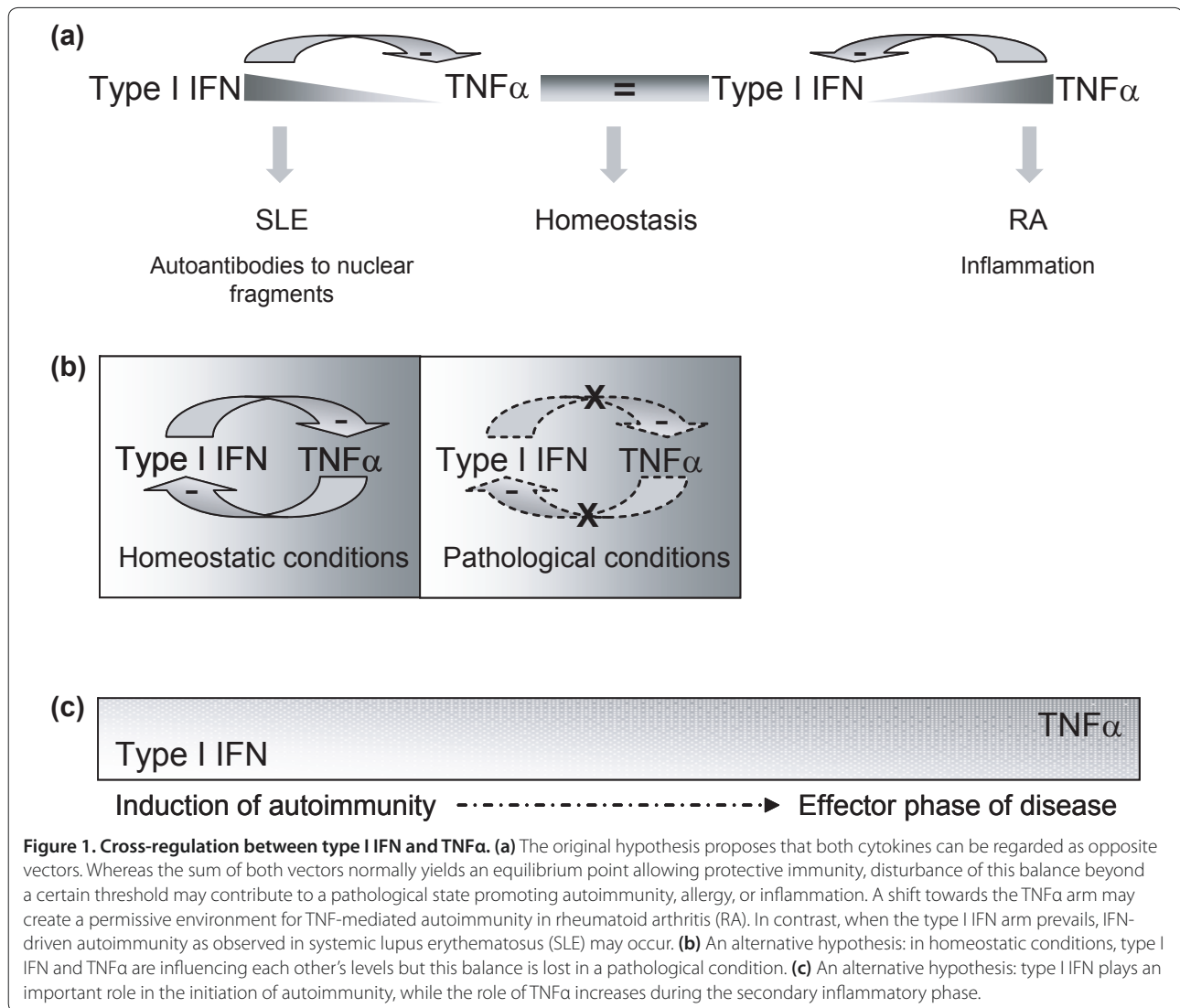
Binding of type I IFNs to their cognate receptor (a heterodimer of IFNAR1 and IFNAR2) leads to the

phosphorylation of signal transducers and activators of transcription (STATs) and transcription of IFN response genes. This results in resistance to viral replication, enhanced MHC class I expression and differentiation of monocytes, all of which contribute to clear infection. Besides an essential role in the host antiviral state, type I IFN has immunoregulatory functions by affecting cell proliferation and differentiation and by inducing anti-inflammatory responses. Considering these important functions of type I IFN in normal homeostasis as well as host response, an aberrant function in type I IFN immunity may contribute to autoimmunity and chronic inflammation. This is illustrated by the observation that melanoma patients treated with IFN α 2 β developed clinical and serological signs of autoimmunity [1] and that patients with a trisomy of chromosome 9, which contains the type I IFN genes, develop high IFN levels and lupus-like disease [2].

