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REVIEW

Type III Interferons (Lambda Interferons) in Rheumatic Autoimmune Diseases

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Abstract
The last 2 decades have witnessed the discovery and characterization of a new family of cytokines with immunological characteristics similar to those described for type I interferons, type III or lambda interferons. Unraveling the molecular mechanisms underlying each type of interferon has allowed us to understand how some autoimmune diseases can be considered as interferonopathies. Under normal conditions, type III interferons play a key role in the defense against viruses by modulating the functioning of several types of innate and adaptive immune cells. These effects include upregulation of major histocompatibility complex molecules by myeloid dendritic cells, increased functioning of pattern recognition receptors by plasmacytoid dendritic cells, decreased activity of regulatory T cells, enhanced production of antibodies by plasmatic cells and increased expression of chemokines and adhesion molecules by leukocytes and endothelial cells. Notably, all these mechanisms have been described to boost autoimmunity, and type III interferons pathway activation has been related to the pathogenesis of autoimmune conditions such as systemic lupus erythematosus, systemic sclerosis and Sjögren's syndrome. This review provides an overview of the current evidence on the contribution of type III interferons in the pathogenesis of rheumatic autoimmune diseases in humans.

Keywords Interferons · Autoimmunity · Inflammation · Jak/STAT pathway · Systemic lupus erythematosus

Introduction

The term interferon encompasses a heterogeneous group of soluble molecules described more than half a century ago, which are part of the class II cytokine family. Interferons were originally identified based on their antiviral activity, but subsequently they were recognized as having antiproliferative and immunomodulatory activities. Recently, its role as key mediators in the pathogenesis of different autoimmune diseases is being recognized (Lazear et al. 2019).

Type III or lambda interferons (IFN-λ) are the most recent addition to the interferon family, since these were described in 2003 by two independent groups, one headed by Kotenko and the other by Sheppard (Kotenko et al. 2003; Sheppard et al. 2003). Type III interferon genes are located on human chromosome 19 (Sabat 2010), and the family includes four members: IFN-λ1 [also called interleukin (IL)-29], IFN-λ2 (IL-28A), IFN-λ3 (IL-28B) and IFN-λ4 (Prokunina-Olsson et al. 2013). Among the different subtypes, IFN-λ3 has the highest functional potency, with a bioactivity twice as high as that observed for IFN-λ1 and 16 higher than that of IFN-λ2 (Dellgren et al. 2009). Given their antiviral, antiproliferative, proapoptotic and immunomodulatory functions, type III interferons fulfill all the premises to be considered interferons, although structurally these are related to the IL-10 family (Lasfar et al. 2006; Sabat 2010).

Type III Interferons Biology

Type III interferons are produced by several cell types, including plasmacytoid dendritic cells, regulatory T cells, macrophages, hepatocytes, and cytolytic cells such as cytotoxic $CD8^+$ T cells and natural killer cells. Under selected conditions, type III interferons are the major type of interferon produced by virus-infected cells. The stimuli that induce gene expression and result in the production of IFN-λs are similar to those that induce type I interferons

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(IFN-α is the main element of the type I interferons family). The nucleotides originating from viruses and intracellular bacteria represent the most potent inducers of the interferonic response (Zhang et al. 2011). Double-stranded RNA and single-stranded RNA are detected by Toll-like receptor (TLR)-3, TLR-7 and TLR-8. DNA detected by TLR-9 is also a potent inducer of interferon production, and analysis of the response to TLR-9 agonists has shown that the induction of IFN-λs exhibits a greater dependence on the nuclear factor (NF)-κB transcription factor than that observed for the induction of IFN-α/β (Iversen et al. 2010). It should be noted that some studies have described that non-RNA/non-DNA pathogen-associated molecular patterns, as well as endogenous triggers such as apoptotic particles containing small ribonucleoprotein complexes (such as the Ro52 antigen, a major autoantigen in cases of systemic autoimmunity) may also trigger the type III interferons pathway (Iversen et al. 2010).

In target cells, type III interferons exert their biological effects through a unique membrane-bound receptor composed of the subunits IFN-λR1 (IL-28RA) and IL-10R2 (Lasfar et al. 2006). This complex triggers the Janus kinase/signal transducer and activator of transcription (Jak/STAT) signal cascade in a similar way as the type I interferon receptor, so both type I and III interferons share biological activities due to the induction of interferon-stimulated gene factor (ISGF)-3 transcriptional complex. Indeed, after binding to their own receptors, type I and III interferons activate the common signaling pathway dependent of Jak/STAT, and the Jak1 and Tyk2 molecules become phosphorylated to generate peptidic motifs containing phosphotyrosin in the intracellular domain, which in turn bind to cytosolic STAT1 and STAT2 proteins. Signal transduction results in the stabilization of ISGF-3 factor (formed by STAT1, STAT2 and the interferon-regulatory factor [IRF]-9), which is transferred to the nucleus where it can bind to response elements located in the promoters of interferon-stimulated genes (ISGs), such as *OAS1*, *MX1* and *IRF7* (Amezcua-Guerra et al. 2015). Given the overlap in the type I and III interferons signaling cascades, it has not yet been possible to describe a single transcriptional signature for IFN-λs, and the overall response seems to be of a lower magnitude than that induced by type I interferons, although the IFN-λs signaling may exhibit a more delayed and longer-lasting gene induction peak (Marcello et al. 2006). The induction of interferon-stimulated genes modulates the functioning of most types of innate and adaptive immune cells. Its effects include the upregulation of major histocompatibility complex (MHC) class II molecules and costimulatory molecules by myeloid dendritic cells, which become more likely to present antigens to helper $CD4^+$ T cells. Effects also include increased expression and signaling of the pattern recognition receptors in the plasmacytoid dendritic cells that lead to a higher production of interferons and other cytokines, a lower activity of regulatory T cells and an increased expression of chemokines and other adhesion molecules by leukocytes and endothelial cells, as well as an increased production of antibodies by plasma cells (Lasfar et al. 2006; Luo et al. 2016).

