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REVIEW

Recent Advances of Type I Interferon on the Regulation of Immune Cells and the Treatment of Systemic Lupus Erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multiple organ damage. Several studies have found that, in addition to significant production of autoantibodies, the majority of SLE patients exhibit increased expression of type I interferon (IFN-I) regulated genes (also known as IFN-I traits), and that IFN-I plays a crucial role in the pathogenesis of SLE. In SLE, virtually all immune cells are dysregulated, and most of these aberrant dysregulations are directly or indirectly affected by IFN-I. The mechanism of action of IFN-I in these immune cells is multifaceted. In this review, we focus on the immune cell types that produce IFN-I and are affected by IFN-I in SLE. Importantly, we explore the research progress of related drugs in terms of IFN-I production, itself, and downstream. Here we provide the most up-to-date information on the mechanisms that lead to the pathogenesis of SLE, providing the basis for the development of innovative future therapies and future research directions.

Keywords: systemic lupus erythematosus, type I interferon, autoimmune, B cell, T cell

Introduction

Systemic lupus erythematosus (SLE) is a persistent, incapacitating, diverse autoimmune condition distinguished by type I interferons (IFN-I), circulating antinuclear antibodies (such as dsDNA and snRNP), and immune complex deposition, leading to multiple organ damage.[1] In addition to multiple organ involvement, SLE manifests three distinct patterns: chronic persistent disease, periodic remissions and relapses, and prolonged quiescence. Symptoms include rashes (71%), arthritis (85%), nephritis (21%), hematological disorders (35%), and neurological disorders (18%).[2] An abnormal immune response plays a key role in SLE pathogenesis, characterized by impaired clearance of apoptotic cells, loss of self-tolerance to autoantigens, alteration of T-cell and B-cell functions, and altered cytokine profiles.[3]

Interferons (IFN) are released by host cells in response to invasion by pathogens. Depending on the specific receptor type, human interferons can be categorized into three distinct groups: interferon I, interferon II, and interferon III (Table 1). IFN-I include IFN-α, β, ε, κ, and ω.[4] Almost all nucleated cells in the body produce IFN-α in response to infection. Particularly notable in this regard are plasmacytoid dendritic cells (pDCs), which produce greater quantities of IFN-I than any other cell.[4] IFN-β is the high-affinity short-lived priming IFN and the major IFN-I produced by fibroblasts.[5] IFN-II is mainly secreted by T lymphocytes, natural killer cells (NKs), and antigen-presenting cells (APCs) such as monocytes, macrophages, and dendritic cells (DCs).[6] IFN-III is produced by APCs and epithelial cells.[4] The innate and adaptive immunity would initiate and produce IFN-I while viruses infected. The genetic association between IFN-I pathway and SLE susceptibility has been extensively investigated. Genome-wide association

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Table 1 Classification of IFN

Classify		Produce Cells	Ref.
IFN-I	Human: IFN-α (contains 13 subtypes), IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-τ and IFN-ω1-3 Mouse: IFN-α (contains 14 subtypes), IFN-β, IFN-ε, IFN-κ and IFN-ξ	Almost all nucleated cells in the body produce IFN-α in response to infection, but the main source of IFN-α is pDCs.	[4]
IFN-II	IFN-γ	It is mainly secreted by T lymphocytes, natural killer cells, and APCs such as monocytes, macrophages, and DCs.	[5]
IFN-III	Human: IFN-λ1, IFN-λ2, IFN-λ3 and IFN-λ4 Mouse: IFN-λ2 and IFN-λ3	It is produced by APCs and epithelial cells	[4]

Abbreviations: IFN, Interferons; pDCs, plasmacytoid dendritic cells; APCs, antigen-presenting cells; DCs, dendritic cells.

studies (GWAS) studies have shown single nucleotide polymorphisms (SNPs) in IFN regulatory factor (IRF)5, IRF7, IRF8, signal transducers and activators of transcription 4 (STAT), and tyrosine kinase 2 (TYK2) are associated with higher risks of developing SLE.[7,8] Epigenome wide association study (EWAS) found that the most pronounced differences in methylation between SLE patients and healthy controls (HC) were in the interferon-stimulated genes (ISGs), including IRF5 and IRF7.[9] Meanwhile, droplet-based microfluidics and other techniques to further define the relationship between IFN-I and SLE.[10] Several studies have found a negative correlation was observed between serum IFN-α levels and Toll-like receptor (TLR)-7 expression, as well as C3 and C4 levels in SLE patients.[11] Recent studies have shown that an elevated baseline level of IFN-α in SLE is associated with poor renal outcomes, including the development of two or more renal flares and a significant decline in kidney function, and could serve as a biomarker for upfront identification of patients at high risk of poor renal outcomes.[12] The physiological importance of IFN-I in SLE patients remains unclear. Next, we will summarize the additional description of IFN-I and SLE.

IFN-I Signaling

IFN-I can be produced by a variety of nucleated cell types through the activation of multiple pattern recognition receptors (PRRs), including TLRs (TLR3 and TLR7/8/9) by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including cyclic GMP-AMP synthase (cGAS), melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I).[13,14] TLRs recognize different PAMPs to induce IFN-I production. TLR3 is a double-stranded RNA (dsRNA) sensor localized in the endosomes of many cell types but not plasmacytoid DCs (pDCs), the most potent producers of IFN-I.[15] TLR7/8 recognises single-stranded RNA and TLR9 recognises DNA.[15] cGAS is a DNA sensor that produces cGMP-AMP (cGAMP) by recognizing cytoplasmic nucleic acids including dsDNA.[16] cGAMP induces IFN-I production and activates the nuclear factor kappa-B (NF-κB) pathway via a stimulator of interferon genes (STING).[17–19] The most common RNA sensors are members of the RIG-I like (RLR) family, including RIG-I, MDA5, and laboratory of genetics and physiology 2 (LGP2).[14,20] The helicase domains and C-terminal domains of the RLR bind to RNA ligands and the N-terminus binds to mitochondria antiviral signaling (MAVS) to induce IFN production.[21–24] Tumor necrosis factor (TNF), receptor activator of nuclear factor kappa-B ligand (RANKL), and macrophage colony-stimulating factor (M-CSF) are also physiological inducers of IFN-I. It induces an antiviral state by activating ISG in a paracrine and autocrine mechanism upon induced IFN-I.[25]

Research has recently highlighted IRFs, a group of transcription factors involved in the IFN signaling cascade that modulate immune responses.[26] The IRF family specifically includes IRF1, IRF3, IRF5, and IRF7,[27] and IRF1 is the first member to activate the IFN-I gene promoter.[28] Studies have recently implicated IRF3 and IRF7 as negative regulators of IFN responses in association with NF-κB pathway.[29] Significantly, targeting IRF3 and IRF7 signaling has only shown partial effects on IFN-I, indicating the potential involvement of other mediators. Methyltransferase 3 (METTL3) promoted plasma cell infiltration and kidney damage by increasing IRF4 expression in MRL/lpr mice.[30] While there is some indication that IRFs may influence IFN characteristics, current evidence is limited.