TNF α is a pivotal pro-inflammatory cytokine produced by macrophages, activated T cells, natural killer cells and mast cells. Also non-immune, stromal cells are able to produce significant amounts of TNF α . TNF α is produced as a 26 kDa transmembrane protein, which can be cleaved by TNF α converting enzyme to form the 17 kDa soluble form. Upon binding to TNFR1 (which is constitutively expressed on most cell types) or TNFR2 (which is expressed on immune cells, endothelial cells and fibroblasts), TNF α activates the mitogen-activated protein kinase and NF- κ B signaling pathways [3] – which in turn can lead to an amplification of the proinflammatory response by increased production of chemokines and cytokines, including TNF α itself. Endothelial cells respond to TNF α by expressing adhesion molecules to facilitate trafficking of immune cells to the inflamed tissue. Macrophages and neutrophils are attracted to the site, increase their cytokine production, and enhance phagocytic capacities. Taken together, TNF α initiates and orchestrates different mechanisms that lead to an effective immune response in the case of infection.

Besides its role in host defense, however, TNF α is recognized to play a key role in many immune-mediated inflammatory diseases (IMIDs), such as rheumatoid

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arthritis (RA), spondyloarthritis, psoriasis, and inflammatory bowel disease [4]. Accordingly, anti-TNF α treatment is very effective in these conditions. Interestingly, a recent animal study showed that the primary cell target of TNF in chronic inflammatory joint and intestinal diseases is mesenchymal cells [5], a cell type that can produce large amounts of type I IFN.

Cross-regulation of TNF α and type I IFN: the hypothesis

The relative contribution of TNF α and type I IFN to different types of autoimmunity and inflammatory disease is not well understood. An even more complex and intriguing picture emerged from the recently proposed hypothesis of an intimate interplay between both pleiotropic cytokines [6,7]. This hypothesis proposes that, similarly to Th1 and Th2 cytokines in T-cell biology, both cytokines can be regarded as opposite vectors in

many innate immune responses. If both vectors are in balance, the sum normally yields an equilibrium point allowing protective immunity. Disturbance of this balance beyond a certain threshold may contribute to pathological conditions such as autoimmunity and inflammation (Figure 1a). A shift towards the TNF α arm may create a permissive environment for TNF-mediated autoimmunity such as RA. In contrast, when the type I IFN arm prevails, IFN-driven autoimmunity such as systemic lupus erythematosus (SLE) may occur.

This concept was first formulated by Ivashkiv in 2003 based on the clinical observation that a fraction of RA patients treated with anti-TNF α therapy develop antinuclear antibodies and even sometimes lupus-like syndromes that reverse with the cessation of the therapy [7]. Banchereau and colleagues further established this hypothesis after the observation that five juvenile chronic arthritis patients treated with anti-TNF α therapy showed

overexpression of IFN α -regulated genes in their peripheral blood mononuclear cell (PBMC) compartment compared with untreated control patients [6,8]. In addition, they showed that IFN α production by virally stimulated pDC is inhibited by TNF α through induction of maturation [8]. As this conceptual model may have important clinical implications for treatment with TNF α blockers or with type I IFN, the present review summarizes and discusses the currently available clinical evidence for the proposed cross-regulation between TNF α and type I IFN at the cellular level as well as *in vivo* in experimental models and in IMID patients. A summary of all studies cited is presented in Tables 1 and 2.

