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Interferons in Systemic Lupus Erythematosus

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Keywords

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Introduction

The past 10 years has witnessed an acceleration in the understanding of the biology of systemic lupus erythematosus (SLE). One of the key discoveries that has prompted this work is the identification of the elevated type I IFN signature in systemic lupus patients[1]. This review will summarize the biology of type I IFN signaling, the mechanisms of production, and the clinical impact of IFNs on disease.

Discussion

Interferons, their subtypes and signaling pathways

Interferons (IFNs) are important cytokines that mediate resistance to virus proliferation and thus maintain a powerful primary defense mechanism against pathogens. IFN signaling results in the coordinated expression of hundreds of genes to increase the expression of major histocompatibility complex, cytokines, and chemokines to recruit immune cells, increase antigen presentation, and thus coordinate immune response[2]. Three subtypes of IFNs are known: the type I IFN family, comprised of 13 subtypes of IFNα, IFNβ, IFNω,

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IFNκ and IFNε type II IFN of which IFNγ is the only member; and type III IFNs, initially referred to as interferon-like cytokines, that include IFNλ1 (IL-29), IFNλ2 (IL28A), IFNλ3 (IL28B) and IqFNλ4 (not expressed in all humans)[2-4].

Type I IFNs

Type I IFNs exhibit a conserved structure with 6 α-helices like other members of the class II cytokine family (interleukins: IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26) and can potentially be produced by every cell type in the body[5]. Baseline expression of IFNβ and IFNκ maintain a basal activation via expression of STAT1 and IRF9 that permits rapid signal amplification when additional IFNs are detected[6-8]. Activation of pathogen recognition receptors (PRRs), such as toll-like receptors (TLRs, plasma membrane and endosomal), or cytoplasmic sensors, such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation associated protein 5 (MDA5) by pathogen and danger-associated molecular patterns (PAMPs and DAMPs) including nucleic acids (viral DNA or RNA or endogenous nucleic acids exposed due to damage) and bacterial macromolecules (lipopolysaccharides, peptidoglycan and flagellin), induce high IFN production[9]. This is followed by a feed-forward IRF7-driven loop that accelerates IFN production in cells like plasmacytoid dendritic cells (pDCs) that are significant sources of type I IFNs[10-15].

All type I IFNs signal through the heterodimeric IFNα receptor (IFNAR) 1 and 2 complex, which triggers Janus kinase 1 (JAK1) and Tyrosine kinase 2 (TYK2) activation and subsequent phosphorylation of signal transducers and activators of transcription (STAT) 1 and 2 (Fig.1). STAT1 and STAT2 bind IFN-regulatory factor 9 (IRF-9) to form ISGF3, which translocates into the nucleus. ISGF3 binds to interferon sensitive response elements (ISREs) containing the consensus sequence TTTCNNTTTC and induces the coordinated transcription of IFN-stimulated genes (ISGs) such as Mx1 and OAS[9,16,17].

Type II IFNs

IFNγ, initially called macrophage activating factor, is mainly produced by immune cells including natural killer (NK) cells, innate lymphoid cells (ILCs) and cells of the adaptive immune system, namely T helper 1 (TH1) cells and CD8+ cytotoxic T lymphocytes (CTLs)[3]. IFNγ is induced by PRR activation as well as certain cytokines (IL-12 and IL-18). IFNγ signals through the ubiquitous heterodimeric IFNγ receptor (IFNGR1 and 2) activating JAK1/JAK2 kinases followed by STAT1 phosphorylation and dimerization (Fig.1). STAT1 dimers bind to IFNγ activation sites (GAS) with the consensus sequence TTCNNNGGA and induce transcription of ISGs, affecting antiviral and antibacterial responses[3,17,18].

Type III IFNs

Type III IFNs (IFNλs) are produced by pDCs, epithelial cells, and myeloid cells after PRR activation and cytosolic nucleic acid sensing[3,19-21]. The IFNλ receptor complex is composed of IFNλ- receptor1 (IFNLR1) and IL-10R2 subunits. Although structurally different from type I IFNs, functionally, IFNλs are similar to type I IFNs and result in JAK1/TYK2- STAT1-STAT2 activation and transcription of ISGs (Fig.1). IFNλs can also be induced by type I IFNs potentially demonstrating the involvement of different IFNs at

different stages of infection[5,22,23]. Interestingly, IFNLR1 is restricted to NK cells, pDCs, DCs and mucosal epithelial cells suggesting a significant role in mucosal regulation. IFNLR is also highly expressed in macrophages, resulting in IFNλ-mediated functional enhancement while also promoting their secretion of chemokines and cytokines for NK cell function (cytotoxicity) and IFNγ production[24].

