Type I Interferons in autoimmunity: implications in clinical phenotypes and treatment response

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Abstract
Type I interferon (IFN-I) is thought to play a role in many systemic autoimmune diseases. IFN-I pathway activation is associated with pathogenic features, including the presence of autoantibodies and clinical phenotypes such as more severe disease with increased disease activity and damage. We will review the role and potential drivers of IFN-I dysregulation in five prototypic autoimmune diseases: systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, primary Sjogren syndrome, and systemic sclerosis. We will also discuss current therapeutic strategies that directly or indirectly target the IFN-I system.
Introduction

Autoimmune diseases are characterized by a breakdown of immune tolerance resulting in inflammation and end-organ tissue damage. Classically, autoimmune disorders have been categorized by clinical features. This is because the molecular drivers and pathogenic causes are not well known. To advance our understanding of these diseases and enable personalized treatment, we must identify the underlying immunopathogenic mechanism in the disease and how these factors differ between diseases and between individuals with the same disease.

The type I interferon (IFN-I) system is dysregulated in several autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE), primary Sjogren’s syndrome (pSS), rheumatoid arthritis (RA), systemic sclerosis (SSc), and dermatomyositis (DM). The excess activation of the IFN-I system in autoimmune diseases can be attributed to multiple mechanisms. Potential drivers of exuberant IFN-I responses include genetic variation, activation of nucleic acid cytosolic sensors and endosomal Toll-like receptors (TLR) due to defective DNA clearance, circulating immune complexes, or the release of DNA-containing neutrophil extracellular traps (NETs).

Recent advances in our understanding of the immunopathogenic mechanisms involved in the initiation and perpetuation of autoimmunity have allowed the development of effective therapeutic strategies, including anti-IFN-I therapy. Herein, we will discuss the role of IFN-I in SLE, pSS, RA, SSc, and DM, the implications of IFN-I dysregulation in clinical phenotypes and treatment response, and the available therapeutic strategies that directly or indirectly target the IFN-I system.

IFN-I in autoimmunity

Plasmacytoid dendritic cells (pDCs) are thought to be one of the main sources of endogenous IFN-I production in SLE and other autoimmune rheumatic diseases. pDCs produce large amounts of IFN-I after sensing viral antigens. In autoimmunity, endogenous nucleic acids can activate pDC interferon production via TLR-dependent and -independent pathways. Internalized nucleic-acid-containing immune complexes and neutrophil-derived oxidized mitochondrial DNA can activate endosomal TLR7 or TLR9 and induce the secretion of IFNα by pDCs, a process that is mainly mediated by the constitutively expressed transcription factor interferon regulatory factor (IRF)79-11, although other transcription factors such as IRF5 and IRF3 also play an important role in mediating cytokine production by pDCs12. DNA and RNA molecules can also bind to and activate the cytosolic sensors cGAS/STING and RIG-I or MDA5/MAVS, respectively, enhancing IFN-I production in a TLR-independent manner.

Supporting the importance of TLR-7 signaling in autoimmunity, a recent study demonstrated that a gain-of-function missense variant in TLR-7 (TLR7Y264H) causes human and murine lupus13. Other gene variants in TLR7 or affecting TLR7-related pathways have also been described in association with SLE14-17. In addition, functional polymorphisms affecting various IRFs have been associated with autoimmunity18-25. For example, genetic variation at IRF5 is associated with cutaneous and SLE, pSS, SSc, and DM20,26-33. Similarly, IRF7 risk haplotypes have been found in association with SLE and SSc sclerosis24,34,35. In addition, a gene variant in IRF8 (rs228038) has been recently described in association with SLE; although it has been postulated that this variant leads to decreased IRF8 expression in a cell-type-specific manner, the exact mechanisms linking the polymorphism to immune dysregulation remain to be elucidated36.

Besides modulating IFN-I production, other gene variants associated with autoimmunity affect IFN-I signaling downstream from the receptor. In this sense, a STAT4 risk haplotype that modulates IFN-I responses37 is associated with RA, SLE, and SSc38-44. Furthermore, IFI3 (an IFN-stimulated gene) has been described as a potential risk locus in DM45.