The binding of IFN-I to the IFN-α/β receptor (IFNAR) phosphorylates STAT1/STAT2, forming a trimer that moves into the nucleus and activates signaling downstream of ISG transcription initiation.[31] RhoA siRNA reduces STAT1 phosphorylation but not STAT2, leading to downregulation of the IFN-I response, and has been demonstrated in patients

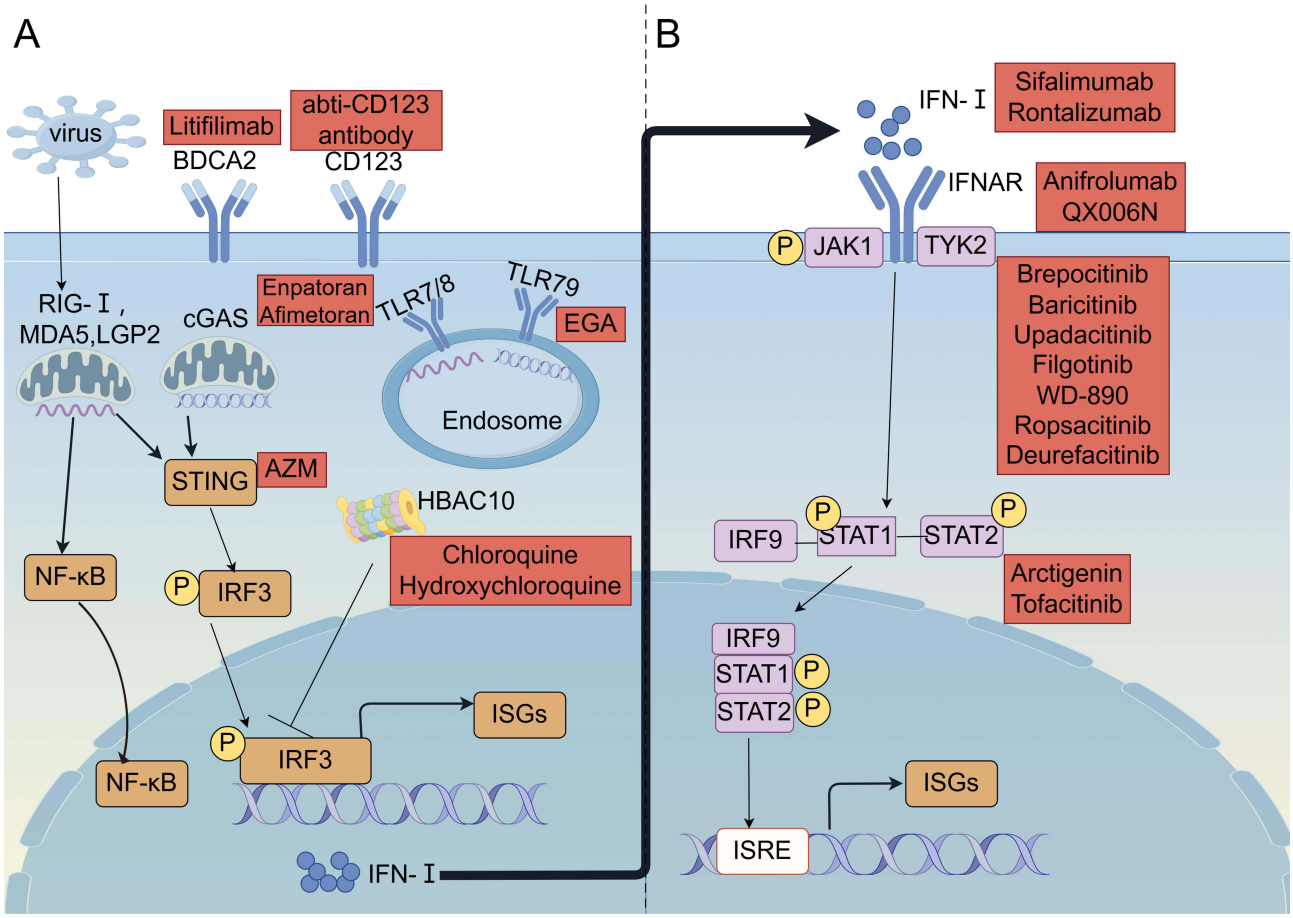

Figure 1 Pathways of action of IFN-I and related drugs. (**A**) IFN-I can be produced by a variety of nucleated cell types through the activation of multiple PRRs, including TLRs (TLR3 and TLR7/8/9) by PAMPs and DAMPs, including cGAS, MDA5, and RIG-I. (**B**) IFN-I binds to IFNAR on target cells and activates the JAK-STAT pathway. This image was created by Figdraw.

Abbreviations: IFN-I, Interferon; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; cGAS, cyclic GMP-AMP synthase; MDA5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid-inducible gene I; IFNAR, IFN-α/β receptor; JAK, janus kinase; STAT, signal transducers and activators of transcription.

with SLE.[32] In response to cytokine binding, janus kinase (JAK) activation facilitates the phosphorylation of STAT and dimerization, resulting in nuclear translocation and regulation of target gene expression. A critical role for TYK2 is to mediate the signaling pathways of IFN-I and interleukin (IL)-12/23.[33] IFN-β stimulation induced an increase in STAT2 phosphorylation for a longer duration in cells with higher HC. This activation induced higher MxA mRNA levels (an ISG), which may be due to insufficient upregulation of the regulatory suppressor of cytokine signaling 1 (SOCS1) protein.[34,35] Individuals with SLE produce T follicular helper (Tfh)- T helper (Th)1-like cells as a result of the IL-12-mediated coactivation of STAT1 and STAT4. Tfh-Th1 type cells may expand through this process, providing a potential mechanism for targeted SLE therapy.[36]

Overall, inborn errors in the production of, or responses to, IFN-I, as well as their autoimmune phenocopies, underlie the threat of SLE pathogenesis (Figure 1). However, current studies have focused on IFN-I causing SLE disease by regulating its downstream targets. We believe that future studies could focus on how IFN-I production is regulated by SLE disease development.

Mechanisms of IFN-I in Innate Immunity in SLE

SLE patients have a systemic immune stimulation marked by hyperactivated and senescent lymphocytes as well as altered myeloid subpopulations, including monocytes, DCs, and neutrophils.[37] The earliest stages of inflammation in SLE involve the activation of the innate immune system, triggered by cellular and nuclear debris. Patients with SLE have been

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found to have elevated serum IFN-I levels.[38] Multiple lines of evidence indicate that the interaction between different immune cells plays a crucial role in systemic inflammation and organ damage associated with SLE, nearly all cells can respond to IFN-I.

pDCs are recognized as the main producers of IFN-I, with their output being modulated by a variety of other immune cells that are key to the development of SLE.[39] There is a marked dysregulation across diverse immune cell types, commonly thought to result from both direct and indirect interactions with IFN in the process of SLE. Additionally, innate immune players, including monocytes and conventional DCs (cDCs), significantly contribute to the IFN-I milieu by chiefly generating IFN-β.[40,41] Ongoing studies aim to reveal the role played by IFN-I in SLE disease in the context of innate immune overactivation.