Non-canonical signaling by IFNs

Type I and II signaling pathways overlap significantly, and characteristic signatures are hard to differentiate[2,3,25]. ISREs as well as GAS sequences in the same genes allow for activation by type I and type II IFNs. In addition to the STAT1-STAT2 heterodimer that forms ISGF3, type I IFNs can induce STAT1 and STAT3 homodimers and heterodimers and STAT4, STAT5 and STAT6 activation in other cell types[26]. The activation of non-canonical STATs can lead to different transcriptional outcomes[18,26]. Type I IFN signaling can also occur through Rap1, Map kinases and PI3- kinase pathways[27-30] (Fig.1).

Suppression of IFNs

IFN activation also induces signal regulatory genes including suppressor of cytokine signaling (SOCS), that compete with STATs, and ubiquitin carboxy-terminal hydrolase 18 (USP18), that helps dissociate JAK1 from IFNAR2, thus reducing downstream signaling. Self-regulation by IFNs also occurs through activation of STAT3 homodimers that lead to anti-inflammatory responses[2]. Other IFN suppression mechanisms are internalization of the receptor complex, regulation by microRNAs (miR146a and miR155) and deactivation of the signaling intermediates by means of proteins such as SH2 domain-containing protein tyrosine phosphatase 2 (PTPN11)[18].

Sex bias in IFN production and activity

Sex bias is predominant in SLE with a significant skew towards women[31]. Loss of X-chromosome inactivation (XCI) of TLR7 and IRAK1 and estrogen-modulated increase in TLR8 are linked to elevated IFN production[32-34]. XCI is implicated in higher expression of CXorf21 which co-localizes with TLR7 in B cells and is linked to lower lysosomal pH and is induced by IFNs[35,36]. In addition, increase in the transcription factor Vestigial like 3 (VGLL3) in females results in altered IFN response gene expression, including B-cell activating factor, IFNκ and CXCL13, all genes important in the pathogenesis of cutaneous and systemic lupus[37].

Activation of IFN pathways in SLE

IFNs are produced downstream of many sensors which respond to pathogens thus affecting immune response. Indeed, genetic polymorphisms in members of these response pathways are genetic risks for SLE.

Toll-like receptors (TLRs)—The lysosomal-localized TLR family is an important source of IFN production in SLE patients. Beyond response to bacteria and viruses, endogenous nucleic acids resulting from environmental insult or uptake of immune complexes containing nucleic acids trigger the production of IFNs. TLR7 (binds ssRNA) and TLR9 (binds

dsDNA) expression in B-cells is critical for spontaneous germinal center development contributing to autoantibody production. Increased expression of TLR7, secondary to genetic polymorphisms or escape of XCI can lead to dose dependent development of SLE in humans and mice[32-34]. Conventional dendritic cells (cDCs) from lupus-prone mice show higher IL-10 and IL-27 (elevated in SLE patients) production upon TLR stimulation and this is enhanced by IFN priming[38]. Hypersensitivity to TLR7 activation and low TRAF5 contribute to autoreactive naïve B cell differentiation into plasma cells and establishes extrafollicular B cell activation in SLE[39]. TLR7/8 activation also induces early IFNβ production followed by IFNα at later time points; in granulocytes, TLR8 but not TLR7 activates IFN production[40].

Cytosolic sensors—Polymorphisms in genes associated with cytosolic nucleic acid detection, breakdown and repair mechanisms, and IFN pathway (SAMHD1, RNASEH2ABC, ADAR1, IFIH1 (MDA5), ISG15, ACP5, TMEM173 (STING))[41] also confer risk for SLE. These risk variants contribute to intracellular nucleic acid accumulation and activation of cytosolic sensors leading to high IFN production[42-46]. The cyclic-GMP-AMP synthase (cGAS) and the cyclic-GMP-AMP receptor stimulator of IFN genes (STING) axis detects cytosolic microbial/self-nucleic acids to induce type I IFNs[47]. Higher expression of cGAS in PBMCs correlated with disease activity in SLE[48]. Genome instability due to RNAseH2 (removes ribonucleotides incorporated into DNA) deficiency can also lead to an autoimmune phenotype by recruitment of cGAS[49]. Pores formed by voltage-dependent anion channel (VDAC) allow short DNA fragments from stressed mitochondria (ROS production) into the cytosol activating robust IFN production via cytosolic sensors such as STING[2,50,51]. Cytosolic viral RNA sensors such as RIG-I and MDA5 (encoded by *IFIH1*) that then recruit mitochondrial antiviral-signaling protein (MAVS) also drive IFN production. *IFIH1* mutations and MDA5 hyperactivation result in increased type I IFN production and possible SLE[52-54]. Mice harboring a gain of function mutation in IFIH1 developed lupus nephritis and ds-DNA autoantibodies supporting a role for increased sensitivity to RNA complexes[55,56].