Cross-regulation of TNF α and type I IFN at the cellular level

At the cellular level, the hypothesis of cross-regulation between TNF α and type I IFN is based on the observation that TNF α inhibits the generation of pDC as well as the secretion of type I IFN by immature pDC upon viral triggering [8]. Incubation of influenza-virus activated pDC with TNF α inhibited the IFN α production by 40%, which was due to maturation of the pDC by TNF α rather than a direct inhibition or cross-regulation. *In vitro* culture of healthy PBMCs with the soluble TNF α receptor etanercept resulted in a dose-dependent increase in the expression of IFN α and IFN α -inducible genes [9]. These studies specifically focused on IFN α and not on IFN β , but similar genes are induced by IFN β . In contrast with these findings in PBMCs, studies on human fibroblasts indicated that stimulation with TNF α induced an approximately 16-fold increase in the steady-state level of IFN β mRNA [10]. Moreover, it has been shown more recently that TNF α induces a type I IFN response program in macrophages through IFN regulatory factor-1 activation, leading to an IFN β -mediated autocrine loop [11]. The TNF α canonical pathway and the IFN β pathway may thereby synergize in the expression of downstream response genes. Taken together, these data suggest that the suppressive effect versus stimulating effect of TNF α on the synthesis of type I IFN is not universal but, rather, is cell-type dependent.

The opposite question related to the presumed cross-regulation is whether type I IFN suppresses TNF α production. Indeed, several studies have shown suppressive effects of type I IFN. Stimulation of peripheral blood cells with IFN β decreases the production of TNF α [12,13]. In addition, IFN β augmented dexamethasone-mediated suppression of TNF α in a human monocytic cell line [14]. A study on human macrophages indicated that IFN α can suppress TNF α production after immune complex, Fc receptor or Toll-like receptor stimulation by induction and activation of Axl, a receptor tyrosine kinase that induces the expression of a transcriptional

repressor of the TNF α promoter [15]. Moreover, IFN β can induce the expression of tristetraprolin, an RNA-binding protein that destabilized the mRNA of proinflammatory cytokines including TNF α [16]. Accordingly, IFN-induced tristetraprolin limits lipopolysaccharide (LPS)-induced expression of several proinflammatory cytokines, including TNF α , by macrophages.

Of interest, the inhibitory effect of IFN β on TNF α production by human monocytes was shown to be stimulus dependent. IFN β diminishes TNF α production in T-cell contact-activated monocytes, while IFN β enhances TNF α production in LPS-activated monocytes [17]. Another study showed that direct stimulation of murine macrophages with IFN β does not suppress TNF α but, on the contrary, induces a fourfold upregulation of TNF α mRNA expression [18]. Whether the same holds true for IFN α awaits further investigation. Besides these direct effects, low constitutive expression of type I IFN in many cell types contributes to boost the responsiveness towards other cytokines. This phenomenon – called cross-priming – implicates that previous exposure to low doses of the pleiotropic type I IFN enhances subsequent response to proinflammatory cytokines such as TNF α [19]. Taken together, these cellular studies yield conflicting results going from cross-priming to cross-regulation of TNF α production by type I IFN. This may be partially due to differences in experimental settings mimicking homeostasis versus inflammatory conditions.

Counterbalance of TNF α and type I IFN in experimental models of inflammation and autoimmunity

The cellular studies indicated that the proposed cross-regulation of type I IFN and TNF α may depend on both cell type and inflammatory conditions, thereby emphasizing the need for additional information on this cross-regulation *in vivo* in the context of tissue inflammation and autoimmunity. The NZB/W mouse, a model for SLE, bears a genetic defect in the TNF α gene that leads to reduced levels of TNF α [20]. These mice develop anti-nuclear antibodies and nephritis. In accordance, treatment of the mice with TNF α resulted in attenuation of the disease.

An IFN α signature has been characterized in the splenic mononuclear cells of pre-autoimmune NZB/W mice that is not observed in BALB/c control mice [21]. Also, whereas IFN α serum levels are undetectable in both Balb/c control mice and NZB/W mice under homeostatic conditions, NZB/W mice but not Balb/c control mice produced IFN α after poly I:C stimulation [22]. On the other hand, IFN β KO mice, which have an increased susceptibility to experimental autoimmune encephalomyelitis, display extensive microglia activation and TNF α