Type III Interferons Expression Pattern and Response by Specific Tissues

Although type III interferons may induce cell responses similar to those observed by type I interferons, the expression of their receptors is more restricted, suggesting that they have specialized functions at specific anatomical sites, such as barrier surfaces. In addition, recent developments have revealed unique non-redundant functions of IFN-λs, which cannot be compensated by type I interferons. In particular, IFN-λs appear to function as immunoregulatory forms of interferons since they possess many of the antiviral and antimicrobial functions of type I interferons while lacking some of their pro-inflammatory effects, thus playing an important role in fine tuning of immune defenses for optimal host protection with minimal tissue damage (Vlachiotis and Andreakos 2019).

Even though type III interferons modulate the expression of ISGs preferentially in cells of epithelial origin, recent studies are defining additional mechanisms in other cell types. An excellent review has already been published (Lazear et al. 2015a). IFN-λR1 is expressed by human hepatocytes, and hepatitis B virus and C virus infections preferentially induce the production of IFN-λs rather than the production of type I interferons (Thomas et al. 2012; Zhang et al. 2011). Interestingly, some polymorphisms in the IFN-λ genes are strongly associated with spontaneous viral clearance as well as with the response to antiviral therapy with pegylated IFN-α in patients with chronic hepatitis C virus infection (Prokunina-Olsson et al. 2013; Sixtos-Alonso et al. 2015). Therapy with IFN-α is accompanied by a series of side effects that make it difficult to adhere to treatment. Given the restricted pattern of IFN-λR1 expression, which is particularly abundant in hepatocytes, therapeutic use of IFN-λs could confer many of the antiviral benefits of IFN-α with reduced adverse effects in patients with hepatitis C virus infection (Lazear et al. 2015a). In the gastrointestinal tract, type I and type III interferons responsiveness are highly compartmentalized, with IFN-λs having a minimal effect on cells of the *lamina propria* and IFN-α having a minimal effect on intestinal epithelial cells. This differential response appears to be associated with IFN-λR1 expression levels observed in intestinal epithelial cells (Mahlakõiv et al. 2015). Moreover, in chronic intestinal inflammation, type III interferons may act directly on neutrophils to inhibit the production of reactive oxygen species through mechanisms

mediated by Jak2, thus accelerating mucosal healing (Broggi et al. 2017; Chiriac et al. 2017). A similar effect of IFN-λs has been described in limiting disease progression by decreasing neutrophils infiltration in collagen-induced arthritis (Blazek et al. 2015).

In the respiratory tract, IFN-λR1 is constitutively expressed by epithelial cells and its level increases dramatically shortly after the onset of a virus or bacterial infection (Cohen and Prince 2013). In addition, type III interferons are the predominant interferon produced by myeloid and bronchial epithelial cells in response to a variety of viruses and the extent of IFN-λ response is inversely correlated with the viral load and the disease severity (Jewell et al. 2010). Polarization towards the Th1 phenotype induced by type III interferons may reduce the severity of allergic asthma (Contoli et al. 2006). Recently, a provocative study suggested a relevant effect of type III interferons at an unexpected site: the blood–brain barrier (Lazear et al. 2015b). The blood–brain barrier protects the central nervous system from a variety of harmful substances while allowing selective exchange of ions and solutes. At this level, type III interferons play an important role in the defense against viruses through non-canonical mechanisms, since the production of IFN-λs in the blood–brain barrier is carried out independently of the ISG activation (Lazear et al. 2015b). In fact, type III interferons appear to exert antiviral activity by modulating the blood–brain barrier properties through an increase in the ability of the endothelium to resist ion flow (Wells and Coyne 2018).

Therefore, type III interferons should be considered as an autonomous viral defense system of the mucosa and epithelial barriers that may have evolved to avoid unnecessarily frequent activation of the type I interferon system, which could induce an exacerbated inflammation (Wells and Coyne 2018).