Oxidation of nucleic acids may further promote IFN production. Reactive oxygen species (ROS) induce MAVS aggregation[57,58] and reducing mitochondrial ROS via oral mitochondrial antioxidants decreased MAVS oligomer formation and type I IFN levels in serum of MRL-lpr mice[59]. Inhibition of oxidized DNA repair results in higher auto-antibody production (anti-dsDNA and anti-RNP), increased total IgG, and ISG expression in a pristane-induced lupus mouse model[60]. Further, amplification of cytosolic nucleic acid signaling occurs through type I IFN-mediated inhibition of autophagy related DNA degradation thus increasing substrates for pathway activation[61].

Role of IFNs in the Pathogenesis of SLE

SLE is a complex, multi-organ system disease most commonly presenting with constitutional symptoms, oral ulcers, rash, and arthritis. Systemic organ involvement can be severe and include lupus nephritis, including glomerulonephritis, central and peripheral nervous system involvement, cardiac and lung manifestations, autoimmune hepatitis, among others. Autoantibodies and deposition of immune complexes have been implicated in the

pathogenesis of these disease manifestations; however, this alone is not sufficient to generate disease: T-cells are now understood to also play a critical role. Additionally, prior to development of autoantibodies, the innate immune system is abnormal and may be a precursor to adaptive immune system changes. Most notably, sustained high levels of IFN function as a central pathogenic mediator in early immune dysregulation bridging the link between innate and adaptive immunopathogenesis in a feed-forward mechanism.

IFNα can induce SLE

The first suggestion that IFN may drive SLE pathogenesis was reported in 1969 after administration of IFN to genetically-susceptible lupus-prone mice resulted in increased autoantibodies and end-organ damage[62]. These data have been corroborated in human observational studies of patients undergoing recombinant IFNα treatment of viral, autoimmune, and malignant diseases[63]. A subset of susceptible individuals treated with IFNα have subsequently developed autoantibodies, a “lupus-like” syndrome, or infrequently, clinical lupus after treatment[64].

In those treated for HCV, patients with pre-existing ANA positivity were found to have a rise in titer with IFNα exposure [65]. Further reports show patients treated for pancreatic or carcinoid tumors with IFNα resulted in development of ds-DNA antibodies [66]. The SLE-like syndrome of patients undergoing IFN treatment includes myalgia, arthritis, oral ulcer, malar rash, lymphopenia, serositis, lymphadenopathy, fever, renal disease and these effects resolve when IFN treatment is discontinued [67-69].

Murine models have also provided evidence that type I IFN exposure can drive SLE. Upregulation of IFNα in inducible IFNα transgenic mice not prone to autoimmunity is sufficient to produce lupus-like findings, including serum immune complexes, anti-dsDNA antibodies, immune-complex glomerulonephritis, alopecia, splenic-onion skin lesions, epidermal liquefaction, and a positive lupus band test of skin [70]. Treatment of mice with adenovirus that drives IFN-expression also induces inflammatory cytokine upregulation and can promote renal immune complex deposition in non-lupus prone mice[71]. Further, IFNα adenovirus can drive increased autoantibody formation and refractoriness to treatment of lupus nephritis in lupus-prone NZB/NZW_{F1} mice[72].

Heritable risk factors for SLE involve IFN pathways

SLE is a complex, heritable, polygenic disease likely resulting from alterations at several genetic loci linked to immune function [43]. Among families, high serum IFNα activity has been observed in both patients with SLE and healthy first-degree relatives independent of autoantibody profiles[73]. Genome-wide association studies have identified more than 40 loci linked to SLE susceptibility with a notable disproportionate number of IFN pathway-related genes which function to regulate IFN production, signaling, function, and downstream effects [74].