IFN-I and Neutrophils

Neutrophils are the most abundant effector cells in the innate immune system and are considered a potential source of endogenous antigenic triggers in SLE.[42] Neutrophils disrupt vascular integrity, show increased sensitivity to IFN-I, and contribute to the development of SLE. In SLE patients, neutrophils exhibit pronounced IFN-I signaling and an elevated tendency to form neutrophil extracellular traps (NETs).[43] NETs have been posited to initiate the activation of IFN-I genes, leading to heightened autoantibody production.[44] Empirical evidence from both in vivo and in vitro studies implicates the link between IFN-I levels and neutrophil behavior.[45] The level of tRF-His-GTG-1 (a transfer RNA-derived small RNAs) in neutrophils was positively correlated with NETs formation in SLE patients and regulated IRF7 activation in neutrophils upon TLR8 binding, leading to upregulation of IFN-α.[46] Additionally, tempering IFN-I could lead to the normalization of neutrophil counts by curtailing non-neutrophilic responses.[47] Genetic markers related to IFN-α and IFN-ω inhibitors, such as JNJ-55920839, have been detected through transcriptomic profiling of whole blood from SLE studies.[45] These markers, however, require further corroboration in broader experiments. The low-density granulocyte (LDG) subset of neutrophils is associated with vascular damage in SLE, characterized by high IFN-I production and inflammatory cytokines.[48] Traditional neutrophils in SLE increased the production of a proliferation inducing ligand (APRIL), IL-21, and the IFN-associated chemokine interferon γ-induced protein 10 (IP-10).[49] Overall, there is growing evidence that neutrophils can participate in SLE by acting as antigens to drive autoantibody production, enhancing IFN-I and cytokine release, and inducing organ damage.[50]

IFN-I and Macrophage

M1 and M2 belong to two types of macrophage (Mφ). M1 is pro-inflammatory, usually activated by Lipopolysaccharide (LPS) and IFN-γ while M2 is anti-inflammatory, depending mainly on IL-10 and transforming growth factor-β (TGF-β).[51] Mφ mediates the activation of innate immunity by recognizing microorganisms via TLR. Mouse bone marrow-derived macrophages induce aconitate decarboxylase 1 (ACOD1) via IFN-I receptor signaling in response to TLR7 stimulation, which plays an important immunomodulatory and vasoprotective role in SLE.[52] Research indicates that IRF4 interacts with the intermediate region of myeloid differentiation primary response protein (MyD88) and induces anti-inflammatory cytokine secretion,[53] the MyD88 adapter-like (Mal) plays a role in the TLR9-driven gene expression of IFN-β and TNF-α, an activity that is mediated by the activation of extracellular regulated protein (ERK) 1/2 kinases in macrophages infected with herpes simplex virus-1 (HSV-1). This process notably relies on the noncanonical NF-κB pathways.[54] In addition, M2 polarisation was significantly reduced in SLE mice, and IRF4 affects Mφ polarisation and is involved in the pathogenesis of SLE.[55] Principal component analysis (PCA) and clustering analyses revealed that IFN-I may be involved in the development of macrophage activation syndrome (MAS) in SLE patients.[56,57] Spermine concentration is reduced in peripheral blood mononuclear cells (PBMC) of individuals with SLE, and spermine binds directly to JAK, thereby inhibiting JAK1 phosphorylation triggered by cytokines IFN-I, IFN-II, IL-2, and IL-6.[58] Mφ in the lupus nephritis (LN) undergo phenotypic changes from inflammation patrolling macrophages to phagocytic macrophages to antigen-presenting macrophages and secrete a variety of pro-inflammatory factors and complement components.[59] Plasma 7α, 25-dihydroxycholesterol is increased in SLE patients and binds to Epstein–Barr virus-induced gene 2 (EBI2) to inhibit the IFN-I response in Mφ.[60] In summary, IFN-I alters the release of inflammatory factors in vivo, Mφ polarisation, and IRF4 are associated with the pathogenesis of SLE.

Monocytes were classified into "classical" Ly6C^{hi} cells (CM) and "non-classical" Ly6C^{lo} cells (NCM).[61] Seunghee Cha performed transcriptome analysis and found that IFN-I signaling on monocytes is essential for SLE, identifying some potential therapeutic targets.[62] In the pristane-induced lupus model, the source of IFN-I is thought to be CM specifically induced by pristane administration.[63] The pathogenic features of the SLE NCM are disturbed DNA repair, enhanced cell cycle and IFN signaling, and cellular differentiation. This is associated with activated macrophage-like and enriched M1 pro-inflammatory responses.[64] SLE monocytes exhibited a cellular senescence phenotype, as evidenced by the upregulation of cyclin dependent kinase inhibitor 2A (CDKN2A), which led to the expression of GATA binding protein 4 (GATA4) and enhanced IFN-α production through activation of the cGAS-STING pathway.[65] IL-10 and IFN-γ induce CD64 expression on the surface of monocytes, which is associated with elevated SLE Disease Activity Index (SLEDAI), blood urea nitrogen levels, and anti-Sm antibodies in SLE patients.[66] Monocytes in SLE patients exhibit a variety of pathological features, including key roles through the IFN-I signaling pathway, a cellular senescence phenotype, impaired DNA repair, enhanced cell cycle, and cellular differentiation associated with an M1-type pro-inflammatory response, all of which may be potential therapeutic targets.

IFN-I and Dendritic Cells

Research into the response of myeloid DCs (mDCs) to IFN-I in SLE remains underexplored. However, Kristen L. Chen's[67] investigation into dermatitis revealed that in patients with moderate to severe dermatomyositis, CD11c^{+} mDCs along with CD69^{+} cells constitute the main cell types present in the skin, underscoring the vital influence of mDCs on the skin's IFN-I profile.

The continuous release of IFN-I is linked to the aberrant stimulation of pDCs by their genetic material. Among circulating leukocytes, pDCs represent a unique class notably responsible for the persistent release of IFN-I in those with SLE.[68] The pDC expresses the Immunoglobulin (Ig)A1 receptor, the Fc α receptor (FcαR), and the IgA1-containing immune complex drives IFN-α production by these cells in vitro. ISG expression is positively correlated with the amount of FcαR in whole blood in patients with SLE.[69] Current research points to exosome-transferred microRNAs as emerging contributors to the development of human autoimmune diseases that are characterized by excessive production of IFN-I.[70] Such as microRNAs induce pDCs to secrete IFN-I more intensely in SLE patients. These insights mark microRNAs as new triggers for pDC activation, implying that more detailed studies are needed to determine their role in IFN-I-driven autoimmune conditions using animal models.[71] Furthermore, EGA, a late endosome trafficking inhibitor, has demonstrated efficacy in reducing both the levels and release of IFN-α by TLR7-activated pDCs. EGA also appears to lessen the number of pDCs that express pro-TNF, ultimately leading to reduced production and release of TNF-α from imiquimod (R837)-encouraged pDC cultures.[72] αvβ3, a receptor for apoptotic cells and cellular debris, regulates TLR signaling and prevents self-reactive B-cell activation in a lupus model providing important environmental cues for pDC and limiting responses to self-produced nucleic acids.[73] pDCs are key drivers in the cellular activation and production of soluble factors seen in SLE.[74]

Effect of IFN-I on Adaptive Immunity in SLE

An elevated IFN-I profile in SLE is implicated in disruptions of both the innate and adaptive immune responses. The augmentation of IFN-I is associated with the development of DCs and B cells, as well as T cell activation, which may lead to the emergence of autoantibodies.[75] Following this, a comprehensive discussion is presented on the role of IFN-I in the maturation of B and T cells, along with its contribution to the pathogenesis of SLE.