The contribution of pDCs to the elevated circulating IFN-I levels has been debated. In autoimmune diseases such as SLE, pSS, and SSc, both the numbers and function, including cytokine production, of circulating pDCs are reduced46-48. In fact, a

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recent study showed that pDCs from SLE and at-risk patients (those with some features of autoimmunity but without a disease diagnosis) exhibit a senescent phenotype. However, it is possible that the population of circulating pDCs is not representative of the tissue infiltrating pDC, which could still have significant pathogenic roles in autoimmunity, both dependent and independent of excessive IFNα production by these cells. Conversely, other cell types are likely contributors to IFN-I dysregulation in specific clinical settings. In mice, monocytes and follicular dendritic cells are a significant source of IFN-I after UV-triggered injury and in response to immune complexes, respectively.

In murine lupus-like disease, Kim et al. demonstrated activation of cGAS by mitochondrial DNA leaked to the cytosol through macropores formed by the oligomerization of voltage-dependent anion channels (VDAC) in the outer mitochondrial membrane. Recently, Caielli et al. showed an accumulation of mitochondria-carrying mature red blood cells (Mito⁺RBCs) in patients with SLE due to defects in programmed mitochondrial removal. These Mito⁺RBCs are often opsonized and undergo antibody-mediated internalization by macrophages, stimulating IFN-I production via the cGAS/STING pathway in these cells. Non-hematopoietic cells can also be a source of IFN-I. In this sense, Keratinocytes have been shown to produce large amounts of IFN-κ, an IFN-I with similar properties to IFNα and IFNβ and are thought to be major contributors to IFN-I dysregulation in cutaneous lupus and SLE.

In normal immunity, IFN-Is exert both antiviral and anti-tumor properties. IFN-Is serve these functions by providing a bridge between innate and adaptive immune responses. IFN-I increase the cell-surface expression of MHC class II and co-stimulatory molecules (e.g., CD40, CD80, CD86), production of proinflammatory cytokines, B-cell activating factor (BAFF), and multiple chemokines in conventional dendritic cells, and promote their migration to lymph nodes, allowing for increased antigen presentation and stimulation of T cells.

There are also direct effects of IFN-I on T-cell responses. For example, IFN-Is promote the differentiation of CD4+ T helper cells into IFN-γ-producing cells. In activated CD8+ T cells, IFN-I can promote survival, clonal expansion, and effector functions. IFN-I can also augment humoral immunity by promoting B cell survival, activation and differentiation into antibody-producing cells, as well as immunoglobulin class switching. IFN-I are potent stimulators of NK cell cytotoxicity, which is associated with the end-organ tissue damage observed in several autoimmune diseases. IFN-I produced by pDCs has also been shown to facilitate extracellular B cell proliferation and differentiation into autoantibody-forming cells.

In addition, IFN-I dysregulation provides a link between autoimmunity and premature atherosclerosis. Cardiovascular disease is a major cause of morbidity and mortality in longstanding rheumatic autoimmune disorders. Both IFNα and IFNβ have been shown to upregulate the expression of the scavenger receptor class A in human peripheral blood mononuclear cells or human macrophage cell lines, facilitating lipid uptake and foam cell formation. IFN-I also induces endothelial dysfunction, affects plaque-residing macrophages and increases the recruitment of neutrophils to the arterial wall. IFN-Is also have been shown to affect endothelial progenitor cell number, phenotype and function in SLE, which impairs the ability of these cells to promote vasculature repair. Furthermore, IFN-I pathway blockade with anifrolumab leads to a significant improvement in immunologic and cardiometabolic parameters in SLE, including a reduction of neutrophil extracellular traps (NET) complexes, glycoprotein acetylation and improvement of cholesterol efflux capacity. These mechanisms likely contribute to premature atherosclerosis and worse cardiovascular outcomes observed in patients with autoimmune diseases.

**Biologic basis of sex bias in autoimmunity**

Several autoimmune diseases occur predominantly in women, with a variable female:male ratio depending on the specific rheumatic autoimmune disease. Interestingly, the relative IFN-I levels in these diseases correlate with the degree of...
female:male-skewing. The presence of ANA or antibodies against extractable nuclear antigens is also correlated with elevated levels of circulating IFN-I and a greater female:male ratio (Fig. 1). However, the underlying mechanisms of the sex bias in autoimmunity are incompletely understood and likely multifactorial, involving genetic/chromosomal, hormonal, and environmental factors, among others.