Many IFN pathway genes are under investigation and several have been implicated in development of disease. *IRF5, IRF7, IRF8*, members of the interferon regulatory factor family, are transcription factors which regulate IFN-related pathways and variants have been associated with risk to development of SLE [75, 76, 77]. Indeed, IRF5, an important mediator of

IFN production induced by the TLR-MyD88 axis, is critical in murine lupus pathogenesis and IRF5 genetic polymorphisms lead to higher IFN production in lupus patients[43,50,78,79]. Further, nuclear localization (activation) is noted in SLE patient monocytes and preclinical treatment with an IRF5 inhibitor improves murine lupus[80]. Impaired TRIM21-mediated proteasomal degradation of IRFs in SLE also contributes to amplified IFN responses, highlighting the impact of defective IFN regulatory mechanisms in SLE risk[81].

Genetic polymorphisms in components of the IFN signaling pathway also confer risk for SLE. *STAT4* functions in cytokine signaling and participates in nonclassical IFN signaling; variants have been associated with dsDNA antibodies, younger age disease onset and history of nephritis[74]. Loss of STAT4 is associated with lower levels of IFNγ, higher mortality, and nephritis in lupus prone mouse models[82]. Loss of function mutations in *STAT3* in patients results in higher ISGs expression and higher neutrophil extracellular trap formation supporting its negative regulatory function in SLE[83]. *TYK2* is a member of the JAK family of signaling molecules associated with the type I IFN receptor and is involved in cytokine signaling cascades; alterations at *TYK2* loci have been associated with SLE [74].

Interestingly, SLE clinical manifestations and pathogenesis show differences based on ancestral background, and the genetics of IFN-related pathways may be a key factor[84]. IFNα production is higher in individuals from non-European ancestry [73]. Ko *et al.*, showed that IFN-pathway activation was dependent on circulating anti-RNA binding protein antibodies in African American patients but not in patients of European ancestry [85]. Genetic differences in IFN pathway activation may prove important in order to determine likelihood of response for therapeutics targeting type I IFNs and their receptor.

IFNs increase prior to onset of disease

Both type I and type II IFN, as well as specific autoantibodies (ANA, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-smith), are found in SLE patients months to years prior to any disease manifestations [86,87] and likely form a key feedback loop that drives innate and adaptive immune system pathology. Autoantibody positivity appears to follow or coincide with type II IFN dysregulation, while IFNα activity and elevation of B-lymphocyte stimulator (BLyS) occurs more proximal to SLE classification [86]. Regression analysis of IFN levels in 248 patients by Oke *et al.*, shows that high IFN activity is associated with active SLE (active lupus nephritis (LN), high SLEDAI, anti-Sm, anti-dsDNA). When different IFN subtypes were evaluated, high IFNα was associated with muco-cutaneous lupus (anti-Ro and anti-La) while IFNγ correlated with high SLEDAI scores and LN, and high IFNλ1 associated with anti-nucleosome antibodies and higher frequency of anti-phospholipid antibodies[88]. Only patients exhibiting both antinuclear antibodies and an IFN signature progress to clinical SLE diagnosis and can help predict advancement to end stage renal disease[50,89].

Even before type I IFN elevation and autoantibody detection, an earlier perturbation in the immune system is elevation of type II interferon (IFNγ), found >4 years prior to disease onset[86]. IFNγ, is expressed by many cells of both the innate and adaptive immune system, including NK cells, NK T cells, T cells and B cells and like other IFNs, signals via JAK-STAT pathway (Fig.1) [90]. IFNγ and IFNγ-related gene activity correlates with SLEDAI

score and dsDNA antibody levels, further suggesting a key role in pathologic autoantibody production[91]. Furthermore, close interaction between type I and type II IFN has been demonstrated with IFNγ induction of type I IFN during viral infection[92] and a role for synergistic amplification of IFN-stimulated gene expression with co-exposure of IFNγ and IFNα [93].

Patients with evidence of autoimmunity but without full criteria for diagnosis can be used to evaluate “early” changes related to interferons. Patients with clinical incomplete lupus (ILE) who demonstrate features of SLE but do not meet classification criteria for the diagnosis, a subset of whom will progress to SLE, demonstrate elevated circulating type I IFN gene signatures that correlate with disease burden [94]. A subset of patients with positive ANA without clinical criteria for systemic autoimmune disease will show elevated IFNα levels and gene expression, correlating with specific autoantibody profiles, including anti-Ro and anti-La [95,96]. More recently, this increased IFN signature has also been demonstrated in the skin of ANA positive patients without SLE[97]. Additionally, IFN gene expression is correlated with markers of inflammation and disease activity such as ESR and IgG levels and negatively correlated with C4 levels and IgM levels, further demonstrating its role in immunoglobulin class switching and disease activity [94,98]. Ongoing trials are evaluating whether intervention via use of hydroxychloroquine, which can lower IFN signatures in ILE[99], can prevent development of SLE.