Type III Interferons in Autoimmunity

There is increasing evidence that IFN-λs modify the adaptive immune response and affect autoimmunity (Amezcua-Guerra et al. 2015). For instance, IFN-λs could have a prominent effect on epithelial tissues in which the expression of IFN-λR1/IL-10R2 is higher, particularly in keratinocytes (Witte et al. 2009). Skin lesions from patients with psoriasis show higher amounts of IFN-λ1 in the absence of differential expression of type I interferons (Wolk et al. 2013). In parallel, it appears that helper T cells with Th17 phenotype are the main source of IFN-λs in psoriasis lesions, and IFN-λs may downregulate Th2 cytokines, including IL-4, IL-5 and IL-13 (Jordan et al. 2007; Srinivas et al. 2008). Nevertheless, treatment with IFN-λ2 reverses the development of collagen-induced arthritis in arthritis-prone mice by drastically reducing the number of IL-17-producing Th17 and γδ T cells in the joints and lymph nodes, as well as by restricting the recruitment of IL-1β-expressing neutrophils, which suggests the existence of negative feedback circuits between type III interferons and the Th17 phenotype (Blazek et al. 2015).

In this review, we will focus on recent evidence, in humans, about the contribution of the type III interferons family in the pathogenesis of systemic autoimmune diseases.

Type III Interferons in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a prototypal autoimmune disorder that is characterized by the production of autoantibodies against nuclear antigens, cytoplasmic antigens, cell surface antigens, and soluble antigens. Clinical manifestations are variable and range from isolated skin or joint involvement to life-threatening multiorgan involvement. SLE is usually associated with a relapsing–remitting course, but some patients have persistent disease activity. Although the etiology of SLE remains unclear, there is increasing evidence that IFN-α plays a crucial role in the disease pathogenesis. In this regard, approximately 50% of patients overexpress genes induced by IFN-α, and the extent of overexpression correlates with disease activity and severity. This pattern is known as the "IFN-α signature", and many animal and human studies have shown the paramount role of this IFN-α signature in the lupus pathogenesis (Obermoser and Pascual 2010).

Zahn et al. (2011) described the activation of type III interferons in keratinocytes from patients with SLE. The authors analyzed the expression of IFN-λs and IFN-λR1 by immunochemistry in skin biopsies from 16 patients with chronic discoid cutaneous lupus and subacute cutaneous lupus (SCLE), six healthy controls, five patients with lichen planus, five patients with psoriasis and five with dermatomyositis. They found the expression of IFN-λs to be highest in active skin lesions of patients with SCLE; in addition, the IFN-λR1 was strongly expressed in the epidermis of SCLE lesions, with low expression in specimens from healthy controls. In addition, they measured the serum levels of IFN-λ1 by enzyme-linked immunosorbent assay and observed the highest levels in patients with generalized skin lesions. Notably, these levels decreased in parallel to the clinical remission of cutaneous lesions following systemic therapy with glucocorticoids and hydroxychloroquine. Finally, the authors investigated the expression of IFN-λs in epidermal explants in vitro by exposing them to synthetic immunostimulatory nucleic acids (double-stranded RNA/polyriboinosinic polyribocytidylic acid or poly [I:C]) and double-stranded DNA CpG-oligoeoxynucleotide. Poly (I:C) induced the expression

of IFN-λ1 protein in the explanted epidermal sheets. Moreover, exposure of human keratinocytes to recombinant IFN-λ1 increased the secretion of IL-6, IL-8, CCL3 and CXCL-9 chemokines in the culture supernatants.

Wu et al. (2011) analyzed serum levels of IFN-λ1, as well as IFN-λ1 mRNA in peripheral blood mononuclear cells (PBMC) from 42 patients with SLE and 25 age- and sex-matched healthy controls. Patients with SLE had higher levels of IFN-λ1 protein and mRNA than controls. In addition, patients with active disease had significantly higher levels of IFN-λ1 protein and mRNA levels than patients with quiescent disease. In subsequent analyzes, the authors demonstrated a positive correlation between serum levels of IFN-λ1 and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, anti-double stranded DNA (anti-dsDNA) antibody levels and C-reactive protein (CRP) concentration. A negative association was observed between serum IFN-λ1 and C3 complement levels. Regarding the association of serum IFN-λ1 with different clinical features, researchers found differences only in patients with renal disease and arthritis compared to patients without these manifestations. Finally, the production of IP-10 and MIG chemokines was higher in PBMC from SLE patients after stimulation with IFN-λ1 (Wu et al. 2011).

As mentioned above, Th17 cells are additional sources of type III interferons, and the Th17 phenotype appears to be relevant since it may drive renal inflammation and renal autoimmunity in SLE (Dolff et al. 2019). In this context, Oke et al. (2017) analyzed 261 patients with SLE and 261 controls for a variety of serum molecules: IFN-λ1, IFN-α (subtypes 1, 2, 4, 5, 6, 7, 8, 10, 13, 14, 16 and 17), IP-10, IL-17 and IL-23. They found that 29% of patients and 20% of controls had detectable serum levels of IFN-λ1, whereas IFN-α was detected in 44% and 33%, respectively. Only 14.5% of patients and 7.5% of controls had both types of interferons detected simultaneously. The levels of IFN-λ1 were correlated with IL-17 and IL-23 levels in patients with SLE. IP-10 levels were weakly correlated with IFN-λ1, IL-23 and IL-17, as well as with the disease activity measured by the SLEDAI score. Afterwards, the authors identified patients with high levels (> 75% or third quartile) of the cytokines assessed. A total of 19 patients (7%) had high levels of both IFN-λ1 and IFN-α. Patients with IFN-λ1^{high} were more often positive for anti-nucleosome antibodies and a lower lymphocyte count, with no significant differences in clinical features. In addition, IFN-λ1^{high} patients had higher serum levels of IL-17, IL-23 and IP-10. Double-high patients (IFN-λ1^{high} and IFN-α^{high}) were younger, with a shorter disease duration, higher frequency of seropositivity for anti-Ro52 antibodies, leukopenia and lymphopenia, seizures, lymphadenopathy, and low levels of C4 complement. Finally, patients with IFN-λ1^{high}, IL-17^{high} and IL-23^{high} showed higher frequency of renal failure, higher frequency of triple seropositivity for antiphospholipid antibodies (anticardiolipins, anti-β_2 glycoprotein-1 antibodies and lupus anticoagulant) and a history of thrombocytopenia (Oke et al. 2017).