Effects of IFN-I on T Cells

Following positive and negative selection processes, T cells depart from the thymus as naïve T (TN) cells, capable of recognizing specific epitopes.[76] Upon engaging with their corresponding antigens (Ag), Double-negative (DN) T cells proliferate and mature into effector cells. Predominantly, they migrate to the periphery and inflammation sites, contributing to the elimination of the offending pathogen. A subset of these T cells evolves into either regulatory or memory variants.[77] Additionally, CD4^{+} T cells may branch into several subsets like Th1, Th2, Th9, Th17, Th22, regulatory T (Treg), Tfh, and peripheral helper T (Tph) cells, contingent on their surrounding milieu. Clinical studies[78] and large-

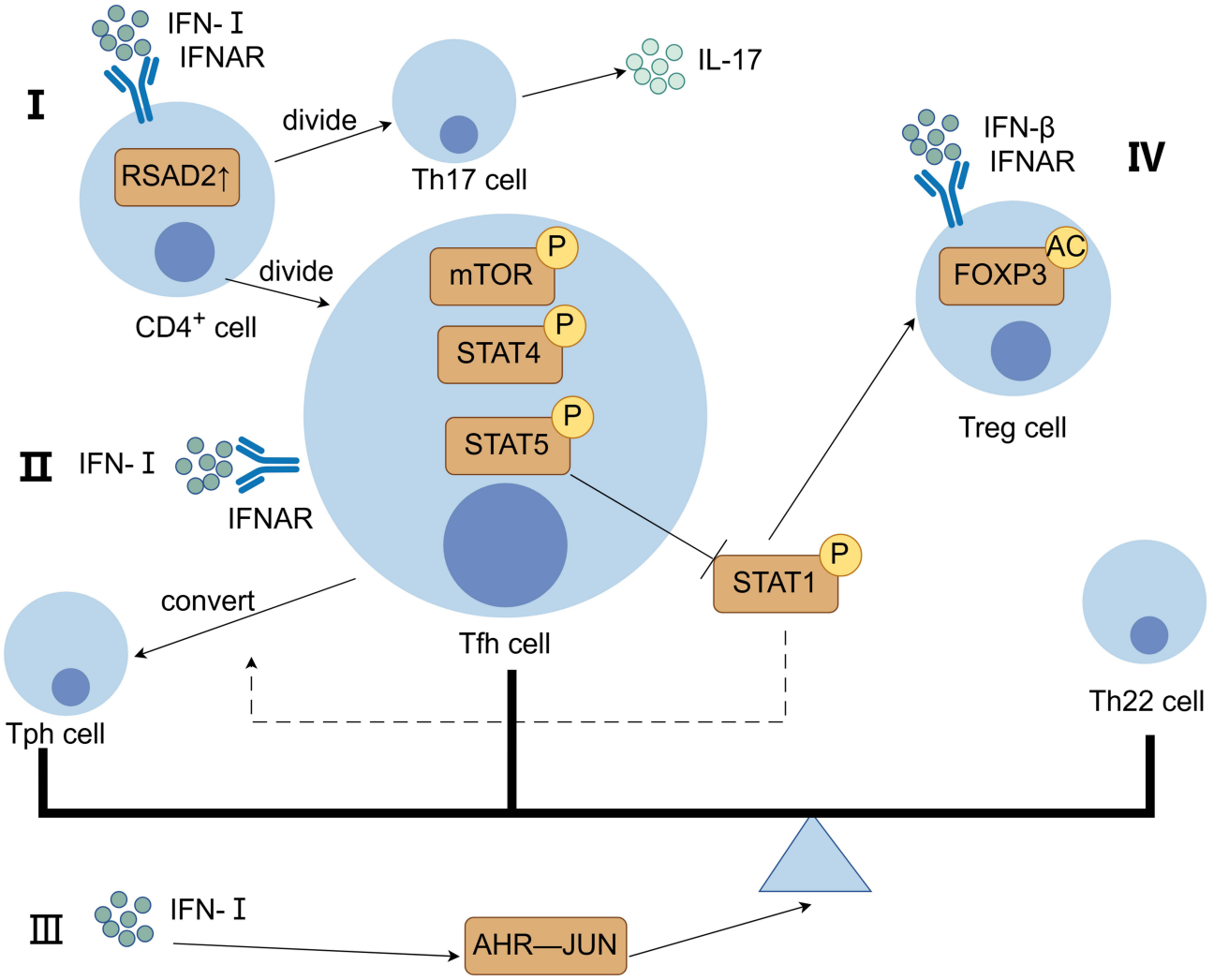

Figure 2 IFN exerts significant impacts on various T-cell subsets in SLE pathology. (**I**) IFN-I enhances RSAD2 expression in naïve $CD4^+$ T cells, contributing to their differentiation into Th17 and Tfh cells. (**II**) IFN-I enhances STAT4 phosphorylation and mTOR hyperactivation in Tfh cells. IFN-α amplifies IL-2-STAT5 pathway activation, impairs STAT1, and promotes the transformation of Tfh cells from Tfh cells into Tph cells. (**III**) AHR and JUN synergistically regulate the balance between Tph/Tfh and Th22, whereas IFN-I is an endogenous inhibitor of AHR and also disrupts the gene binding site of JUN. (**IV**) IFN-β directly promotes Treg cell induction through STAT1- and P300-dependent Foxp3 acetylation. This image was created by Figdraw.

Abbreviations: IFN, Interferon; SLE, Systemic lupus erythematosus; RSAD2, Radical S-Adenosyl Methionine Domain Containing 2; Th17, T helper 17; Tfh, T follicular helper; STAT, signal transducers and activators of transcription; mTOR, mammalian target of rapamycin; IL-2, Interleukin 2; Tph, peripheral helper T; AHR, aryl hydrocarbon receptor.

scale single-cell RNA sequencing analysis[79] confirmed the inverse association between IFN-I activity and the abundance of circulating lymphocytes or TN cells in SLE patients. Conversely, $CD8^+$ T cells primarily transform into cytotoxic T lymphocytes (CTL). (Figure 2)

Effects of IFN-I on Th1

Increased levels of IL-12 and IL-18 initiate the activation of $CD4^+$ T cells, leading to the subsequent activation of the STAT4 transcription factor. This activates specific transcription factors, namely STAT1 and T-bet within Th1 cells, prompting the transformation of $CD4^+$ T cells into Th1 cells and later producing IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, and TNF-α consequently.[80–83] A study showed that Lipocalin-2 (LCN2)-deficient mice, exhibited decreased glomerular IgG deposition, and reduced macrophage and neutrophil infiltration, alongside a diminished presence and quantity of Th1 cells in the LN model.[84] This indicates that the exacerbation of lupus is influenced by the enhanced differentiation of Th1 cells. Reactivation of T cell immunoglobulin and ITIM domain (TIGIT) reversed Th1 polarization of Tregs by suppressing protein kinase B (AKT)/mammalian target of rapamycin

(mTOR) and STAT4 signaling, a potential therapeutic target for SLE.[85] Furthermore, immunization with a CD4αβ Th1 clone stimulated an anti-allogeneic T-cell reaction in individuals suffering from lupus. The Th1-specific transcription factor, T-bet, plays a crucial role in SLE, with recent findings suggesting that T-bet acts to obstruct Th17 cell differentiation and the synthesis of associated transcription factors and cytokines.[86] Research into the role of IFN-α produced by Th1 cells in SLE has been sparse, primarily focusing on studies related to IFN-γ.

