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Clinical & Translational Immunology (2016) 5, e79; doi:10.1038/cti.2016.26

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REVIEW

Targeted therapeutics in SLE: emerging strategies to modulate the interferon pathway

Shereen Oon[1,2,3], Nicholas J Wilson[4,5] and Ian Wicks[1,2,3,5]

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by impaired immune tolerance, resulting in the generation of pathogenic autoantibodies and immune complexes. Although autoreactive B lymphocytes have been the first targets for biologic therapies in SLE, the importance of the innate immune system, and in particular, pathways involved in interferon (IFN) signaling, has emerged. There are now data supporting a central role for a plasmacytoid dendritic cell-derived type I IFN pathway in SLE, with a number of biologic therapeutics and small-molecule inhibitors undergoing clinical trials. Monoclonal antibodies targeting IFN-α have completed phase II clinical trials, and an antibody against the type I IFN receptor is entering a phase III trial. However, other IFNs, such as IFN gamma, and the more recently discovered type III IFNs, are also emerging as targets in SLE; and blockade of upstream components of the IFN signaling pathway may enable inhibition of more than one IFN subtype. In this review, we discuss the current understanding of IFNs in SLE, focusing on emerging therapies.
Clinical & Translational Immunology (2016) **5,** e79; doi:10.1038/cti.2016.26; published online 13 May 2016

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a predilection for women of childbearing age. Its prevalence has been reported to range between 20 and 150/100 000, and its incidence from 1 to 10/100 000;[1] the latter has risen in recent years, most likely due to better detection of milder disease. The incidence of SLE is higher in certain ethnic groups, such as Asians, Hispanics, African Americans and Australian Aborigines. The disease follows a chronic course, with periods of remission and exacerbation. SLE has a complex pathogenesis, probably resulting from the interplay of immunological, genetic and environmental factors. A key derangement in the immunological system is the production of autoantibodies from autoreactive B cells, which form immune complexes with self-antigens and can deposit in various organs, causing inflammation and tissue damage. Almost any organ system can be affected, with disease manifestations and severity displaying heterogeneity within and between patients, ranging from the more common involvement of skin and joints, to life-threatening renal or central nervous system lupus. This heterogeneity presents challenges in the diagnosis and management of SLE, and also for the design of clinical trials. Novel therapeutic strategies are clearly required in this disease, which causes significant morbidity and mortality, despite current treatment regimens.

To date, specific biologic agents for SLE have targeted the B cell, given the importance of autoantibodies in driving the pathogenesis. However, other promising therapeutic targets have emerged, including the plasmacytoid dendritic cell (pDC)-type I interferon (IFN) pathway. The most advanced therapeutics targeting the IFN pathway are monoclonal antibodies (mAbs) that block type I IFNα or its receptor, IFNAR; the latter has commenced a phase III clinical trial. However, recent data point to alternate ways of modulating the IFN pathway, such as by targeting the primary IFN producing cell, the pDC, or with therapeutics directed at other signaling molecules in the pathway, such as toll-like receptors (TLRs), or JAK and STAT molecules. Additionally, although type I IFN is most strongly implicated in SLE pathogenesis, there is evidence for the contribution of other IFN types, including type II and the more recently discovered type III IFNs. The downstream signaling pathways of these IFNs overlap with type I IFN, and blockade of the components of these common signaling pathways may confer greater efficacy in inhibiting IFN-driven pathology. The purpose of this review is to provide a current understanding of the contribution of IFNs to SLE pathogenesis, with a focus on the emerging strategies by which these might be targeted.

OVERVIEW OF THE IMMUNOPATHOGENESIS OF SLE

The pathogenesis of SLE is complex (Figure 1), and as yet not fully elucidated; however, abnormalities in almost every aspect of the immune system have been documented. SLE has traditionally been considered to be caused by cells of the adaptive immune system.[2] However, it has become evident that aberrations in the innate immune system, including in dendritic cells and phagocytes, are also important, as these cells contribute to the production and processing of autoantigens that might initiate or perpetuate disease.