Zickert et al. (2016) measured IFN-λ1 and IFN-α in the serum of 56 patients with active lupus nephritis and 163 healthy controls. Thirty-seven (66%) patients had detectable levels of IFN-α and 17 (30%) had detectable levels of IFN-λ1. At baseline, serum levels of IFN-λ1 were higher in patients compared to controls, although there were no associations between IFN-λ1 and laboratory findings. In patients with proliferative nephritis, 27% of cases had detectable IFN-λ1 versus 45% in those with membranous nephritis. In the subset of patients with a successful histopathological response, levels of IFN-λ1 decreased after treatment. Nine renal biopsies were evaluated with immunohistochemistry for the expression of IFN-λ1. Higher staining was observed in glomeruli with cellular crescent formation, in areas with inflammatory infiltrates of CD3$^+$ cells (CD3 is a T cell co-receptor that helps activate naïve cytotoxic and Th cells), and in tubular cells. In renal biopsy specimens obtained at follow-up, patients with successful histopathological response had no glomerular staining, although tubular staining was still present (Zickert et al. 2016).

Even though IFN-λ3 has the highest biological activity, previous investigations had not evaluated this type III interferon in SLE. Lin et al. (2012) determined the serum levels of IL-28 by an enzyme-linked assay capable of detecting both IL-28A and IL-28B, and the transcript levels of IL-28 and IFN-λR1 in PBMC and peripheral blood T cells. Only 65.4% of patients with SLE compared to 34% of healthy controls had detectable serum levels of IL-28. In addition, there was no correlation between IL-28 levels and disease activity. Patients with SLE had the highest levels of IL-28 transcripts in activated CD4$^+$ T cells compared to normal controls. Patients with SLE had a higher detection of IL-28 transcripts in PBMC than controls, although no statistical significance was noted (Lin et al. 2012).

Our group assessed the levels of IFN-λ1, IFN-λ2, IFN-λ3 and IFN-α in the serum of 93 patients with SLE and 67 healthy controls (Amezcua-Guerra et al. 2017). In this study, we found that IFN-λ3 levels were higher in patients (median: 83 pg/ml) than in controls (median: 42 pg/ml; $P = 0.02$). The concentration of IFN-λ1 and IFN-λ2 was similar between SLE patients and controls; in the same way there was no difference in the IFN-α levels between study groups. Serum IFN-λ3 was influenced by the use of glucocorticoids, i.e., patients receiving prednisone had IFN-λ3 concentrations three times higher than those no receiving glucocorticoids (median: 104 pg/ml versus 30 pg/ml; $P = 0.009$). In this regard, the induction of transcripts of type III interferons by glucocorticoids has already been described in patients with asthma and it has recently been shown that dexamethasone may up-regulate genes of type I and III interferons, as well

as ISGs in sinonasal epithelial cells (Bullens et al. 2008; Hwang et al. 2019). Alternatively, glucocorticoid-treated patients are usually those who have a more severe disease. Indeed, our SLE patients treated with glucocorticoids showed a significantly higher disease activity than those who did not receive steroids. The use of immunosuppressants, hydroxychloroquine and statins were not associated with significant changes in the interferon levels. Regarding clinical associations, higher IFN-λ3 levels were found in patients with serositis (median: 135 pg/ml versus 40 pg/ml; $P<0.01$) and cutaneous involvement (median: 66 pg/ml versus 40 pg/ml; $P<0.05$) than in their counterparts without these manifestations. There were no differences in other clinical manifestations or IFN-λ1 and IFN-λ2 levels. No correlation could be identified between IFN-λ3 and disease activity (SLEDAI score) or cumulative organ damage (assessed by the Systemic Lupus International Collaborating Clinics damage index). A positive association was found between IFN-λ3 levels and anti-Ro/SSA antibodies (median: 122 pg/ml versus 0 pg/ml; $P=0.001$) and anti-dsDNA antibodies (median: 93 pg/ml versus 0 pg/ml; $P=0.021$). In addition, a negative correlation was observed between IFN-λ3 and C3 and C4 complement proteins. In the multivariate analysis, an association was observed between high levels of serum IFN-λ3 and positive anti-Ro/SSA antibodies, regardless of the presence of cutaneous involvement. No statistical significance was found for other associations, including active nephritis and anti-dsDNA antibodies (Amezcua-Guerra et al. 2017).