Sex hormones have been proposed as key contributors to the pathogenesis and perpetuation of autoimmunity. Sex hormone receptors are expressed in most immune cell types and have numerous immune-modulating effects. For example, estrogens upregulate the expression of genes associated with innate immune responses, such as IRF5 and UNC93B1 (a critical regulator of endosomal TLR trafficking)\textsuperscript{76,77}, and downregulate the autoimmune regulator (AIRE), which has key roles in promoting central tolerance. Interestingly, pDCs from healthy women have been shown to express higher levels of IRF5 and generate greater TLR-7 induced IFNα responses compared to pDCs from healthy men, a difference that could be at least partially mediated by the estrogen receptor α signaling\textsuperscript{78}. In contrast, progesterone has been generally associated with immunosuppressive effects, including inhibition of NK cells, macrophages, dendritic cells, Treg induction, and suppression of Th17 differentiation\textsuperscript{79,80}.

Although sex hormones account for some of the female bias in autoimmunity, there are several other factors contributing to sex differences in the immune response. For example, patients with an additional X chromosome, including those with Klinefelter syndrome (47, XXY) and trisomy X (47, XXX), have an increased risk of developing pSS, SLE, SSc, and idiopathy inflammatory myositis (including DM)\textsuperscript{81-84}, supporting the idea of an X chromosome gene-dose effect as a contributor for the female bias in many autoimmune diseases. The X chromosome is also enriched for genes related to immune activation and IFN-I production, such as TLR7 and CXorf21 (TASL, an adaptor protein in the IRF5 activation pathway\textsuperscript{85}), some of which may escape random X-chromosome inactivation during early development\textsuperscript{86-88}. Similarly, several microRNAs related to immune tolerance are X-linked and overexpressed in female patients with SLE\textsuperscript{89}.

Recently, the transcription factor VGLL3 was identified as a sex-hormone-independent regulator of the immune response and contributor to the female bias in autoimmunity. VGLL3 expression is greater in the skin of healthy women compared to men’s skin, and it is overexpressed in the lesional skin of lupus patients\textsuperscript{90}. Interestingly, VGLL3 modulates IFN-I responses in immune and non-immune cell types and promotes the expression of several inflammatory molecules such as B Cell activating factor (BAFF) and IL-7\textsuperscript{90}. In mice, overexpression of VGLL3 can induce a Lupus-like phenotype, with autoantibody formation, immune complex deposition, and skin involvement\textsuperscript{91}. Although the mechanisms underlying the sex differences in VGLL3 levels are still not fully understood, it has been recently proposed that female-biased expression of VGLL3 confers evolutionary advantages by helping nonplacental tissues adapt to metabolic stress\textsuperscript{92}.

**IFN-I and rheumatic autoimmune diseases**

Evidence of IFN-I dysregulation is seen in many patients with SLE, RA, pSS, and SSc. Recent studies have aimed to stratify patients with autoimmune diseases based on their molecular characteristics using novel tools such as cytometry by time of flight and multi-omics approaches, regardless of their clinical manifestations and specific diagnoses\textsuperscript{48,93}.

In a recent study by Barturen et al. that used transcriptome and methylome data from peripheral blood cells from patients with SLE, pSS, and RA, patients with active disease were classified into three distinctive pathological molecular clusters: inflammatory, lymphoid, and IFN signaling\textsuperscript{89}. Interestingly, the cluster assignment was overall stable over time, largely regardless of diagnosis or therapy. Although it remains to be elucidated whether these clusters are useful in predicting treatment response, these findings warrant future studies. For example, it is possible that anti-IFN-I therapy,
such as anifrolumab, could be more effective in treating patients in the IFN signaling cluster compared to those in the inflammatory or lymphoid clusters.