Effects of IFN-I on Th17

TGF-β, IL-6, and IL-23 initiate the activation of Th17 cell-specific transcription factors RAR Related Orphan Receptor C (RORC) and STAT3, facilitating their differentiation into Th17 cells that secrete IL-17, IL-22, and IL-23.[87] In SLE, Tregs are reduced in comparison to the increased presence of Th17 cells in inflammatory tissues.[88] Additionally, IFN-I elevates Radical S-Adenosyl Methionine Domain Containing 2 (RSAD2) expression in TN cells, which aids in their transformation into Th17 and Tfh cells, leading to the secretion of inflammatory cytokines and the development of SLE.[89] Moreover, research into the dynamics between IFN-γ and Th17 in SLE is ongoing.[90–92]

Effects of IFN-I on Th22

Recent studies have demonstrated that the TNF-α and IL-6 can activate the aryl hydrocarbon receptor (AHR), which in turn encourages the conversion of $CD4^+$ T cells into Th22 cells, known for their IL-22 production.[93] In cases of SLE, a significant increase in both Th22 and IL-22 levels has been linked to the severity of disease symptoms. The percentage of Th22 cells in SLE patients with renal damage was positively correlated with erythrocyte sedimentation rate (ESR).[94] In the SLE environment, AHR acts synergistically with AP-1 family member JUN to regulate the balance between Tph/Tfh and Th22, and IFN-I is an endogenous inhibitor of AHR that also disrupts the gene-binding site of JUN.[95] However, research focusing on the influence of IFN on Th22 cells in SLE has been notably scarce in recent years.

Effects of IFN-I on Follicular Helper T Cells

Among the $CD4^+$ T cells, Tfh cells, which can directly interact with B cells, have attracted attention as key factors in the pathogenesis of SLE. Tfh cells were identified using several markers including C-X-C Motif Chemokine Receptor (CXCR)5, programmed cell death protein 1 (PD-1), B-cell Lymphoma 6 (BCL6), B And T Lymphocyte Associated 4 (BTLA4), Inducible T Cell Costimulator (ICOS), IL-21 and SH2 Domain Containing 1A (SH2D1A).[96] Tfh cells are correlated with SLE disease activity and organ damage.[97] Tfh cells are implicated in the pathogenesis of autoimmune diseases such as SLE and rheumatoid arthritis (RA), where they drive aberrant germinal center (GC) reactions, aid B cell differentiation and proliferation, and contribute to increased autoantibody production.[98] IFN-I has been found to intensify STAT4 phosphorylation in Tfh cells, leading to aberrant IL-21 and IFN-γ production.[99] Overactivation of mTOR in Tfh cells by elevated IFN-I is another contributing factor to the lymphocytopenia phenotype in lupus.[100] IFN-α was noted to upregulate CD25 on Tfh cells, amplifying IL-2-STAT5 pathway activation in SLE patients, further, STAT5 effectively competed at the BCL6 gene site by repressing the regulatory marker H3K4me3, to the detriment of STAT1, down-regulating BCL6 and facilitating a shift from PD-1^+CXCR5^+ Tfh-like cells to a PD-1^+CXCR5^- Tph-like phenotype, thus disrupting Tfh cell stability and growth.[101] Additionally, IFN-I offers protection for Tfh cells against NK cell-mediated cytotoxicity.[102] IFN-I promotes aberrant activation and differentiation of Tfh in autoimmune diseases such as SLE through multiple mechanisms, leading to increased auto-antibody production and aberrant B-cell differentiation, and thus blocking IFN-α signaling may be a potential strategy for treating SLE.

Effects of IFN-I on Peripheral Helper T Cell

Tph cells, initially identified in RA, are a subset of T cells that localize to tertiary lymphoid follicles and contribute to SLE pathology.[103] Tph cells share several phenotypic markers with Tfh cells, including C-X-C Motif Chemokine Ligand 13 (CXCL13), IL-21, ICOS, SH2D1A, Maf, TIGIT, CD38 and CD57. However, they express distinct chemokine receptors, such as CCR2, CX3CR1, and CCR5, which facilitate their migration to inflammatory sites.[104] Studies have shown that the abundance of Tph cells increases in patients with high disease activity and LN.[105] IFN-α-induced Tph-like cells promoted B cell differentiation into CD38^{hi} CD27^{hi} plasmablasts.[101] Therefore, blocking IFN-α signaling could

reduce Tph-like cell differentiation thus affecting the generation of $CD38^{hi}$ $CD27^{hi}$ plasmablasts in SLE patients.[106] Tph cells promote B cell differentiation through IFN-α signaling, making them a potential therapeutic target for SLE.

Effects of IFN-I on Treg

Upon receiving signals from TGF-β, $CD4^+$ T cells initiate the activation of Foxp3, a transcription factor essential for Treg cells. Francisco Fueyo-González et al found that IFN-β directly promotes Treg cell induction through STAT1 and P300-dependent Foxp3 acetylation.[5] In the context of SLE, the compromised functionality or scarcity of Treg cells diminishes immunosuppressive action.[107] Treg cells also impact bone metabolism via IFN-γ activity. The dysregulation of Treg operations and the disturbed equilibrium between Tregs and Th17 cells in SLE hinder Tregs' capacity to control osteoclast functionality and uphold a negative feedback mechanism.[108] Presently, the focus of numerous studies remains on IFN-γ.[109–111]

Effects of IFN-I on $CD8^+$T Cells

The primary cytokine produced by $CD8^+$ T cells is IFN-γ.[112] In patients with LN, accumulation of $CD8^+$ T cells in the periglomerular region correlates with disease severity. IFN-I signaling affects $CD8^+$ T cell differentiation by overexpressing ISG and promoting $CD8^+$ T cell cytotoxicity and migration.[113] In IFNAR-cKO mice, Nba2-driven accumulation of $CD44^{hi}CD62L^{lo}$ effector $CD8^+$ T cells was reversed, whereas $Foxp3^+$ $CD8^+$ regulatory cells were up-regulated.[92] Coziana Ciurtin[114] also demonstrated that the transcriptome of SLE $CD8^+$ T cells is distinguished from HC by a dysregulation in pathways associated with both ISG and mitochondrial biology, with IFN-α specifically increasing SLE effector memory (EM) $CD8^+$ T cell apoptosis in vitro. IFN-I is associated with dysregulation of mitochondrial metabolism in $CD8^+$ T cells, and modulation of the nicotinamide adenine dinucleotide (NAD^+) pathway is a major mechanism by which it affects SLE.[115]

IFN-I and B Cells

IFN-I enhances the sensitivity of naïve B cells to RNA-associated antigens by up-regulating RNA-binding TLR7.[116] Additionally, IFN-I up-regulates co-stimulatory molecules, thereby improving the ability of B cells to present antigens, receive T-cell help, and engage in GC reactions.[117] Moreover, IFN-I supports the differentiation of B cells into plasma cells (PCs) and boosts antibody production. In SLE B cells, the transcriptional profile of IFN-I is up-regulated (Figure 3). Human B cells express the IFN-I gene in response to IFN-λ.[118] In SLE, an increase in B cell subpopulations is commonly observed.