Roles of type I IFNs in organ-specific inflammation

Beyond a global risk for SLE, research has identified specific effects of IFNs that contribute to specific organ involvement (summarized in Fig.2).

Blood and Blood Cells—Circulating type I IFN levels, as measured by response assays, have been shown to correlate with SLE disease activity [100, 101, 102]. Newer technologies have confirmed elevated circulating IFNα protein levels in SLE patients, ranging from 10 fg/mL to 10 pg/mL. Further, type I IFN activity is functional in SLE serum, as serum from SLE patients can induce monocytes to differentiate into DCs via IFNα [103] and promotes endothelial dysfunction[104].

IFN-pathway over activation is closely tied to B-cell dysregulation, another salient feature in SLE pathogenesis. New-onset-SLE-patient transitional B cells (Btr) have higher IL-6 producing capacity and increased survival via type I IFN signaling[105]. Btr cells have been identified previously as a source of IL-10 regulatory B cells; however, this is disrupted in SLE patients and chronic stimulation by type I IFN has been a proposed mechanism[106]. Single cell RNA-sequencing has also identified subsets of many circulating inflammatory cell populations that have been exposed to type I IFNs and consequently express increased inflammatory markers and correlate with disease activity measures in pediatric and adult lupus[107].

In addition, there may be direct effects of type I IFNs on the bone marrow. IFNα administration suppresses bone marrow production resulting in leukopenia, anemia, and thrombocytopenia [108]. The contribution of type I IFNs to lymphopenia in SLE patients is further supported by phase III clinical trial data with anifrolumab, a monoclonal antibody to

type I IFN receptor, which improves lymphocytopenia with blockade of type I IFN receptor[109].

Skin—The pathogenesis of cutaneous lupus erythematous (CLE) is incompletely understood but IFN-driven, cytotoxic inflammation likely plays a key role. Upregulation of type I IFN signatures is a hallmark of lesional SLE and CLE skin[110]. Myeloid cells, including plasmacytoid dendritic cells, are recruited to CLE skin which likely contributes to the IFN signature. In addition, epidermal production of IFNκ, a member of the type I IFN family, is increased in lesional and non-lesional SLE skin and contributes to inflammatory cytokine production and photosensitivity [711197,112]. Additionally, patients with subacute cutaneous lupus and discoid lupus demonstrate an increased IFN signature in blood that correlates with skin disease activity, suggesting IFN production in the skin may contribute to amplification of systemic disease[113].

Further demonstrating the importance of IFN in pathogenesis of CLE in vivo, skin disease improves with blockade of type I IFN and also with targeting of pDCs. This was demonstrated in phase III clinical trial data from anifrolumab where cutaneous lupus erythematosus disease area and severity index (CLASI) activity score of >10 at baseline improved over 50% with treatment [109]. PDC targeted therapies have shown success in early phase trials [114].

Renal—Mouse and human studies have established a role for IFNs in the pathophysiology of lupus nephritis (LN). Murine models have shown that deficiency of the type I IFN receptor is protective in some models of nephritis and that systemically administered IFNα renders mice resistant to therapeutic intervention [72115]. Renal tubular epithelial cells and infiltrating pDCs in kidney of patients with LN demonstrate a type I IFN signature which is associated with local production of IFNα by the proximal tubular cells, suggesting an autocrine effect leading to tubulo-interstitial damage [116]. Indeed, tubular IFN signatures may also have prognostic implications[117]. Circulating IFNs may also be involved in pathogenesis as the IFN signature in infiltrating leukocytes in the kidney correlate with IFN signature in blood [118]. Further, murine models and in vitro studies have shown systemic IFNα and IFNβ increase glomerular inflammation and proteinuria and decrease differentiation of renal progenitor cells to podocytes, promoting scar formation [119].

The role for IFN-γ is less studied but may also contribute to lupus nephritis. Deficiency of IFNγ or blockade of its receptor prevents disease development [120]. IFNγ-positive cells are a prominent feature of kidney-infiltrating immune cells in lupus nephritis and correlate with predominance of CD8+ T cell infiltrates on biopsy, suggesting this cell population as the source for IFN-γ and a role in pathogenesis of lupus nephritis [121]. Human monoclonal antibodies to IFN-γ, AMG 811, was tested in a phase Ib randomized-controlled trial in patients with LN; however, no effect in SELENA-SLEDAI, proteinuria, C3, C4 or anti-dsDNA was noted [122]. Further research will hopefully determine whether the presence of renal IFNγ is pathologic or a result of inflammation itself.