**DM**

An IFN-I signature has been identified in patients with adult and juvenile DM, both in circulation and at target tissues such as the skin and muscle\textsuperscript{94-99}. Furthermore, the degree of organ affection may correlate with the presence of IFN-I signature in DM\textsuperscript{98,100,101}. For example, MDA5 antibody-positive patients demonstrate a stronger IFN-I signature in the skin, blood and vasculature, whereas antibody-negative patients have a stronger signature in the muscle\textsuperscript{102}. Interestingly, the overactivation of IFN-I pathways seems to be associated with metabolic reprogramming of T and B cells in MDA5\textsuperscript{+} DM\textsuperscript{96}, which has been previously described in the setting of viral infections in vitro\textsuperscript{103}. In vitro, high doses of IFNβ inhibit the proliferation of muscle stem cells, possibly related to the induction of a senescent phenotype, which could impact myogenesis and tissue repair in DM\textsuperscript{104}.

Patients with DM have significantly greater IFN-I-inducible gene expression than patients with immune-mediated necrotizing myopathy and inclusion body myositis\textsuperscript{105}. Moreover, the presence of an IFN-I signature in blood correlates with disease activity in untreated patients with DM, with a potentially useful role as a biomarker of treatment response, as the signature is down-regulated with an improvement of disease activity after therapy\textsuperscript{95,106-109}. In this sense, upregulation of Siglec-1 (an IFN-inducible gene) has been postulated as a potential biomarker in juvenile DM, as it is associated with clinical disease activity and suboptimal treatment response\textsuperscript{99}.

MDA5\textsuperscript{+} DM patients have been shown to have elevated circulating levels of IFNα and IFNγ\textsuperscript{96,110}. Furthermore, a potential role for immune complexes of MDA5 and MDA5 autoantibodies in inducing TLR7 mediated IFNα production by pDCs has also been suggested\textsuperscript{111}. pDCs are found in the inflammatory infiltrates of muscle and skin in patients with DM, suggesting these cells could represent a local source of IFNα\textsuperscript{94}. However, other studies evaluating all DM patients have identified increased levels and expression of IFNβ in the blood and skin, respectively\textsuperscript{97,112}. Upregulation of IFN-κ by keratinocytes has also been identified in the skin of patients with DM compared to healthy controls\textsuperscript{113}. Taken together, these findings illustrate the importance of IFN-I dysregulation in DM and highlight the complexity of identifying which of the IFN-I is the main pathogenic driver.

**pSS**

An IFN-I signature has been observed in peripheral blood mononuclear cells, isolated monocytes, minor salivary glands, and ocular epithelial cells in patients with pSS\textsuperscript{114-116}. The presence of infiltrating pDCs in the salivary glands of patients with pSS suggests a potential role of local IFNα production by these cells\textsuperscript{117}.

Interestingly, a recent study showed that the presence of an IFN-I signature in pSS patients is associated with increased antigen uptake by type 2 conventional dendritic cells (cDC2), which are potent inductors of B and T cell responses. Furthermore, treatment of healthy controls’ cDC2s with IFNα in vitro leads to impairment of antigen processing and increase antigen uptake capacity in these cells, reaching similar levels to those seen in pSS patients\textsuperscript{118}. Additionally, it has been proposed that the aberrant release of NET could be another mechanism associated with IFN-I dysregulation in pSS. In this sense, local IFN-I could lead to mitochondrial damage and increase reactive oxygen species production by neutrophils, with subsequent increased NETosis and eventual salivary gland damage\textsuperscript{119}.

While salivary duct epithelial cells have an IFN-I signature, lymphoid aggregates and duct epithelial cells exhibit an IFN-II (i.e., IFNγ) signature\textsuperscript{120}. IFN-I signature was associated with higher disease activity and a more pronounced production of autoantibodies\textsuperscript{115}. IFN-II signature is increased in the salivary glands of patients who...
develop lymphoma in pSS, suggesting that the IFNγ/IFNα ratio is a potential marker to predict lymphoma development among pSS patients.\textsuperscript{121}