The most recently study, published by Chen et al. (2018), investigated whether IFN-3/4 genes are associated with SLE susceptibility. The authors included 831 patients with SLE and 1620 healthy controls for genetic analysis of four single-nucleotide polymorphisms (SNP; rs8099917, rs12979860, rs3682134815 and rs4803217) at the IFNL3/4 locus. All minor alleles of IFNL3/4 SNP were significantly associated with susceptibility to SLE in nephritis-negative patients compared to healthy controls adjusted for sex and age. In contrast, minor alleles of IFNL3/4 SNP were not associated with SLE susceptibility in nephritis-positive patients. Importantly, homozygosity for the major alleles of the four IFNL3/4 SNP was a significant risk factor for lupus nephritis in the entire lupus cohort. Researchers also found that serum IFN-λ3 levels were increased in SLE patients with high disease activity, defined by a SLEDAI score > 4, (9.19 ± 1.35 pg/ml compared to patients with low disease activity, 3.41 ± 0.31 pg/ml; $P<0.0001$). Patients with low levels of C3 and C4 complement had higher concentrations of IFN-λ3 (8.28 ± 1.69 pg/ml versus 4.15 ± 0.45 pg/ml; $P=0.0013$) than those with normal complement levels.

Recently, our group investigated whether the genotype IFNL3 rs12979860 could influence both circulating levels and production of IP-10 and MCP-1 by PBMC from patients with SLE and healthy controls (unpublished data). We found that serum IP-10 and MCP-1 levels were higher in SLE patients compared to healthy controls. PBMC from patients with SLE and healthy controls carrying the CC/CT combination rs12979860 genotype had higher IP-10 secretion following IFN-α stimulation compared to cells from individuals carrying the TT genotype. Thus, apparently the IFNL3 rs12979860 SNP modulates the ex vivo response of PBMC to IFN-α through the production of IP-10 chemokine.

Type III Interferons in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic and systemic disease, in which autoimmunity is primarily directed against synovial membrane antigens, leading to synovial inflammation and proliferation, loss of joint cartilage, and erosion of the juxta-articular bone. Although the etiology of RA remains elusive, genetic contribution is substantial with more than 30 loci identified to confer risk. The strongest association is with the HLA-DRB1 alleles, an MHC class II molecule that is directly involved in the antigen presentation to Th cells. In particular, the HLA-DRB1 alleles encoding "shared epitopes" confer risk only for those RA cases associated with antibodies against citrullinated proteins (anti-CCP antibodies), which are present in approximately 70% of RA patients.

The cytokine pathways that operate in RA are a complex network, with many soluble molecules that show pleiotropic actions and different targets. Tumor necrosis factor (TNF), IL-6 and IL-1β represent key proinflammatory cytokines in RA; however, blocking these mediators does not completely control the disease activity in all patients. Recent advances on cytokines such as IL-17 and IL-18 have allowed us to better understand the pathogenesis of chronic arthritis and could contribute to the improvement of current therapies. Given recent research on the effects of type III interferons in autoimmunity, interest in its role in the pathogenesis of RA has increased, opening a new path of possible blockage as an option for treatment.

Wang et al. (2012) measured IFN-λ1 in patients with RA, patients with osteoarthritis and in healthy individuals. Apart from blood samples from 54 patients with RA and 60 healthy controls, synovial fluid was obtained from 20 patients with RA and 20 patients with osteoarthritis, as well as synovium samples from six patients with RA and five healthy controls after therapeutic synovectomy or amputation (Wang et al. 2012). The mRNA expression of IFN-λ1 and IFN-λR1 was higher in PBMC from RA patients compared to healthy individuals. Serum IFN-λ1 levels were found elevated in RA compared to controls (mean: 24.5 pg/ml versus 5.6 pg/ml; $P<0.001$); in addition, patients with RA had higher levels of IFN-λ1 in synovial fluid compared to patients with osteoarthritis (mean: 16.2 pg/ml versus 9.3 pg/ml; $P=0.039$). There was no correlation between serum IFN-λ1 levels and disease

activity measured by the Disease Activity Score (DAS28), CRP or erythrocyte sedimentation rate (ESR) levels, rheumatoid factor or anti-CCP antibodies. Patients with RA and active disease (DAS28 score > 3.2) had higher levels of IFN-λ1, both protein and mRNA, than patients with quiescent disease. In the immunohistochemical analysis, the authors found that IFN-λ1 was expressed in the lining layers of rheumatoid synovium. Using double immunofluorescence staining, it was shown that macrophages and synovial fibroblasts expressed IFN-λ1. Finally, they examined the cytokine profile produced by cells of the fibroblast cell line-MH7A after stimulation with IFN-λ1, and found that the expression of IL-6, IL-8 and matrix metalloprotease-3 were upregulated, while the expression of IL-10 was regulated downwards (Wang et al. 2012).