Joints—Synovial tissue of SLE patients with arthritis has shown down-regulation of genes involved in extracellular matrix homeostasis and increased expression of type I IFNs,

distinctly different from rheumatoid arthritis and osteoarthritis [123]. Recent analysis suggests that IFNγ signatures may more strongly correlate with lupus arthritis vs. other manifestations such as the skin, which is dominated by a type I IFN signature[88]. Further research into the role of IFNs in lupus arthritis is needed.

Cardiovascular Disease—Cardiovascular risk is elevated in SLE patients. IFNs have been shown to impact endothelial cell function and overall cardiovascular risk in SLE patients[124] and this has been extensively reviewed[125]. The presence of increased neutrophil NETosis and the IFNs produced by low density granulocytes likely contribute as well[126]. Indeed, recent data from systemic blockade of type I IFN signaling has shown improvement in markers of cardiovascular risk[127], suggesting that IFN blockade may have positive impacts on cardiovascular function and risk for ischemic events.

Clinical applications

Targeting the type I IFN receptor—Anifrolumab is a monoclonal antibody against subunit 1 of the type I IFN receptor which antagonizes effects of all type I IFNs including IFNα, IFNβ, IFNω, IFNκ [128]. A phase IIb randomized-controlled trial (MUSE trial) showed a higher percentage of subjects in the anifrolumab treatment group met the primary endpoint of SLE responder index (SRI-4) compared to placebo with sustained reduction in corticosteroid use at week 24. The treatment arm also showed improvement in SRI-4, modified SRI-6, BICLA, BILAG-2004 at week 52, as well as improvement in CLASI score and tender and swollen joint counts [129].

Given the success of the MUSE trial, two phase III randomized-controlled clinical trials, TULIP-1 and TULIP-2, were performed to evaluate the efficacy and safety of anifrolumab in moderate-to-severe SLE patients receiving standard of care therapy. TULIP-1 was a multicenter, multinational, double-blind, parallel-group trial with subjects stratified by disease activity and IFN-signature (high vs low). The study failed to meet its primary endpoint with percentage of subjects achieving SRI-4 response at week 52 similar in both treatment and placebo groups. Given the discrepancy in results from the MUSE trial, a re-analysis was performed. Patients who used NSAIDs during the trial were initially classified as non-responders were reclassified. After this alteration, improvement in CLASI score, decrease in tender and swollen joint count, higher percentage of patients achieving BICLA response were noted in the anifrolumab group at week 52, although primary end point was still not met [130].

With improvement in the BICLA response but not SRI-4, TULIP-2 sought to evaluate efficacy of anifrolumab in moderate-to-severe SLE patients with the primary endpoint of BICLA response. Similarly, TULIP-2 was a multicenter, multinational, double-blind, parallel-group trial with subjects stratified by disease activity and IFN-signature (high vs low). The primary end point was met with improved BICLA response in the treatment group compared to placebo at week 52. Additionally, anifrolumab treatment arm showed reduced corticosteroid use, improved CLASI score, and higher percentage of patients with improved swollen and tender joint count [109]. Long term extension and lupus nephritis trials are ongoing with anifrolumab.

Anti-IFN antibodies—Two monoclonal antibodies targeting specifically IFNα, sifalimumab and rontalizumab, have been studied in Phase II clinical trials. Sifalimumab met its primary endpoint with a higher percentage of patients achieving SRI-4 in the treatment group. Patients also showed improvement in the CLASI score, Physician's Global Assessment, BILAG, and reduction in tender and swollen joint counts with administration of sifalimumab [131]. Rontalizumab failed to meet its primary endpoint of reduction in BILAG-2004 or secondary endpoint of reduction in SRI; it is no longer being developed [132]. Subgroup analysis from this phase II trial showed patients with low IFN signature had higher SRI response, lower steroid use, and reduction in the SELENA-SLEDAI flare index with rontalizumab treatment [132]. Phase 3 studies of anifrolumab were pursued over sifalimumab as it targets a broader range of type I IFN and more subunits of IFNα possibly making it more efficacious.

Recent results of a phase 1, randomized, double-blinded, placebo-controlled trial of JNJ-55920839, a monoclonal antibody which neutralizes most IFNα subunits and IFNω, showed it is safe and well tolerated in healthy participants and those with mild-moderate SLE and elevated type I IFN signature [133].