Table 1. Complex relation between TNF α and type I IFN in human studies

Cross-regulation	Cell type	Activation state	Experimental model	Results	Reference
TNF \downarrow \Rightarrow IFN \uparrow	PBMCs	JIA	Anti-TNF α -treated vs. untreated patients	Patients treated with anti-TNF α showed higher IFN α -regulated genes	[8]
	PBMCs	Healthy	<i>In vitro</i> culture with etanercept	Dose-dependent increase in transcription of IFN α inducible genes	[9]
	Blood	RA	Infliximab-treated RA patients	Upregulation of type I IFN response genes only in patients with a poor clinical response	[52]
	Serum	SpA	Etanercept-treated SpA patients (all good clinical response)	Small increase in IFN α activity after 12 weeks of treatment	[53]
	Plasma	SS	Etanercept-treated SS patients (poor clinical response)	Increase plasma in IFN α activity after 12 weeks of treatment	[9]
	Plasma	Inflammatory myopathy	Infliximab-treated patients (no clinical response)	Increase in serum type I IFN activity	[55]
TNF \downarrow \Rightarrow IFN \downarrow	Serum	SpA	Infliximab-treated SpA patients (all good clinical response)	Slightly decrease in IFN α activity after 2 weeks that returns to baseline after 12 weeks	[53]
TNF \uparrow \Rightarrow IFN \downarrow	pDC	Influenza virus	Incubation of virus-activated pDC with TNF α	TNF α inhibited IFN α , probably due to pDC maturation	[8]
TNF \uparrow \Rightarrow IFN \uparrow	Fibroblasts	Healthy	<i>In vitro</i> stimulation with TNF α	TNF α induced IFN β mRNA levels	[10]
	Macrophages	Healthy	<i>In vitro</i> stimulation with TNF α	TNF α induced type I IFN response program through IFN regulatory factor-1, leading to an IFN β -mediated autocrine loop	[11]
	Serum	Juvenile DM	TNF-308 promotor polymorphism	Only in untreated patients: increased levels IFN α in carriers of minor allele, which is associated with increased TNF α production	[43]
	PBMCs	RRMS	Concanavalin A-stimulated PBMCs obtained from IFN β -treated MS patients	More production of TNF α in concanavalin A-stimulated PBMCs after IFN β treatment	[57]
IFN \uparrow \Rightarrow TNF \downarrow	Monocytes	Healthy	Pre-incubation (30 min) with IFN β , subsequent stimulation with LPS	IFN β pretreatment enhanced LPS-induced TNF α production by monocytes	[17]
	Macrophages	Healthy	<i>In vitro</i> pretreatment with IFN α (100 U/ml) and subsequent immune complexes, Fc receptor or TLR stimulation	IFN α suppressed Fc γ R-induced, TLR2-induced and TLR4-induced TNF α production through induction of Axl, a repressor of TNF α promoter	[15]
	PBMCs	RRMS	Anti-CD3-stimulated PBMCs obtained from IFN β -treated MS patients	IFN β therapy decreased the production of TNF α by anti-CD3-stimulated PBMCs	[57]
	Synovial tissue	RA	Type I IFN treatment of RA patients	Decreased levels of TNF α in synovial tissue in some patients	[58]
	PBMCs	Healthy	PHA and IFN β -treated PBMCs	IFN β decreased PHA-induced TNF α production by PBMC	[12]
	Co-cultures of T lymphocytes and monocytes	Healthy	Co-cultures of T lymphocytes and monocytes stimulated by PHA in the presence of IFN β	IFN β inhibits the ability of stimulated T lymphocytes to induce cell contact-mediated TNF α production in monocytes	[13]
	THP-1	Cell line	Pre-incubation (24 hours) with IFN β 1b, subsequent stimulation with LPS in the presence or absence of dexamethasone	LPS-induced TNF α production by THP-1 cells was suppressed by dexamethasone. This suppressive effect was augmented by pre-incubation with IFN β	[14]
	Monocytes	Healthy	Pre-incubation (30 min) with IFN β , subsequent stimulation with plasma membranes of PHA + PMA-stimulated HUT-78 cells	Pretreatment with IFN β decreased TNF α production by contact-activated monocytes	[17]
	PBMCs	Healthy	IFN β administration and <i>ex vivo</i> mitogen stimulation of PBMCs	IFN β induced a transient decrease of inflammatory cytokines including TNF α	[56]
	IFN \downarrow \Rightarrow TNF \downarrow	Blood and skin lesions	SLE	Treatment with an anti-IFN α antibody in SLE patients	Downmodulation of TNF α mRNA levels

DM, dermatomyositis; HUT-78, human T-cell line; JIA, juvenile idiopathic arthritis; LPS, lipopolysaccharide; MS, multiple sclerosis; PBMC, peripheral blood mononuclear cell; pDC, plasmacytoid dendritic cells; PHA, phytohemagglutinin; PMA, phorbol myristate acetate; RA, rheumatoid arthritis; RRMS, relapsing-remitting multiple sclerosis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SS, Sjögren's syndrome; THP-1, human monocytic cell line.