The same group of researchers studied the effect of IFN-λ1 on the TLR-mediated production of IL-6 and IL-8 in RA (Xu et al. 2013). They used MH7A cells and demonstrated first that cells express mRNA of IFN-λR1 and IL-10R2, and second that IFN-λ1 induced the production of IL-6 and IL-8 in culture cells from patients with RA. The MH7A cells were pre-treated with IFN-λ1 (100 ng/ml) and then stimulated with the TLR-ligands peptidoglycan (PGN), poly (I:C), or lipopolysaccharide (LPS). They found that IFN-λ1 increased IL-6 mRNA expression by approximately 1.4-, 2.0- and 2.7-fold and IL-8 mRNA expression by 1.8-, 2.8- and 3.6-fold after stimulation with PGN, poly (I:C) or LPS, respectively. After 24 h of incubation with IFN-λ1, RA fibroblast-like synoviocytes displayed an important upregulation in the mRNA TLR-2, TLR-3 and TLR-4 expression (Xu et al. 2013).

An independent group studied the levels of IFN-λ1 protein and mRNA in PBMC from 42 patients with RA, 41 patients with ankylosing spondylitis and 42 healthy controls (Wu et al. 2013). Although all three groups had measurable levels of IFN-λ1, patients with RA had the highest IFN-λ1 protein levels, as well as a higher IFN-λ1 mRNA expression in PBMC. The authors also identified that RA patients with knee involvement had higher serum IFN-λ1 levels. However, this study failed to find a significant correlation between serum IFN-λ1 and rheumatoid factor, anti-CCP antibodies and ESR (Wu et al. 2013).

The lack of association between IFN-λ1 and several RA markers was recently corroborated by our group (Castillo-Martínez et al. 2017). However, we found a significant association between serum IFN-λ1 levels and anti-mutated citrullinated vimentin (anti-MCV) antibody titers (Spearman's rho = 0.36, 95% CI from 0.36 to 0.61; $P = 0.02$). Anti-MCV antibodies are a member of the anti-citrullinated protein antibody family that are specifically directed against citrullinated epitopes of human vimentin instead of targeting cyclic peptides (anti-CCP) synthesized in the laboratory. Apart from occurring naturally in patients with RA, anti-MCV antibodies show strong correlation to disease activity, disease severity, success of therapy and seem to be even more specific for the diagnosis of early RA than anti-CCP antibodies (Reyes-Castillo et al. 2015). In our study, we evaluated 43 patients with RA and 43 healthy controls. Patients with RA had higher IFN-λ1 (mean: 113.5 ± 118.6 pg/ml versus 55.9 ± 122.3 pg/ml; $P < 0.0001$) and IFN-λ2 (mean: 245.4 ± 327.7 pg/ml versus 5.1 ± 11.0 pg/ml; $P = 0.009$) levels than healthy controls, but not IFN-λ3 levels. We also found that IFN-λ1 levels were higher in patients with active disease (DAS28 score > 2.6) (mean: 124.9 ± 135.9 pg/ml; $P < 0.001$) and quiescent disease (mean: 99.0 ± 93.7 pg/ml; $P < 0.01$) than in controls, while IFN-λ2 levels were higher only in patients with active disease (mean: 264.0 ± 356.1 pg/ml; $P = 0.02$). No differences were found in serum IFN-λ3 levels between groups (Castillo-Martínez et al. 2017).

Chang et al. (2017) recently analyzed 68 patients with RA and 68 healthy controls. As was the case in our study, they found that serum IFN-λ1 levels were higher than in controls (median: 965.7 pg/ml versus 468.1 pg/ml; $P = 0.019$). However, serum IFN-λ1 levels were higher in RA patients positive to anti-CCP antibodies compared to both healthy controls and RA patients negative to anti-CCP antibodies. They also observed a positive correlation between IFN-λ1 levels and rheumatoid factor and anti-CCP antibody titers. In addition, the authors found that serum IFN-λ1 level decreased after three months of treatment with disease modifying antirheumatic drugs, and this decrement was even more marked after six months of treatment. In RA patients with anti-CCP antibodies, changes in serum IFN-λ1 showed correlation with reductions in the DAS28 score during treatment.

Finally, a provocative study using tolerogenic dendritic cells has recently shown that intradermal injection of autologous dendritic cells modified with a NF-κB inhibitor and exposed to citrullinated peptide antigens results in decreased disease activity in RA patients with citrullinated peptide-specific autoimmunity, with parallel decreases in the serum concentration of IFN-λ1 and some other cytokines (Benham et al. 2015).

Type III Interferons in Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc, often called scleroderma) is a chronic, multisystem, connective tissue disorder characterized by low-grade inflammation, autoimmune diathesis, widespread functional and structural abnormalities in the smallest blood vessels, and progressive fibrosis of the skin and visceral organs. Into the broad spectrum of disease, diffuse cutaneous variant is featured by widespread skin fibrosis and increased risk of serious organ disease including interstitial lung disease, severe gastrointestinal dysmotility,

cardiomyopathy, and scleroderma renal crisis. In contrast, the limited cutaneous variant presents with longstanding Raynaud phenomenon and digital ischemia, distal skin fibrosis (sclerodactyly), calcinosis, multiple telangiectasia, and pulmonary artery hypertension.