**RA**

An IFN-1 signature is observed in a subset of patients with RA.\textsuperscript{122} IFN-I dysregulation is thought to contribute to the initiation or persistence of pathogenic pathways in RA. In individuals with early inflammatory arthritis, the presence of an IFN-I signature distinguishes patients with self-limiting disease from those who progress to RA.\textsuperscript{123} Synovial dendritic cells in RA express TLR3 and 7, and expression of these pattern recognition receptors is correlated with IFNβ, IL-1, and IL-18, and stimulation of RA synovial cells with TLR3 and TLR7 agonists resulted in type I IFN production.\textsuperscript{124} In peripheral blood, elevated IFN-I signature is associated with higher anti-citrullinated protein antibodies (anti-ACPA) titers, more persistent inflammation, and progression of erosive disease.\textsuperscript{122,123,125} The presence of an IFN-I signature has been associated with non-response to therapy, including rituximab.\textsuperscript{126-128} In addition, increased pretreatment serum IFN-β/α ratio can predict non-response to tumor necrosis factor inhibitors (TNFi) in RA.\textsuperscript{129}

**SLE**

The role of IFN-I dysregulation in SLE is well established.\textsuperscript{130} Approximately 75% of adult and 90% of pediatric SLE patients have an enhanced IFN I signature in peripheral blood.\textsuperscript{131,132} The IFN-I signature is stable over time, generally unaffected by flares of the disease, and associated with younger age, presence of autoantibodies (anti-Ro, anti-RNP, anti-dsDNA, and anti-Sm), increased frequency of flares, and specific organ involvement (e.g., nephritis, skin disease, arthritis).\textsuperscript{131-134} Furthermore, blocking IFN-I signaling with anifrolumab has proven effective in SLE, particularly in patients with an IFN-I signature in blood.\textsuperscript{135-137} In addition, early-phase trials assessing the efficacy of pDC-depleting agents in SLE and cutaneous lupus seem promising, showing that these agents can decrease IFN-I activity and overall disease activity.\textsuperscript{138,139}

**SSc**

SSc is characterized by the presence of skin fibrosis, extensive vasculopathy, and in some cases, interstitial lung disease (ILD). IFN-I signature is observed in whole blood and peripheral blood mononuclear cells in approximately 50% of SSc patients.\textsuperscript{140-146} IFN-I signature is a prominent feature in early SSc,\textsuperscript{146} and a higher IFN-I signature is associated with the presence of anti-topoisomerase antibodies, anti-U1-RNP antibodies, and more severe skin, lung, and skeletal muscle involvement.\textsuperscript{147,148} Increased IFN-II signature has also been observed in skin and lung tissue with ILD.\textsuperscript{149-151} pDCs infiltrating the skin of patients with SSc are chronically activated and secrete IFNα and the chemokine CXCL4, with the latter being due to the aberrant presence of TLR8, an RNA-sensing TLR, in these cells. Interestingly, a recent study highlighted the importance of endoplasmic reticulum stress and CXCL4 in modulating IFN-I responses via metabolic reprogramming of pDCs, which may have therapeutic implications.\textsuperscript{152} Furthermore, pDCs can promote the development of skin fibrosis, and the depletion of pDCs was associated with the stabilization of skin fibrosis in a mouse model of SSc.\textsuperscript{153} An increased expression of IFN-I-stimulated genes is also associated with a higher ILD progression rate.\textsuperscript{154}

**Anti-IFN-I therapies in systemic autoimmunity**

Several clinical trials using therapeutics targeting IFN-I in autoimmune diseases are ongoing or have been completed, mostly focused on SLE. Anifrolumab, a monoclonal antibody targeting the IFN-I receptor subunit 1 (IFNAR1), has recently been approved by the FDA for SLE treatment. Anifrolumab has been shown to substantially reduce SLE disease activity measures compared to placebo in patients with moderate-to-severely
active SLE. Anifrolumab use was also associated with lower glucocorticoid dose and severity of skin disease in patients with SLE.\textsuperscript{135,136,155} While phase 2 studies suggested a more pronounced response in SLE patients with a high IFN-I signature at baseline, this was not confirmed in the subsequent phase 3 studies individually\textsuperscript{135,137}. However, a recent posthoc analysis of pooled phase 3 trials data showed that patients with SLE and a high IFN-I signature at baseline derived greater benefit from anifrolumab treatment across multiple domains when compared to low IFN-I patients, including being more likely to attain sustained BICLA response, oral glucocorticoid taper, annualized flare rate, and $\geq 50\%$ reduction in CLASI-A score and swollen/tender joint counts\textsuperscript{137}. A recent phase 2 study to assess the efficacy of anifrolumab in active lupus nephritis did not meet its primary outcome; however, more patients attained a complete renal response in the anifrolumab group compared to the placebo group\textsuperscript{156}.