Table 2. Complex relation between TNF and type I IFN in murine studies

Cross-regulation	Cell type	Activation state	Experimental model	Results	Reference
IFN \uparrow \Rightarrow TNF \downarrow	Embryonic fibroblasts (MEF) and macrophages	p38 MAPK stimulus	<i>In vitro</i> stimulation with IFN β and p38 MAPK stimulus simultaneously	In the presence of a p38 MAPK stimulus, IFN β induces – via STAT1 activation – TTP, which destabilizes mRNA of several proinflammatory genes including TNF α	[16]
	Macrophages	IFN γ and LPS	Priming by IFN γ , stimulation by LPS in the presence of IFN β -EF supernatant	IFN β suppressed LPS/IFN γ induced TNF α production	[26]
	Synovial tissue	CIA	Daily treatment of CIA using recombinant IFN β injection (7 days)	IFN β treatment reduced TNF α production in the synovial tissue	[28]
IFN \uparrow \Rightarrow TNF \uparrow	Macrophages	Healthy	<i>In vitro</i> stimulation with IFN β	IFN β mediated upregulation of TNF mRNA	[18]
IFN \downarrow \Rightarrow TNF \uparrow	Macrophages	LPS and IFN γ	EAE in IFN β KO mice	Increased TNF α production compared with wild-type controls	[23]
	Spleen-derived macrophages	LPS and IFN γ	Cells isolated from IFN β -deficient mice. Priming by IFN γ with subsequent stimulation with LPS	Increased TNF α production compared with control mice	[24]
	Synovial tissue	CIA	CIA in IFN β -deficient mice	Increased TNF α production in synovia of arthritic IFN β -deficient mice	[24]
IFN \downarrow \Rightarrow TNF \downarrow	Liver	TNF α -induced lethal shock	IFNAR1 or IFN β KO mice	Lack of type I IFN signaling protects against TNF α -induced inflammation	[25]
TNF \downarrow \Rightarrow IFN \uparrow	Serum	Poly I:C	NZB/W mouse (defect in TNF) injected with poly I:C	NZB/W mice produce more poly I:C-induced IFN α	[22]

CIA, collagen-induced arthritis; EAE, experimental autoimmune encephalomyelitis; EF, expressing fibroblasts; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; poly I:C, polyinosinic-polycytidylic acid; STAT, signal transducers and activators of transcription; TTP, tristetraprolin.

production in the effector phase of the disease [23]. Macrophages isolated from these mice after experimental autoimmune encephalomyelitis induction produced increased amounts of TNF α after stimulation with LPS and IFN γ , compared with wild-type controls [23]. In addition, these IFN β KO mice are also more susceptible to collagen-induced arthritis and develop an exacerbated disease compared with control mice, with a greater production of TNF α [24]. Of interest, mice lacking the receptor for type I IFN (IFNAR1) or IFN β are protected against TNF α -induced lethal shock [25] – showing that the absence of type I IFN signaling may not only impact TNF α production, but also the outcome of the TNF α -induced inflammation.

These observations also raise the reverse question: does increased type I IFN signaling downregulate TNF α production and/or TNF-induced inflammation? IFN β treatment has a significant therapeutic effect in collagen-induced arthritis in mice and rhesus monkeys as well as in adjuvant arthritis in rats [26-28]. In these models, IFN β was shown to have an inhibitory effect on the production of TNF α by LPS-stimulated macrophages [26]. Indirect upregulation of type I IFN also showed beneficial effects in mouse models of arthritis [29,30]. In addition, mice treated with IFN β had a 50% lowered expression of TNF α in the synovial tissue [28].

Taken together, these animal models demonstrate the presence and functionality of the cross-regulation

between TNF α and type I IFN, but also indicate that this cross-regulation occurs mainly in a context-dependent manner during inflammatory conditions (Table 2). These observations in turn raise the question of whether and to what extent the inflammatory conditions seen in these experimental models are relevant for human IMIDs.