A single communication aimed to assess serum IFN-λ1 levels and its association with clinical manifestations in systemic sclerosis has been published to date by Dantas et al. (2015). This study included a total of 52 patients with SSc (28 with limited cutaneous SSc and 24 with diffuse cutaneous SSc) and 53 matched healthy controls. Serum IFN-λ1 levels in patients were significantly higher than in controls (mean: 24.8 ± 8.7 pg/ml versus 11.0 ± 3.0 pg/ml; $P < 0.0001$). Interestingly, the highest IFN-λ1 levels were observed in patients with scleroderma-associated myositis, defined as proximal muscle weakness and elevated serum creatine-kinase levels. No other clinical association was found. In addition, the authors measured serum IFN-γ levels, which were also higher in patients than in controls (mean: 32.1 ± 8.1 pg/ml versus 10.7 ± 2.7 pg/ml; $P < 0.0001$), and a positive correlation (r = 0.352) between IFN-λ1 and IFN-γ levels was noted in SSc patients (Dantas et al. 2015).

Type III Interferons in Sjögren's Syndrome

Primary Sjögren's syndrome (SS) is a chronic autoimmune disorder characterized by xerostomia (dry mouth) and keratoconjunctivitis *sicca* (dry eyes) due to lymphocytic infiltration of the salivary and lachrymal glands, respectively. Beside the typical involvement in exocrine glands, SS may involve other structures since the self-reactive process primarily affects the lining epithelium of various organs, thus constituting an "autoimmune epithelitis". Although the pathogenesis of SS remains to be elucidated, recent advances suggest interferons are relevant in the glandular involvement typically observed in the syndrome (Nocturne and Mariette 2013). Indeed, patients with primary SS display a pathological overproduction of IFN-α by circulating dendritic cells, IFN-α-containing cells infiltrate salivary gland biopsy specimens, and an interferon signature in association with disease activity has been described (Gottenberg et al. 2006).

Apostolou et al. (2016) studied 46 patients with primary SS and 17 non-sicca-complaining individuals. Patients with SS were classified according to the degree of minor salivary glands infiltration in mild, intermediate and severe inflammatory lesions (Apostolou et al. 2016). The presence of IFN-λ1, IFN-λ2, IFN-λ3 and its common receptor IFN-λR1 was evaluated in minor salivary glands by immunohistochemical analysis. The percentage of tissue surface and the intensity of IFN-λ2 positive signal in the total gland area, as well as the ductal epithelium, were significantly higher in the minor salivary glands of SS patients with intermediate infiltrates compared to the sicca controls. There were no differences in the other types of IFN-λs or the IFN-λR1. Using the double immunofluorescence analysis of IFN-λR1 and specific markers for T cells, B cells, macrophages and plasmacytoid dendritic cells, it was found that a strong staining with IFN-λR1 occurred mainly in plasmacytoid dendritic cells. Despite having found infiltrates in minor salivary glands, the authors found no mRNA of any of the type III interferons in PBMC from SS patients or controls. However, they observed higher levels of IFN-λ1 protein in patients with SS compared to controls, with the highest levels found in the subgroup of patients with intermediate infiltrates. There was no difference in other IFN-λs subtypes. Finally, they stimulated non-neoplastic salivary gland epithelial cells cultures that did not constitutively express any of the members of the type III interferons family at the level of mRNA or protein. Notably, poly (I:C)-mediated stimulation of TLR-3 induced the expression of all types of type III interferons (Apostolou et al. 2016).

Recently, another group of researchers evaluated the expression of type III interferons in minor salivary glands from 20 patients with primary SS and five individuals matched by sex and age who did not fulfill the classification criteria for SS (Ha et al. 2018). In this study, an antibody against human IL-28/29 capable of detecting human IFN-λ1, IFN-λ2 and IFN-λ3 was used for immunostaining. In salivary tissues from SS patients, the presence of IFN-λs was detected in acinar/ductal epithelial cells and in some infiltrating mononuclear cells. While, IFN-λR1 was detected in tissue specimens from both groups, mainly in acinar/ductal epithelial cells. The authors calculated the percentage of IFN-λ^+ acinar epithelial cells and noted that it was higher in patients with primary SS than in non-SS controls. After stratifying the SS patients according to the number of inflammatory foci, there were significant differences in the fractions of acinar epithelial cells staining with IFN-λs. Expression of IFN-λR1 was similar between the study groups. They also studied the TLR ligand-induced expression of IFN-λ1 and IFN-λ2 in salivary gland cell lines (NS-SV-AC and NS-SV-DC cells). After stimulation of the NS-SV-DC cells with poly (I:C), there was a significant increase in the mRNA levels of IFN-λ1 and IFN-λ2 compared to unstimulated cells. The mRNA expression of IFN-λR1 was not modified. When stimulated with 100 ng/ml IFN-λ2 or 100 ng/ml IFN-λ1, transcript levels of BAFF, CXCL10 and TLR-3 increased significantly. Finally, serum levels of IFN-λ1 did not show a significant difference between patients with primary SS and controls (median: 151, 120 to 177 pg/ml versus 138, 124 to 171 pg/ml; $P = 0.683$). No associations between serum IFN-λ1 levels and clinical or laboratory variables were observed (Ha et al. 2018).