The efficacy and safety of anifrolumab are also being assessed in other autoimmune diseases. For example, a multicenter, randomized, double-blind, placebo-controlled Phase 2A study (NCT03435601) is evaluating the efficacy and safety of anifrolumab versus placebo in patients with moderately to severely active RA who did not respond to biological disease-modifying anti-rheumatic drugs and who have a high IFN-I signature is currently recruiting patients. In SSc, a phase 1, multicenter, open-label trial (NCT00930683) of anifrolumab has shown benefits and supported further studies\textsuperscript{157}. By analyzing serum samples from this study, investigators showed that anifrolumab was associated with significant downregulation of T cell-associated proteins and upregulation of type III collagen degradation marker, suggesting a potential mechanism through which tissue fibrosis may be reduced\textsuperscript{145}.

In inflammatory myopathies, initial clinical trials using anti-IFN-I therapy have shown promising results. Sifalimumab, an anti-IFN-I monoclonal antibody, was able to suppress the IFN-I signature in blood and muscle tissue of patients with inflammatory myositis, resulting in coordinated suppression of T cell-related proteins such as soluble IL-2RA, TNF receptor 2 (TNFR2), and IL-18\textsuperscript{158}. Treatment with sifalimumab also resulted in clinical improvement.

Early-phase studies evaluating the pDC-targeting agents VIB7734 (anti-ILT7) and litifilimab (BIIB059, anti-BDCA2) have shown promising results in cutaneous lupus and SLE, including acceptable safety profiles, reduction in IFN-I activity, and improvement in disease activity, including arthritis.\textsuperscript{138,139,159,160} A phase 1 study of VIB7734 in SLE, pSS, DM, SSc, and cutaneous lupus has been completed, but the full results are not yet publicly available, although preliminary results demonstrate an acceptable safety profile as well as a reduction in IFN-I levels in the blood and inflamed skin in cutaneous lupus\textsuperscript{160,161}. A phase 3 trial of litifilimab in SLE is ongoing (NCT04895241).

The Janus kinases (JAK) mediate the intracellular signaling of multiple cytokines, including IFN-I. Therefore, JAK inhibitors (JAKi) are thought to exert anti-IFN-I effects in autoimmune diseases. The efficacy and safety of several JAKi are well-established in RA, although it is likely that their efficacy in this disease is more due to the blockade of proinflammatory cytokines like IL-6 and IFN\textsubscript{\gamma} rather than their anti-IFN-I effect\textsuperscript{162}. A phase 1 randomized, double-blind, placebo-controlled clinical trial of tofacitinib in SLE subjects was found to be safe and tolerable in SLE\textsuperscript{163}. In addition, tofacitinib was also found to decrease the systemic IFN-I signature and improve cardiometabolic parameters associated with premature atherosclerosis in patients with SLE\textsuperscript{163}. A phase 2 study of baricitinib demonstrated improvement in the signs and symptoms of active SLE in patients who were not adequately controlled despite standard of care therapy, with a safety profile consistent with previous studies of this drug\textsuperscript{164}. However, based on discordant efficacy results from two phase-3 trials (SLE-BRAVE-I and -II)\textsuperscript{165}, Lilly...
discontinued the development program for baricitinib in SLE\textsuperscript{166}. Recently, a phase 1 trial of Deucravacitinib, a highly selective TYK2 inhibitor that has already been FDA for plaque psoriasis, demonstrated a favorable pharmacokinetics and safety profile and inhibition of IL12/IL-23 and IFN-I pathways in healthy volunteers\textsuperscript{167}. Preliminary results of a phase 2 trial of deucravacitinib in SLE are also promising, demonstrating patients on the drug experienced significant improvement across multiple clinical domains compared to the placebo group\textsuperscript{168}.