Cross-regulation of TNF α and type I IFN in immune-mediated inflammatory diseases

Upregulation of type I IFN-response genes has now been observed in peripheral blood cells and/or target tissue in many different IMIDs – for example, RA [31], SLE [32], systemic sclerosis [33], multiple sclerosis (MS) [34,35], psoriasis [36,37], Sjögren's syndrome (SS) [38], dermatomyositis [39] and type 1 diabetes [40]. These findings suggest that an activated type I IFN gene expression program may be a common denominator in chronic inflammatory diseases in general. If cross-regulation is present and effective, this activated type I IFN response program should lead to a repressed TNF α profile. Most of these diseases, however, also have an elevated expression of TNF α both systemically and locally in the target tissues. For example, upregulation of both TNF α and type I IFN has been shown in lesional skin in psoriasis [37] as well as in synovial tissues of RA [41] and juvenile idiopathic arthritis patients [42]. The question therefore arises of whether cross-regulation might be insufficient in specific pathological conditions.

The relative balance between IFN α and TNF α has been studied in more detail in juvenile dermatomyositis. By measuring serum IFN α activity, higher serum IFN α levels were shown to be associated with the presence of the TNF α -308 promotor polymorphism [43]. This polymorphism leads to increased production of TNF α in 50% of the carriers of the minor allele [44]. In early untreated patients, serum IFN α activity and TNF α are positively correlated. As the disease progresses, however, serum IFN α activity levels go down while TNF α levels remain stable [43]. This observation indicates that type I IFN might be more important in the earliest phases of the autoimmune phase of disease, while TNF plays a more prominent role in the secondary effector phase of the disease (Figure 1b). Collectively, the relationship between both cytokines is influenced by timing and disease progression.

The relationship between type I IFN and TNF α also appears to be complex in SLE. Patients with SLE display a strong type I IFN signature but also systemic overexpression of TNF α . Moreover, serum TNF α levels correlate with disease activity [45]. Recently, serum levels of both TNF α and IFN α were measured by ELISA in 171 SLE patients. The patients showed elevated levels of both cytokines, and the correlation between both was highly significant [46]. Another study, however, indicated that clustering of SLE patients according to serum IFN α activity and TNF α levels resulted in three groups: a group in which IFN α levels were much higher than TNF α levels, a group in which IFN α and TNF α levels were correlated, and a group in which TNF α levels were much higher than IFN α levels [47]. The latter group had a weaker association with PTPN22 SNPs than the former two groups. This study suggests that the relative balance between both cytokines may also be heterogeneous within one single disease.

This heterogeneity was also confirmed in MS, where a subgroup of patients displayed increased expression levels of type I IFN response genes in the peripheral blood [34]. The extent of this type I IFN signature before treatment was inversely associated with the biological and clinical response to IFN β treatment [35,48]. Elevated TNF α levels have been detected in the peripheral blood and brain lesions of MS patients, and correlated with disease activity [49], but it remains unknown whether there is a relationship with the type I IFN signature.

In RA, TNF α is overexpressed in the primary target tissue of the disease – the synovial membrane [50]. In addition, the expression of IFN β as well as the number of IFN α -expressing and IFN β -expressing pDC is significantly elevated in RA synovial tissue compared with synovial tissues from patients with osteoarthritis or reactive arthritis [41]. A similar picture emerges from peripheral blood, as about one-half of the RA patient

population shows elevated expression levels of type I IFN response genes compared with healthy controls [31]. In the other half of the patients, the type I IFN response gene expression profile is similar to that of healthy controls. Of interest, the peripheral blood IFN gene signature can already be observed in the preclinical phase of the disease [51]. The clinical significance of this elevated type I IFN expression profile in blood is still unknown, as there is no difference in patient characteristics or disease severity between patients with elevated or normal expression levels of type I IFN response genes. Thus, in RA both cytokines appear to be elevated systemically as well as in the target tissue.

Together, these studies in different IMIDs clearly indicate that there is no straightforward balance between the levels of type I IFN and TNF α , and that factors such as the specific type of IMID, the disease phase, and patient-specific factors may contribute to create a complex picture. One also has to consider that it is not completely clear how the absolute levels of these cytokines relate to their functional activity and role in disease pathogenesis.

Cross-regulation of TNF α and type I IFN during targeted treatment

Targeted therapies aimed at regulating cytokine activity provide an experimental approach to study cross-regulation between TNF α and type I IFN in patients. In fact, the concept of TNF α /type I IFN cross-regulation proposed by Banchereau and colleagues was based on the observation that juvenile chronic arthritis patients treated with infliximab (anti-TNF α monoclonal antibody) displayed increased transcription of IFN α -regulated genes compared with untreated patients. However, the inter-individual variability in the expression of IFN α , the relative small number of patients, and the cross-sectional design warranted further translational confirmation of these findings in prospective studies.