IFN-I and B-Cell Differentiation

IFN-I is pivotal for the expansion of antibody-forming cells (AFCs) and $ICOS^{hi}$ $ExFO^-$ Th cells, triggering the emergence of an autoantibody response in SLE. In vitro evidence has demonstrated that IFN-I is vital in driving the differentiation of B cells into $CD138^+$ plasmablasts, a process that relies on B-cell receptor (BCR) and CD40 signaling.[116] Autoantibody prevalence is associated with diminished IFN-I levels and clinical scores, suggesting the contribution of long-lived PCs to this antibody production.[119] Studies have observed a reduction in double-negative (DN) B cells in SLE patients harboring neutralizing autoantibodies against IFN-I (anti-IFN-I-Abs).[119] In SLE, the selection of self-reactive B cells is intensified within the mature B cell population, resulting in a higher proportion of APC cells within the mature naïve B cell compartment.[120] There has been an observation of deficient B cells entering the GC and morphing into cells that produce autoantibodies in SLE. However, it remains unresolved whether these patterns are reliant on IFN.[121] Furthermore, heightened levels of IFN-α augment the development of autoreactive B cells (ABC) in SLE mice by increasing their sensitivity to IL-21 and endosomal TLR ligands.[121] Stimulation of $CD19^+$ B cells by IFN-α induces the development of plasmacytoid cells and the production of antibodies, while also enhancing mitochondrial function.[122] IL-4R and IFN-I receptor signaling plays a crucial role in regulating distinct pathways of memory B cell development, starting at the transitional stage of B cell development and progressing through differentiation to DN1 and classical memory (cMEM) B cells.[123]

IFN-I and B-Cell Function

IFN-α can alter B cell function in vitro, resulting in heightened BCR signaling, activation, and differentiation. High levels of IFN-α disrupt multiple B-cell tolerance checkpoints and lead to autoantibody production.[121] IFN-α signaling enhances

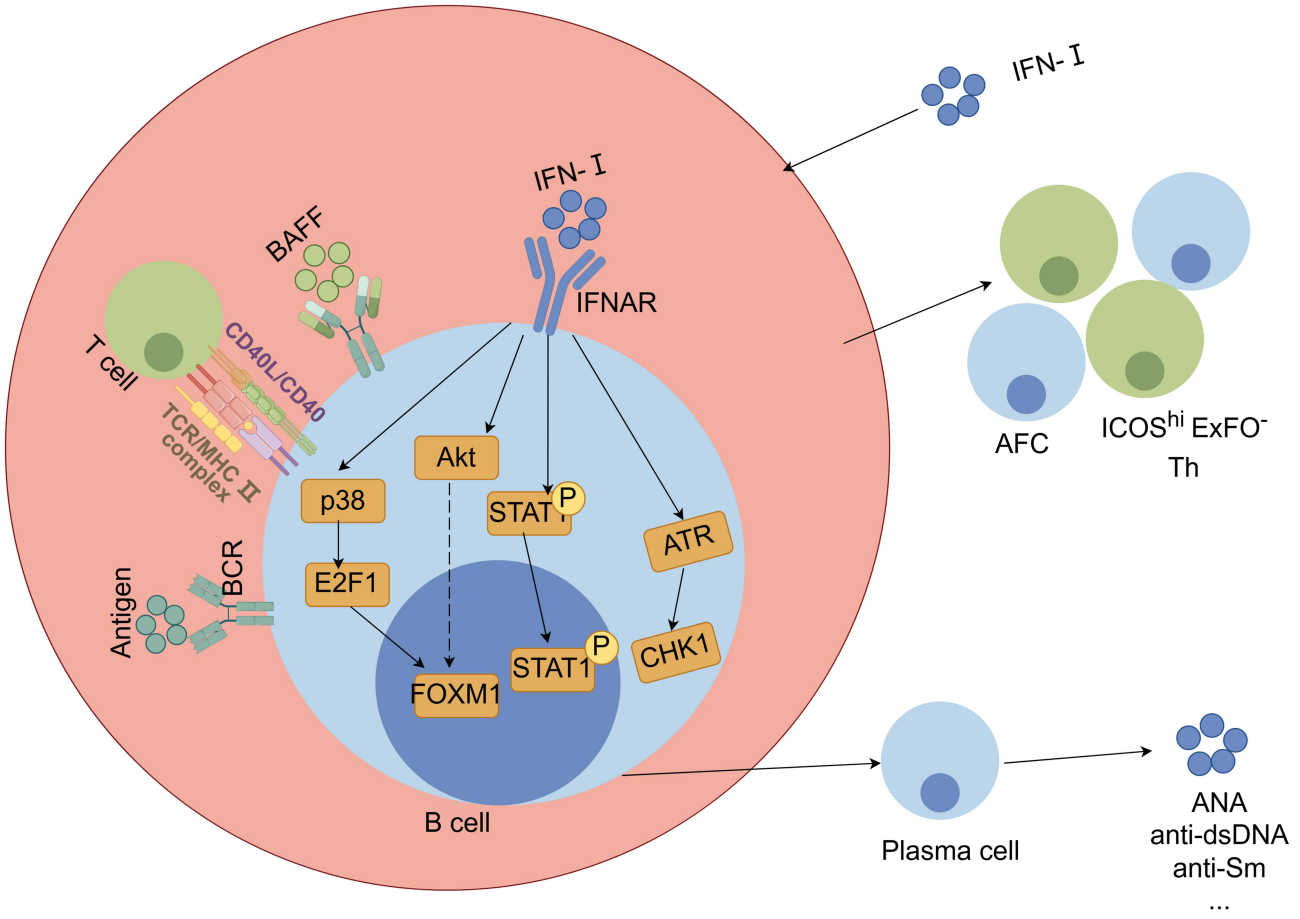

Figure 3 Effects of IFN-I on B cells. IFN-I promotes the expansion of AFC and ICOS^{hi} ExFO^{-}Th cells, triggering an autoantibody response. IFN-I triggers the hyperactivation of the ATR-Chk1 pathway in B cells. IFN-I activates FOXM1 by activating p38 and Akt in B cells. IFN-I drives the differentiation of B cells into PCs. This image was created by Figdraw.