Regarding inflammatory myositis, tofacitinib use in ten adults with active, treatment-refractory DM was associated with improvement in disease activity in an open-label pilot study\textsuperscript{169}. Similarly, case reports and series of cases have been published on the effectiveness of JAKi (mainly tofacitinib and ruxolitinib) in patients with refractory DM, particularly for the management of skin manifestations\textsuperscript{170-173}. Ref Taken together, these findings support the development of additional trials using JAKi for DM. A phase 2 trial of baricitinib in DM is ongoing (NCT04972760). For SSc, a study assessing the effect of ruxolitinib (NCT04206644) is currently in the process of recruitment.

Hydroxychloroquine (HCQ) interferes with the endosomal pH and prevents activation of TLR7 and TLR9, thus indirectly impairing IFN-I production by pDCs\textsuperscript{174}. Several studies have shown the clinical benefits of maintaining adequate serum levels of HCQ to reduce damage over time in SLE\textsuperscript{175}. In pSS, HCQ has been shown to reduce systemic IFN-I activation\textsuperscript{176}. However, this drug is inconsistent in improving pSS-related symptoms\textsuperscript{177}. A phase 2 trial of lanraplenib and filgotinib in pSS was recently reported demonstrating some improvement in biomarkers, but the primary and secondary endpoints were not met\textsuperscript{178}.

Although using type IFN-I as a phenotypic marker to predict response to anti-IFN agents has remained challenging and generated controversial results in some studies\textsuperscript{179,180}, this continues to be a logical biomarker to stratify patients in clinical trials targeting agents that result in IFN-I blockade. Possibly, using the classic IFN signature or less sensitive measurements such as ELISA may be contributing to the conflicting findings. Thus, more sensitive and specific assays to characterize patients by IFN-I levels may be required in this setting.

**Conclusion**

IFN-I dysregulation is an important feature of several systemic autoimmune diseases. While there are unifying features such as antinuclear autoantibody response and autoimmune inflammation in various tissues, the clinical features of the group of high IFN conditions are diverse. It is not clear why high IFN-I is observed across all of these diseases with relatively disparate clinical manifestations. It could be that IFN-I is more involved in early loss of tolerance, and later events dictate tissue specificity and clinical inflammation, but this is speculative.

Therapeutics directly or indirectly targeting IFN-I are promising in a number of connective tissue diseases, and one approval has already been achieved in the case of anifrolumab in SLE. An improved understanding of the immunopathogenic mechanisms involved in the initiation and continued activation of the IFN-I pathway in autoimmunity will hopefully lead to additional novel targets and hopefully a more pathologically directed and individualized approach. It seems likely that a more comprehensive assessment beyond the IFN-I signature will be needed if we are to subclassify patients by their specific type of IFN-I pathway activation. Hopefully, such an approach will facilitate stratification techniques that are based on underlying molecular mechanisms and can be used as a predictor of treatment response.
Figure 1. Relationship between female sex bias, elevated circulating type I interferon (IFN), and the presence of antibodies against extractable nuclear antigens in dermatomyositis (DM), primary Sjogren’s syndrome (pSS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc). Rheumatic autoimmune disorders can be positioned within a spectrum of female skewness, the presence of autoantibodies, and the degree of elevated circulating type I IFN. SLE and pSS are greatly female-skewed (9:1 ratio) and strongly associated with ENA-specific autoantibodies and high circulating type I IFN. In contrast, RA has a female:male ratio of 3:1, less than 30% of patients have positive ANA or ENA-specific autoantibodies, and most patients have no evidence of increased circulating type I IFN levels.

* Anti-Ro refers to antibodies to both Ro52 and Ro60

ANA, Antinuclear antibodies; Anti-ENA, anti-extractable nuclear antigens; Anti-RNP; anti-ribonucleoprotein; anti-Sm, Anti-Smith; DM, Dermatomyositis; pSS; IFN, Interferon; Primary Sjogren’s syndrome; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; SSc, Systemic Sclerosis.
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Frequency of ANA and anti-ENA antibodies

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ANA, Antinuclear antibodies; Anti-ENA, anti-extractable nuclear antigens; Anti-RNP, anti-ribonucleoprotein; anti-Sm, Anti-Smith; DM, Dermatomyositis; pSS, IFN, Interferon; Primary Sjogren’s syndrome; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; SSc, Systemic Sclerosis.

* Anti-Ro refers to antibodies to both Ro52 and Ro60