Our group recently described that the number of circulating $CD8^+$IFN-$\lambda3^+$ cells (cytotoxic T lymphocytes) and

$CD56^+IFN\text{-}\lambda3^+$ cells (natural killer cells) is decreased in patients with primary SS as compared to healthy individuals or patients with SLE (Mora et al. 2015). Despite this finding, we observed infiltration of the ductal and acinar epithelia by $CD8^+IFN\text{-}\lambda3^+$ cells and $CD56^+IFN\text{-}\lambda3^+$ cells in minor salivary gland biopsies from primary SS patients as compared to *sicca*-complaining, non-SS individuals. This suggests the existence of an important stimulus hitherto unknown (probably a viral infection), which could cause the migration and homing of highly producing IFN-λ3 cytotoxic cells from the peripheral blood to the target tissues (Mora et al. 2015).

Type III Interferons in Juvenile Idiopathic Arthritis

The term juvenile idiopathic arthritis encompasses a collection of disorders characterized by chronic joint inflammation during childhood. Classification of subtypes is based on a mixture of patterns of joint involvement, circulating antibodies, age of onset, and the presence of extraarticular manifestations. Non-infectious anterior uveitis is the most common extraarticular complication of juvenile idiopathic arthritis and it may occur in up to 45% of children with the oligoarticular phenotype. In these patients, analysis of the aqueous humor has been a useful tool for extracting information on crucial factors that may orchestrate the ocular microenvironment in childhood uveitis. In this vein, a recent study demonstrated decreased levels of IFN-λ1 in samples of aqueous humor from patients with juvenile idiopathic arthritis and associated uveitis as compared to those from patients with chronic anterior uveitis, idiopathic uveitis, and noninflammatory conditions (controls), while no differences in serum IFN-λ1 levels were noted (Haasnoot et al. 2016). Notably, IFN-λ1 was specifically and significantly decreased in patients with active uveitis as compared with either patients with inactive uveitis or those receiving systemic immunomodulatory therapies (anti-TNF agents plus glucocorticoids and/or methotrexate). Finally, logistic regression analysis revealed that IFN-λ1 was significantly decreased in patients with uveitis associated to juvenile idiopathic arthritis (odds ratio 0.61, 95% CI 0.38–0.98; $P = 0.042$) even after adjusting for multiple variables including uveitis activity, use of systemic immunosuppressants, and uveitis duration. This study suggested that aberrant IFN-λ1 signaling might be important in the pathogenesis of uveitis associated to juvenile idiopathic arthritis (Haasnoot et al. 2016). Indeed, recent knowledge has shown that IFN-λ1 is crucial to strengthen the blood–brain barrier permeability by regulating microvascular endothelial cells to inhibit viral infection (Lazear et al. 2015b). Type III interferons are expressed in the human eye, and it is tempting to speculate that they can also regulate the retina-ocular barrier permeability (Yang et al. 2010). Then, a decrease in intraocular levels of IFN-λ1 may be related to insufficient barrier functioning, which may indicate distinct and site-specific effects of type III interferons in juvenile idiopathic arthritis compared to RA (Haasnoot et al. 2016).

Type III Interferons in Behçet's Disease

Behçet's disease is a rare condition in which most of the tissue damage results from vasculitis. Although Behçet's disease typically affects small- and medium-sized arteries, it may involve larger arteries and has a proclivity to involve veins as well as arteries. Behçet's disease is characterized by the triad of recurrent mouth ulcers, genital ulcers, and eye inflammation; in addition, Behçet's disease may also affect non-mucosal skin surfaces, central nervous system, gastrointestinal tract, and some other organs.

The pathogenesis in Behçet's disease is still unknown, although laboratory findings suggest a strongly polarized Th1 and Th17 immune response both in experimental autoimmune uveitis and in Behçet's-associated uveitis. In this line, Li et al. (2014) studied the expression of IFN-γ and IL-17 in PBMC from patients with Behçet's disease or healthy individuals following the stimulation with IFN-λ2 (Li et al. 2014). The authors found that IFN-γ and IL-17 were undetectable in the sera from patients with Behçet's disease and control subjects. However, mRNA expression and protein production of IFN-γ by IFN-λ2-stimulated cells from patients with Behçet's disease were significantly increased compared to cells from healthy individuals, while no differences were observed for IL-17. This study provided the first evidence for a potential participation of type III interferons in the pathogenesis of Behçet's disease (Li et al. 2014).

Concluding Remarks

In recent years, therapeutic strategies aimed at blocking type I interferons have been tested in several autoimmune diseases, with a special focus on systemic lupus erythematosus. These strategies have been shown to effectively inhibit the IFN-α gene signature, especially in those patients with high gene expression at baseline. Unfortunately, this initial excitement has been overshadowed by the results of several clinical trials showing that interfering type I interferon pathway is not superior to placebo in modifying the extent of disease activity. Although the cause of this lack of efficacy is still unknown, it has already been proposed that the continuous disease activity could rest on the shared signaling pathways between type I and III interferons (Amezcua-Guerra et al. 2015).

In this vein, although many of the activities induced by type III interferons are actually superimposed on those induced by type I interferons, there are spatial and kinetic differences that allow type III interferons to provide first-line protection at the anatomical barriers such as mucous membranes and epithelia, thus modulating the activation of the systemic response of type I interferons and the subsequent reaction in different organs and tissues. Growing knowledge about the biology of interferons is paving the way for new therapeutic strategies based on the dual modulation of type I and III interferons at the level of circulating cytokines, membrane-bound receptors or the common post-signaling pathway.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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