Studying 33 RA patients during treatment with infliximab, we observed no overall modulation of the expression of type I IFN response genes by TNF α blockade. Further analysis, however, revealed that infliximab induced an upregulation of the type I IFN genes in a subset of patients with a poor clinical response to treatment [52]. In contrast, the type I IFN response genes were not affected in patients with a good response to TNF α blockade. In spondyloarthritis, a disease that responds very well to TNF α blockade, infliximab treatment induced a small decrease of type I IFN serum activity after 2 weeks but the levels returned to baseline after 12 weeks of treatment. TNF α blockade with the soluble TNF α receptor etanercept led to a small increase in type I IFN serum activity after 12 weeks of treatment in a comparable patient population [53]. Similar results

have been reported for patients with SS and inflammatory myopathies. In SS patients, treatment with the soluble TNF α receptor construct etanercept, which is not clinically effective in SS [54], increased serum IFN α activity [9]. In patients with inflammatory myopathies, infliximab induced an increase in type I IFN serum activity without any clinical improvement and even disease exacerbation in some patients [55]. Collectively, these longitudinal studies indicate that the effect of TNF α blockade on type I IFN is not universal and may depend on the disease, the type of TNF α blocker, as well as the clinical response to treatment.

How are TNF α levels and/or activity affected by type I IFN treatment? In healthy volunteers, administration of IFN β induced a transient decrease of the production of TNF α as well as other inflammatory cytokines such as IL-1 β , IL-6 and lymphotoxin by PBMCs upon *ex vivo* stimulation [56]. In MS, IFN β treatment was also associated with decreased production of TNF α by anti-CD3-stimulated PBMCs. In contrast, concanavalin A-stimulated PBMCs produced more TNF α after IFN β treatment [57], indicating again that the proposed cross-regulation is not universal but is dependent on factors such as stimulus and cell type. In a proof-of-concept trial in RA patients [27], type I IFN treatment had an immunomodulatory effect on synovial tissue inflammation with decreased levels of synovial TNF α expression in some but not all patients [58]. Conversely, treatment with an anti-IFN α monoclonal antibody downmodulated TNF α mRNA expression in peripheral blood and skin lesions in SLE patients [59]. Before treatment TNF α levels were increased compared with healthy controls, but the levels returned to normal 1 day after anti-IFN α treatment. These data indicate that administration of type I IFN β may lead to suppression of TNF α production in RA, whereas blocking IFN α does not directly entail elevation of TNF α levels. Consistent with preclinical studies, this experience with targeted interventions in patients highlights the dependence of the interaction between TNF α and type I IFN on the specific type I IFN subtype, the pathogenesis of the disease, and the intrinsic characteristics of the patient.

Clinical relevance of proposed cross-regulation between type I IFN and TNF α

The cellular, experimental, and human data reviewed here indicate that cross-regulation between type I IFN and TNF α may occur in homeostatic conditions but is certainly not a universal principle in IMIDs. The presence or absence of the cross-regulation seems to depend on many factors, including the exact cell type, the type and level of activation, the specific IMID and, within a single IMID, the individual patient. This complexity questions the potential clinical implications of the conceptual framework of type I IFN–TNF α cross-regulation. Three

relevant questions in this context are as follows: Can the type I IFN signature in IMID contribute to prediction of response to TNF α blockade? Can successful TNF α blockade induce type I IFN-driven adverse effects? And would IFN treatment be a viable option in TNF-driven IMIDs?

Since not all IMID patients respond well to anti-TNF α therapy, it is very relevant to identify biomarkers predicting clinical efficacy. Could the type I IFN signature be such a biomarker contributing to the prediction of response? The expression of type I IFN response genes are upregulated after TNF blockade, especially in patients who have a poor clinical response to treatment [9,52]. In patients with a good response to treatment, the expression of type I IFN response genes seems unaffected by TNF α blockade.