Of note, all of the above treatments, including anifrolumab, sifalimumab, rontalizumab, and JNJ-55920839 showed elevated rates of herpes zoster (HZV) infections in the treatment group compared to placebo [109,129, 131, 132, 133]. Mitigation strategies on how to prevent HZV or other viral infections with IFN-targeting therapies, such as vaccination, should be considered and further studied.

JAK inhibitors/Tyk2 blockade—The JAK-STAT pathway mediates intracellular signaling from a variety of type I/II cytokine receptors, including type I IFN, IFNγ, IL-6, IL-2 [134]. This pathway has been implicated in SLE pathogenesis through IFN regulatory factor-related gene expression [135]. Several JAK-inhibitor small molecules are currently under development for treatment of a variety of autoimmune diseases, including SLE. Murine models have shown modulation of this pathway with JAK inhibition leads to decreased anti-dsDNA antibodies, decreased proteinuria and improved nephritis and skin disease [136-138]. Other murine models have shown lesional keratinocytes and dermal immune cells strongly express phospho-JAK1 and blockade of JAK1 decreases expression of pro-inflammatory mediators including BLyS and CXCL2, as well as decreases skin lesions [139].

Baricitinib, a JAK1/2 inhibitor that has been approved for rheumatoid arthritis, underwent a phase II placebo-control trial for treatment of non-renal SLE with active skin or joint disease [140]. This study found the proportion of patients achieving resolution of arthritis or rash was significantly higher in baricitininb 4 mg group compared to placebo, as defined by the Systemic Lupus Erythematous Disease Activity Index-2000 (SLEDAI-2K) ($p = 0.04$) [140]. Currently there are two phase III randomized-controlled studies of baricitinib in non-renal SLE (NCT03616912, NCT03616964). In the future, new applications for JAK-inhibitors in lupus may provide an additional therapeutic treatment option for SLE, primarily skin and joint disease.

Role as a biomarker—Many IFN-regulated chemokines have demonstrated correlation with SLE disease activity, showing promise for future biomarkers. Given the importance of preventing renal damage with early diagnosis of lupus nephritis (LN), there is a search to replace invasive renal biopsy with noninvasive biomarkers. Recent interest in urine proteomics has led to the discovery that urine chemokines mirror inflammatory cell infiltrates driven primarily by IFNγ [121]. Three IFN-inducible chemokines, CXCL10 (IP-10), CCL2 (MCP-1) and CCL19 (MIP-3B) have shown correlation with SLE disease activity and CXCL10 is consistently the strongest predictor [141,142]. A recent meta-analysis showed serum CXCL10 levels correlated with SLE disease activity and urine CXCL10 level detected active LN [143].

Summary

IFN signaling, particularly for type I IFNs, is elevated in SLE patients and contributes to many aspects of disease. Murine models have shown the benefits of IFN blockade, and now tools to block IFN function in patients are becoming available to simultaneously treat disease manifestations and to further understand the biology of IFNs in SLE.

Disclosures:

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Key Points:

- Interferons are elevated in the blood and organs of patients with SLE.
- Genetic risk and environmental signals can drive interferon production.
- Interferons are important for disease pathogenesis in some, but maybe not all, manifestations of SLE.
- Targeting interferons and their signaling pathways is an exciting therapeutic avenue in SLE.

Synopsis

Skewing of type I interferon (IFN) production and responses is a hallmark of systemic lupus erythematosus (SLE). Genetic and environmental contributions to IFN production lead to aberrant innate and adaptive immune activation even before clinical development of disease. Basic and translational research in this arena continues to identify contributions of IFNs to disease pathology, and several promising therapeutic options for targeting of type I IFNs and their signaling pathways are in development for treatment of SLE patients.

Clinical Care Points

- Type I and Type II IFNs are elevated many years prior to disease onset; this offers opportunity for prevention.
- Type I IFNS contribute to many aspects of SLE including bone marrow suppression, skin disease, arthritis, lupus nephritis, and cardiovascular disease.
- A wide range of drugs are being explored to block IFN signaling and will offer new tools for mechanistic understanding and treatment of SLE.