[1]Division of Inflammation, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia; [2]Rheumatology Department, The Royal Melbourne Hospital, Parkville, Victoria, Australia; [3]Department of Medical Biology, The University of Melbourne, Parkville, Victoria, Australia and [4]CSL Limited, Parkville, Victoria, Australia
[5]These authors contributed equally to this work.
Correspondence: Professor I Wicks, Division of Inflammation, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3052, Australia.
E-mail: wicks@wehi.edu.au
Received 9 February 2016; revised 12 April 2016; accepted 12 April 2016

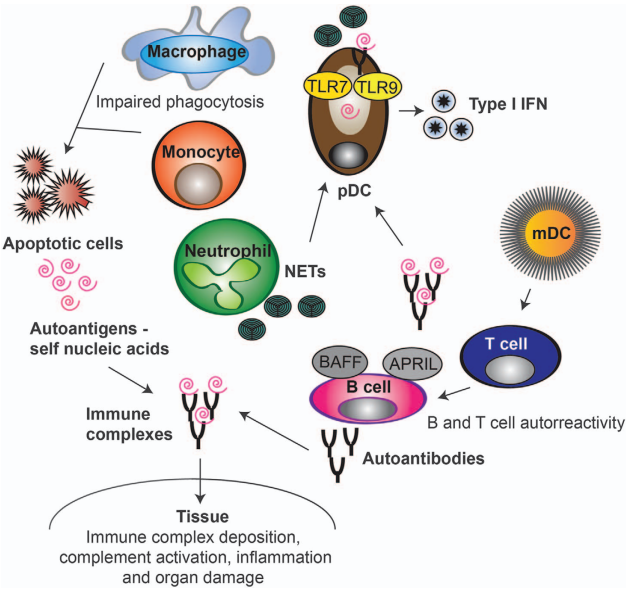

Figure 1 Overview of SLE pathogenesis. Impaired phagocytosis or increased NETs formation results in a higher burden of apoptotic material in SLE, increasing exposure of potential autoantigens to the immune system. A pathological cascade is triggered, with interaction between autoreactive T and B cells leading to the production of autoantibodies. These form immune complexes with self-antigens, depositing in tissues and causing inflammation and organ damage. Type I IFN is produced by pDCs, which are activated by self-nucleic acids contained in immune complexes, or released by dying neutrophils.

During apoptosis, there is transient expression of autoantigens on apoptotic cell membranes and the generation of apoptotic cell debris. In SLE, there is an increased burden of apoptotic material, with elevated levels of circulating DNA, RNA and nuclear proteins.[3] Why this occurs is incompletely understood, but these host-derived molecules can be recognized as antigenic by the immune system, triggering an inflammatory cascade. In humans, the increased apoptotic burden might result from impaired phagocytosis,[4] with decreased phagocytosis observed in SLE monocyte-derived macrophages *in vitro*;[5] increased apoptosis has also been seen in murine models of SLE. Autoantigenic material is opsonized by autoantibodies and internalized as immune complexes by dendritic cells after binding cell surface Fc-receptors. Binding of immune complexes to Fc receptors can stimulate the immune system through receptor cross-linking. Pattern recognition receptors such as the TLRs are also activated by self nucleic acids contained within immune complexes. Of particular relevance in SLE are TLR7 and TLR9, which are intracellular TLRs that recognize RNA and DNA, respectively. Both TLR7 and TLR9 are expressed by pDCs and activation initiates the release of type I IFN. A specific form of cell death in neutrophils, called NETosis, results in the release of neutrophil extracellular traps (NETs), which are meshwork-like structures containing chromatin and peptides with anti-microbial activity. Some SLE patients display abnormal NET accumulation, due to low DNAse (deoxyribonuclease) I activity, which is the main enzyme responsible for NET clearance in humans.[6] NETs have also been shown to trigger TLR7 and 9.

Normally, immature DCs present self-antigens in the absence of costimulatory signals, inducing a tolerogenic effect on autoreactive lymphocytes. However, in SLE, self-antigen presentation can occur in the presence of costimulatory signals.[7] T-cell hyperreactivity has also been reported, due to exaggerated intracellular calcium influx, resulting from abnormalities in the T-cell receptor signaling pathway. These include accelerated tyrosine phosphorylation of signaling intermediates and decreased expression of the T-cell receptor CD3ζ chain, with increased expression of the Fc receptor gamma chain. The latter recruits spleen tyrosine kinase (Syk) in preference to the normally recruited ZAP70.[8] Exaggerated Th1, Th2 and Th17 responses can occur, as can a reduced ability to suppress autoreactive T cells due to a decrease in, or defective function of T regulatory cells.[8]