Abbreviations: IFN-I, Interferon-I; AFC, antibody-forming cell; ICOS, Inducible T Cell Costimulator; ATR, ataxia-telangiectasia mutated and Rad3 related; FOXM1, forkhead box M1; Akt, protein kinase B; PCs, plasma cells.

responses to T cell signals such as CD40 ligand (CD40L), thereby replacing B cell-activating factor (BAFF) as the differentiation signal for transitional 1 (T1)- transitional 2 (T2) transition.[121] IFN-I has been demonstrated to enhance the production of serum BAFF as well as induce B cell proliferation and loss of tolerance.[124] The pathogenic B cells contribute to SLE pathogenesis through autoantibody production, inflammatory cytokine secretion, and autoantigen presentation.[125] Moreover, autoantibodies generated by these pathogenic B cells form immune complexes (ICs) in SLE. In particular, the IgE ICs further stimulate IFN-I in pDCs to participate in SLE disease activity.[126] In SLE, specific DNA damage response (DDR) pathways are excessively activated in B cells, with IFN-I triggering the ataxia-telangiectasia mutated and Rad3 related (ATR)-Chk1 pathway. Targeted drugs that inhibit ATR activity have been found to suppress key aspects of SLE pathophysiology, such as B-cell activation, plasmacytoma formation, antibody production, and pro-inflammatory responses.[127] Dysfunction of B cells plays a crucial role in SLE patients, while oxidative phosphorylation (OXPHOS) profiles show a correlation with IFN-I signaling-related genes (ISRGs) profiles.[128]

IFN-I and B Cell Receptor Signaling

IFN-I typically induces anti-proliferative and pro-apoptotic responses in target cells, with JAK/STAT activation being the primary signal transduction pathway triggered by IFN-α and other IFN-I upon binding to IFNAR. STAT3 and STAT5 become activated in a range of immune cell types, including monocytes, CD8^{+} T and CD4^{+} T cells, and B cells, in reaction to IFN-β.[129] Using siRNAs or chemical inhibitors targeting enhancer of zeste homolog 2 (EZH2) has demonstrated a decrease in STAT1 phosphorylation and the induction of ISGs stimulated by IFN-I in vitro experiments. These

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findings suggest that an excess of EZH2 may be implicated in the heightened activity of the IFN-I signaling pathway in SLE.[130] Elevated levels of ISGs prompt BCR activation in B-cells, which in turn more robustly activates Akt and p38, which would induce the upsurge in expression of forkhead box M1 (FOXM1).[131] In MRL/lpr mice, NEAT1, the long non-coding RNA, is overexpressed in granulocytic-myeloid derived suppressor cells (G-MDSCs), which results in B cell activation of the IFN-I signaling through the secretion of the BAFF, triggered by G-MDSCs.[132]

Therapeutics Targeting IFN-I Pathway in SLE

Significant progress has been made with therapeutic agents targeting the IFN-I signaling pathway in SLE. This review will address three aspects, IFN-I production, IFN-I itself, and downstream of IFN-I. The monoclonal anti-blood dendritic cell antigen 2 (BDCA2) antibody Litifilimab inhibits IFN production in cutaneous lupus lesions by directly targeting pDC.[133] CD123, the receptor for IL-3, is a cell surface marker for pDC and eosinophils. Anti-CD123 antibody reduces IFN-I production by targeting pDC.[74] Cordycepin promotes STING autophagic degradation to alleviate autoimmunity upon DNA stimulation and might be a potential therapeutic candidate for alleviating aberrant IFN-I in autoimmune and autoinflammatory diseases.[134] Clobenpropit binds effectively to CXCR4, significantly inhibiting IRF7 phosphorylation and reducing interferon production, and lowering levels of pro-inflammatory cytokines in a mouse model of lupus.[135] HDAC10, which inhibits IRF3 phosphorylation, is a negative regulator of IFN-I production. HDAC10 is degraded by autophagy in SLE, so the autophagy inhibitors chloroquine and hydroxychloroquine are also commonly used in the treatment of SLE.[136] The TLR7/8 inhibitors Enpatoran and Afimetoran are currently in Phase II SLE trials.[137] The selective Sphingosine-1-phosphate (S1P) receptor modulator cenerimod reduces IFN-related biomarkers and has been shown in phase III clinical trials in patients with moderate to severe SLE.[138] Methylprednisolone (MP) pulse therapy induces apoptosis in $CD4^+$ T cells, promotes TGF-β production by monocytes, and further promotes Tregs differentiation. The newly differentiated Tregs inhibit $CD4^+$ cell proliferation and IFN-γ production and contribute to the immunomodulatory environment after MP treatment for SLE.[139]

Drugs targeting IFN-α itself and IFNAR are currently used to treat SLE. Sifalimumab and rontalizumab are monoclonal antibodies targeting IFN-α. Using Sifalimumab reduces SLE disease activity,[140] while rontalizumab is ineffective in the treatment of SLE[141] and the reason for this has not been found. One of these drugs, Anifrolumab, is a therapeutic monoclonal antibody approved by the Food and Drug Administration (FDA) and the European Union for the treatment of moderate and severe SLE.[142–144] QX006N monoclonal antibody that specifically targets IFNAR1, QX006N creates a spatial site-block on binding to IFNAR1-SD3 to prevent IFN binding and inhibit IFN/IFNAR1/IFNAR2 complex formation, has been used to treat SLE.[145]

A variety of small molecule inhibitors targeting JAK and TYK2 are currently in development, several of which are in clinical trials for autoimmune diseases. Phase II clinical trials have been completed for Baricitinib, which is more selective for JAK1 and JAK2 than JAK3, and is effective in relieving SLE rash and joint swelling.[146] Another JAK inhibitor, Upadacitinib, has entered Phase III trials, and its specific effects are still being studied.[147] Filgotinib (FIL) is a preferential inhibitor of JAK1 and improves cutaneous manifestations in SLE. Inhibition of JAK1 by FIL in SLE warrants further investigation.[148] TYK2 inhibitors could represent a new class of drugs that inhibit interferon signatures and IL-12 signaling while preserving IL-2-mediated Treg cell differentiation, unlike other JAK inhibitors.[149] Deurefacitinib is a potent, highly selective, small molecule inhibitor of TYK2 that strongly inhibits IFN-α-induced lymphopenia. This finding has important implications for the treatment of autoimmune diseases such as SLE.[150] Tofacitinib was associated with inhibition of STAT1 phosphorylation in $CD4^+$ T cells and downregulated ISG expression after treatment.[151] Ruxolitinib reduced the level of ISG expression and inhibited JAK-STAT signaling for the treatment of SLE.[152] IFN-I stimulated the production of BAFF, and the anti-BAFF antibody belimumab has been effective in treating SLE, especially in patients with active LN when added to therapy to improve remission rates and reduce relapse rates.[153] The IFN signature score, defined based on the changes in the ISGs, can efficiently predict the SLE responder index (SRI) response after 12 months of belimumab treatment.[154] Imatinib, an immune checkpoint molecule V-domain immunoglobulin suppressor of T-cell activation (VISTA) agonist, modulates VISTA through IFN-I and non-classical NF-κB pathways to alleviate symptoms in lupus-like mice.[155]