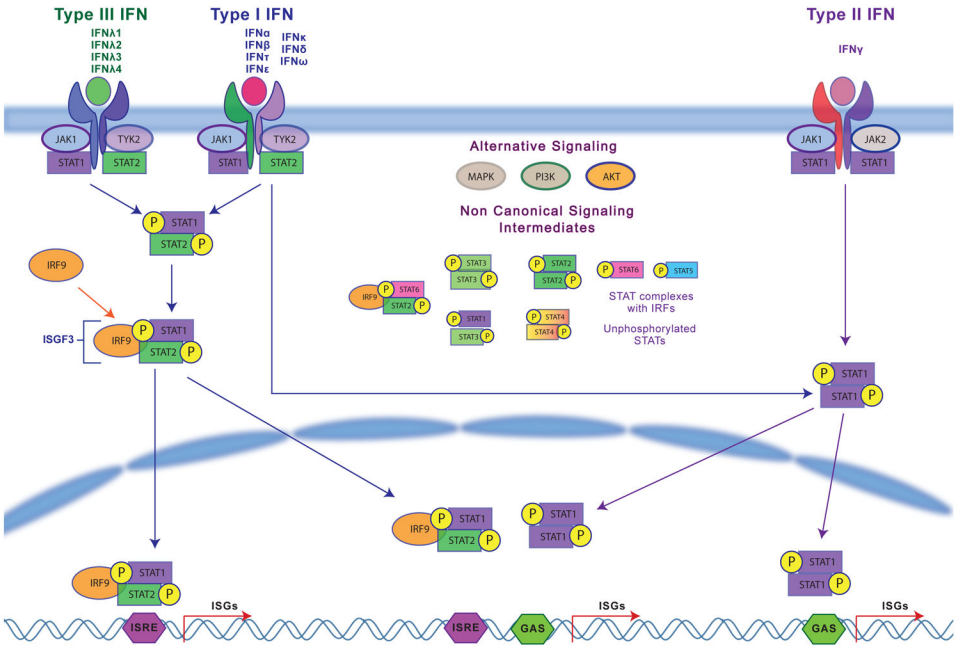

Figure 1:
Interferon Signaling Pathways for type I, type II and type III interferons

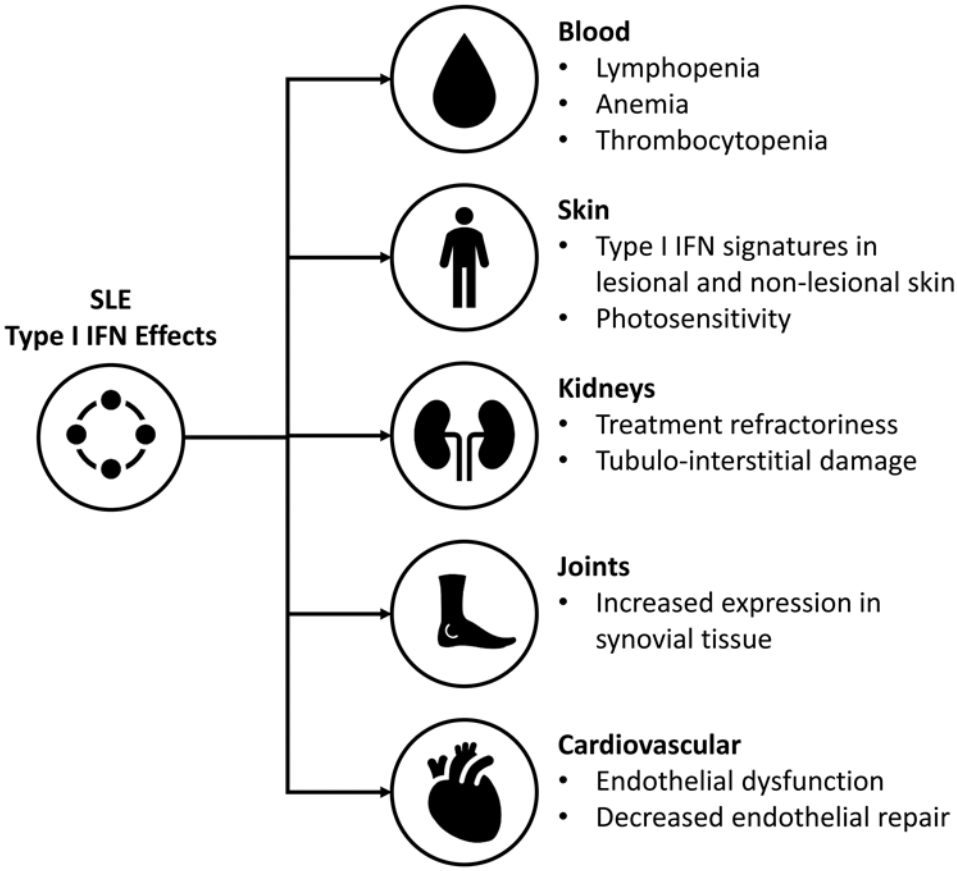

Figure 2:
Summary of the effects of type I IFN on SLE manifestations