B lymphocytes have a central role in SLE, due to the production of pathogenic autoantibodies against soluble and cellular components, which form immune complexes that subsequently deposit in various organs and cause tissue damage. However, B cells can also act as antigen-presenting cells, presenting autoantigens to activate T cells.[9,10] Similar to T cells, B cells have been reported to exhibit hyperactivation in SLE, including augmented calcium influx following crosslinking of the B-cell receptor, and increased antigen-receptor mediated phosphorylation of downstream protein tyrosine residues.[11,12] Elevated levels of cytokines that influence B-cell activation, proliferation and survival have been documented in SLE, such as BAFF/BLys (B lymphocyte stimulator) and APRIL (A proliferation inducing ligand).[13,14]

Genetic, environmental and hormonal contributions to SLE

Monozygotic twins display a higher rate of concordance (34%) than dizygotic twins (3%) for SLE and several genes have been identified that increase SLE susceptibility. These include genes in the IFN pathway, including IRF5, IFIH1 and STAT4.[15] The greatest genetic risk for SLE is conferred by deficiencies of complement pathway components C1q, C4A and B, and C2. Low complement activity contributes to defective phagocytosis of apoptotic material. Damaging mutations in the TREX1 gene, which encodes a 3′ repair endonuclease, causes accumulation of DNA. These single gene defects are, however, relatively rare, and susceptibility in most patients probably results from a combination of common variations in multiple genes. The most common genetic predisposition occurs at the MHC locus, with susceptibility loci including HLADR2, HLADR3 and HLA-DRB1.[16] Other genes involved in immune regulation have been implicated in SLE. These include those that affect the function or survival of T or B cells (PD-1, LYN, BLK, OX40L, PTPN22, BANK-1), or are involved in immune complex clearance (FcγRIIa, ITGAM and complement components). Other predisposing genes and microRNAs influence DNA methylation and hypomethylation, which can alter the apoptotic clearance rate or increase inflammatory cytokine levels.

A number of hormonal and environmental factors are thought to perpetuate SLE. Given the strong female skewing of the disease, female sex hormones have been implicated. Increased estrogen, and decreased androgen levels, have been found in females with SLE, and inflammatory cytokine production is elevated in dendritic cells, T cells and B cells exposed to estrogens.[1] UV light is a recognized trigger of disease, as it induces apoptosis in keratinocytes and release of pro-inflammatory cytokines. Infections are also postulated to contribute to SLE through molecular mimicry, for example, between EBV nuclear antigens and self-antigens. A number of medications, including the anti-TNF-α mAbs used to treat other autoimmune diseases, can induce autoantibodies typical of SLE. Although the development of overt disease is uncommon, these observations suggest that cytokine cross-regulation can influence susceptibility to SLE.[1]

CURRENT TREATMENT PARADIGM AND USE OF BIOLOGIC AGENTS IN SLE

Treatment of SLE has traditionally involved non-specific anti-inflammatory or immunosuppressive medications. Non-steroidal

anti-inflammatory drugs and the immunomodulatory agent hydroxychloroquine (HCQ), which is a TLR7/TLR9 antagonist, are used for milder disease, and stronger immunosuppressants such as azathioprine, mycophenolate or cyclophosphamide are employed for major organ involvement. Corticosteroids are generally used to treat flares of disease, although these agents are often continued long term.[17] However, this conventional approach to treatment is ineffective in many patients, and can be associated with dose-limiting toxicities and many undesirable side effects.[18]

Only two biologic agents, both B-cell-targeted mAbs, have entered clinical practice in SLE. The first of these is rituximab, an mAb targeting CD20, which is expressed on B cell from the late pro-B cell stage to memory B cells. Despite failing to meet primary end points in two phase III trials of renal[19] and non-renal[20] lupus, rituximab remains part of the therapeutic armamentarium for refractory disease, due to apparent efficacy in earlier phase and post-marketing studies. The second mAb, belimumab, which targets BAFF, a B-cell survival factor, was the first drug in 50 years to be specifically approved for use in lupus (by the US FDA in 2011). However, the benefits of belimumab in two phase III trials were modest. It was not evaluated in more severe disease, as initial trials excluded severe lupus nephritis and central nervous system lupus. Such trials are now underway, with a clinical trial of belimumab in lupus nephritis due to be completed in 2019 (trial number NCT01639339).