Table 2 Drugs That Treat SLE by Affecting the IFN-I

IFN-I	Action Site	Drug	Mechanism of Action	Ref.
IFN-I production	pDC	Litifilimab	Monoclonal anti-BDCA2 antibody litifilimab directly targets pDC.	[133]
		Anti-CD123 antibody	CD123 is a receptor for IL-3, a cell surface marker for pDC and eosinophils.	[74]
	HDAC10	Chloroquine	HDAC10 inhibits IRF3 phosphorylation and promotes IFN-I production	[136]
		Hydroxychloroquine	through autophagic degradation.	[136]
	TLR	Enpatoran	TLR7/8 Inhibitors Currently in Phase II SLE/SLE Trials.	[137]
		Afimetoran		[137]
IFN-I itself	IFN-α	Sifalimumab	Reduce SLE disease activity.	[140]
		Rontalizumab	Treatment of SLE is ineffective, but its cause has not yet been determined.	[141]
	IFNAR	Anifrolumab	Blocking IFN-I signaling inhibits apoptosis and the NETs cell death pathway.	[142, 143]
		QX006N	A monoclonal antibody specifically targeting IFNAR1, QX006N creates a spatial site barrier upon binding to IFNAR1-SD3 to prevent IFN binding and inhibit IFN/IFNAR1/IFNAR2 complex formation.	[145]
Downstream of IFN-I	JAK	Baricitinib	JAK1/2 inhibitor that reduces IFN-α-induced STAT1 phosphorylation and affects downstream IFN targets.	[146]
		Upadacitinib	It has entered phase III trials and its specific role is still under investigation.	[147]
		Filgotinib	A preferential inhibitor of JAK1 modifies the cutaneous manifestations of SLE. The inhibition of JAK1 by FIL in SLE deserves further study.	[148]
	TYK2	Deurefacitinib	A potent and highly selective TYK2 inhibitor that strongly inhibits IFN-α-2-α autoimmune diseases.	[150]
	STAT and ISG	Tofacitinib	Associated with inhibition of STAT1 phosphorylation in $CD4^+$ T cells and down-regulation of ISG expression after treatment.	[151]
		Ruxolitinib	Ruxolitinib reduced the level of ISG expression and inhibited JAK-STAT signaling for the treatment of SLE.	[152]
	BAFF	Belimumab	IFN-I stimulates BAFF production and has a significant role in LN patients.	[153]
	VISTA	Imatinib	VISTA agonists modulate VISTA through IFN-I and non-classical NF-κB pathways to alleviate symptoms in lupus-like mice.	[155]

Abbreviations: IFN, Interferons; pDCs, plasmacytoid dendritic cells; BDCA2, anti-blood dendritic cell antigen 2; IL-3, interleukin-3; IRF, IFN regulatory factor; TLR, Toll-like receptor; SLE, Systemic lupus erythematosus; NETs, neutrophil extracellular traps; IFNAR, IFN-α/β receptor; JAK, janus kinase; STAT, signal transducers and activators of transcription; FIL, Filgotinib; TYK2, tyrosine kinase 2; ISG, interferon-stimulated gene; BAFF, B cell-activating factor; LN, lupus nephritis; VISTA, V-domain immunoglobulin suppressor of T-cell activation; NF-κB, nuclear factor kappa-B.

In summary, multiple drugs and cellular therapies targeting the IFN-I signaling pathway have made significant progress in the treatment of SLE, offering a variety of potential therapeutic strategies (Table 2). However, current studies are still mainly focused on IFN downstream targets, and more in-depth studies in the direction of upstream sources of IFN for the treatment of autoimmune diseases can be conducted in the future.

Conclusion

Considerable evidence shows that IFN-I levels are significantly elevated in SLE patients, thereby contributing to the onset and progression of the disease. Research on the process of IFN production is well-established, and current studies focus on polymers that contribute to SLE disease by affecting IFN-I. The role of IFN-I in SLE pathogenesis has become a focal point in recent research, offering fresh insights into the disorder. Primarily produced by pDC, IFN-I significantly influences the pathophysiological progression of SLE by affecting various immune cells. This review clarifies the complex relationship between IFN-I and various immune cells, leading to a deeper understanding of SLE, advancing our comprehension of immune regulation, and opening up new possibilities for treatment (Figure 4). The limitations of this study include the lack of in-depth exploration of the differential effects of IFN-I on various tissues in SLE, such as the kidneys, skin, and hematopoietic system, as well as the absence of detailed analysis on the potential challenges of related drugs, including side effects and drug resistance. Nonetheless, more studies are needed to delve into IFN-I signaling transmission in B cells and its effects on Treg, as these aspects are not fully covered in existing studies.

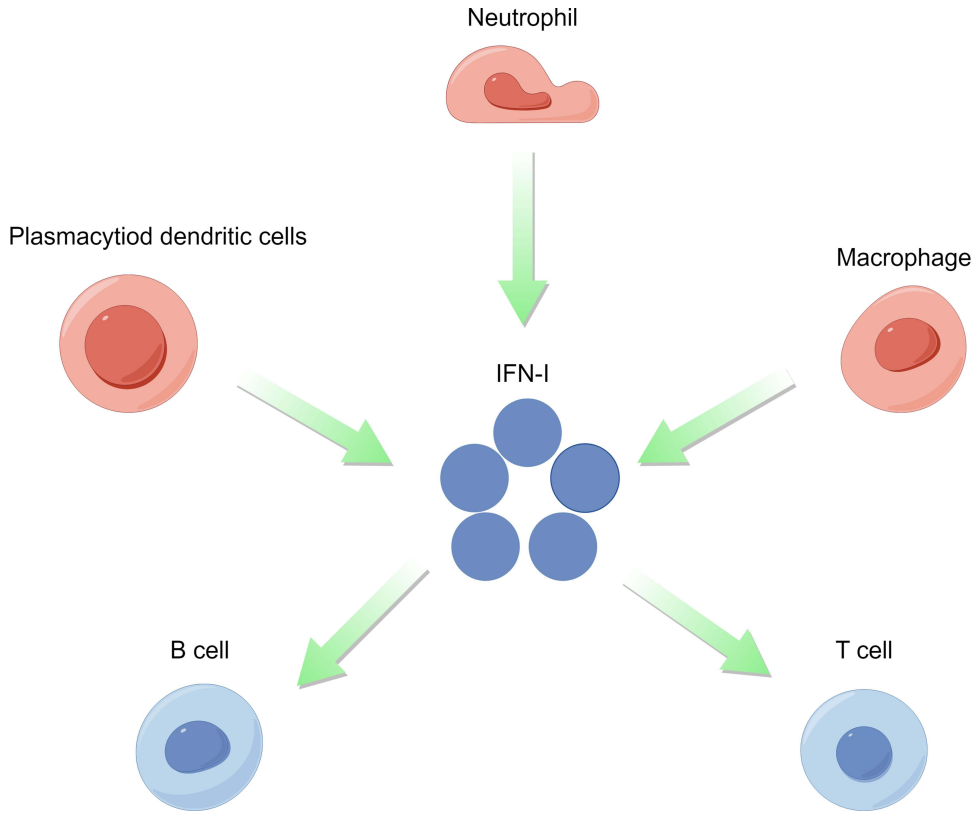

Figure 4 Major effects of IFN-I on multiple immune cells in the pathogenesis of SLE. pDC are the major IFN-I-producing cells. SLE neutrophils have strong IFN-I signaling and have a greater NET capacity. Monocyte macrophages are the main IFN-β producing cells. IFN-I differentiates B cells into plasmablasts. IFN-I can alter Th1/Th2 and Th17/Treg balance. This image was created by Figdraw.
Abbreviations: IFN-I, Interferon-I; SLE, Systemic lupus erythematosus; pDC, plasmacytoid dendritic cell; NET, neutrophil extracellular trap; Treg, regulatory T.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

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