If the regulation of type I IFN is impeded by successful TNF α blockade, does this subsequently lead to type I IFN-driven adverse events? Type I IFN is known to play an important role in B-cell activation and plasma cell differentiation, and the levels are associated with the presence of autoantibodies in SLE [60]. Accordingly, it is conceivable that modulation of type I IFN by TNF blockade may have an impact on autoantibodies. In RA patients, however, TNF blockade had similar effects on the levels of circulating autoantibodies such as rheumatoid factor or anti-citrullinated protein antibodies in type I IFN^{high} patients and type I IFN^{low} patients [61]. Moreover, the induction of anti-nuclear antibodies by TNF blockade, a phenomenon that is frequently observed in both RA and spondyloarthritis [62], was not related to changes in the serum type I IFN activity [53]. From this we can conclude that there is no influence of the interplay between TNF α and type I IFN with respect to autoantibody production during TNF blockade.

Another intriguing side effect of TNF blockade is the induction of psoriasis-like disease in 3 to 5% of arthritis patients without pre-existing psoriasis, which was completely unexpected considering the excellent clinical response of psoriasis to TNF blockade [63]. This side effect was hypothesized to be due to the proposed cross-regulation between TNF α and type I IFN. Recent studies of human psoriatic tissue demonstrate that IFN α is present early in the disease process but is not detectable in the stable plaque, although downstream IFN α signaling continues to be upregulated. [64]. Indeed, skin biopsies of four patients with anti-TNF α -induced psoriasis displayed increased expression of myxovirus-resistance protein A (a protein specifically induced by type I IFN) compared with biopsies from patients with psoriasis vulgaris [65]. It would be of interest to extend this cohort and analyze in more detail the type I IFN profile to provide formal evidence for the hypothesis that TNF α blockade can induce or enhance type I IFN, and thereby psoriasis, in these patients.

A third clinically relevant question based on the potential cross-regulation is whether type I IFN treatment could be a successful treatment strategy in TNF-driven IMIDs. In animal models for arthritis, a beneficial effect of IFN β treatment on both swelling and joint destruction has consistently been observed [26,28]. Similar results have been obtained in a collagen-induced arthritis model in rhesus monkeys [27]. A multicenter, randomized, double-blind, placebo-controlled phase II study of subcutaneous IFN β 1a in 209 patients with active RA, however, did not indicate a clinical or radiological effect [66]. This discrepancy might relate to the mode of administration and the difference in IFN β 1a dosages used in man and mice. A successful example of IFN β treatment is observed in MS, a disease in which TNF α has been shown to play an important role [49]. Further investigation of type I IFN therapy using innovative approaches is thus warranted in RA and other TNF-driven IMIDs.

Conclusion

The present review summarizes the currently available clinical evidence for the proposed cross-regulation between TNF α and type I IFN at the cellular level as well as *in vivo* in experimental models and in patients with IMIDs (Tables 1 and 2). Since both cytokines have pleiotropic effects that depend on the timing, dosage and cell type, the *in vitro* studies yielded conflicting results and indicated that the proposed cross-regulation is not as clear cut as anticipated. Moreover, the molecular mechanism of cross-regulation between both cytokines is completely unclear and might be an indirect result through the induction of other factors. Most experimental *in vivo* models support the concept of cross-regulation between both cytokines but again some studies yielded opposite results, confirming the fact that the cross-regulation may be context dependent.

The studies in patients with different IMIDs show there is not necessarily a direct balance between the levels of type I IFN and TNF α , and that factors such as the type of IMID, the disease phase, and patient heterogeneity may contribute to create a complex picture. It is also possible in patients with IMIDs that both cytokines are elevated and are still influencing each other's levels from rising even further.

An additional layer of complexity is added by the subtle differences in function of the different subtypes of type I IFN and the difficulty to directly measure these individual isoforms. The usage of type I IFN-induced genes is valuable, but this signature is not always a synonym for the presence of type I IFN specifically. Moreover, how the levels of these cytokines relate to their functional activity and role in disease pathogenesis is still to be investigated.

Abbreviations

ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IL, interleukin; IMID, immune-mediated inflammatory disease; LPS, lipopolysaccharide; MS, multiple sclerosis; NF, nuclear factor; PBMC, peripheral blood mononuclear cell; pDC, plasmacytoid dendritic cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; SS, Sjögren's syndrome; Th, T-helper type; TNF, tumor necrosis factor.

Competing interests

TC, DB and LGMvB have no competing interests. PPT is Chief Scientific Officer of Arthrogen and holds shares in Arthrogen b.v. PPT is owner of the following patent: Method for prognosticating the clinical response of a patient to B-lymphocyte inhibiting or depelting therapy.

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