Several mAbs with encouraging outcomes in phase II trials were recently reported to have failed in phase III. These include epratuzumab, an mAb targeting CD22 on B cells[21] and tabalumab, an anti-BAFF mAb.[22] Trials of atacicept, which blocks the activity of two B-cell survival factors, BAFF and APRIL were terminated prematurely in phase II/III due to safety concerns; however, the data showed a trend to benefit for the higher dose tested.[23] Studies of B cell-directed agents continue, with modifications to improve efficacy, such as obinutuzumab, an anti-CD20 mAb engineered for enhanced cytotoxicity (NCT02550652). However, although there has been some success with B cell-directed agents, these have not, to date, demonstrated major benefit for the treatment of SLE.

TYPE I IFN AS A THERAPEUTIC TARGET

Type I IFNs, and in particular IFNα, have emerged as key pathogenic cytokines in SLE. In humans, type I IFNs comprise at least 13 IFNα subtypes, in addition to IFNβ, IFNε, IFNκ and IFNΩ. Type I IFNs have antiviral, antiproliferative and immunomodulatory effects. Signaling through the canonical type I IFN pathway is initiated upon binding to the ubiquitously expressed type I IFN receptor (IFNAR)—a receptor complex consisting of two transmembrane proteins, IFNAR1 and IFNAR2, activating two cytoplasmic tyrosine kinases, JAK1 and TYK2. Following IFNAR binding, STAT1 and STAT2 proteins undergo JAK-mediated tyrosine phosphorylation. Together with IRF9, these form the ISGF3 transcription factor complex, which translocates to the nucleus and binds to IFN-stimulated response elements in the promoter regions of IFN-inducible genes.[15] Type I IFNs induce an array of biological effects that can augment autoimmunity through altering the function of key effector cells such as B cells, T cells and dendritic cells (Figure 2). For example, *in vitro*, IFNα promotes the differentiation of autoreactive B cells into Ig-secreting plasma cells, and upregulates the expression of BAFF and APRIL on myeloid-derived DCs (mDCs), promoting B-cell survival. IFNα in SLE serum induces myeloid-derived DC differentiation when cultured with CD34+ hematopoietic precursors and monocytes, and IFNα also causes upregulation of T-cell costimulatory molecules MHC class II, CD80 and CD86 *in vitro*. IFNα-primed naive

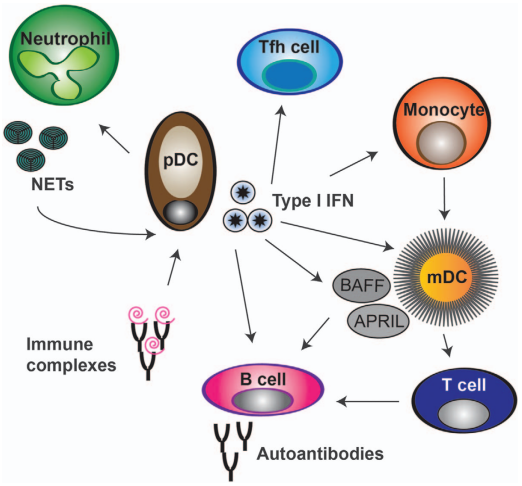

Figure 2 Effects of type I IFN promote autoimmunity. Type I IFN is produced by pDCs upon stimulation with self-nucleic acids contained in immune complexes or NETs. It induces monocyte differentiation into dendritic cells, and myeloid dendritic cells to upregulate MHCII and costimulatory molecules to activate autoreactive T cells. BAFF and APRIL expression is upregulated, which promotes autoreactive B-cell survival and proliferation. Type I IFN also stimulates the generation of lymph node-resident Tfh cells (follicular T helper cells) and induces autoreactive B cells to differentiate into autoantibody producing plasma cells. Neutrophils are stimulated by type I IFN to undergo apoptosis, causing the release of NETs. Figure adapted from Chan *et al*.[25]

CD8+ T cells have been shown to undergo proliferation and acquire effector functions in C57BL/6 mice,[24] and type I IFN also stimulates myeloid-derived DCs to induce differentiation of naive T cells into helper T cells.[25] Additionally, IFNα causes human Treg inactivation *in vitro* by downregulating intracellular cAMP and negatively regulating T-cell receptor signaling,[26] and stimulates the generation of lymph node-resident follicular T cells in mice.[27]

Observational data studies suggested a link between IFNα and SLE, with IFN therapy for malignancy and viral hepatitis in humans sometimes inducing a SLE-like syndrome.[28–30] Numerous findings from both animal models and human studies subsequently confirmed a central role for this cytokine in SLE. These included the revelation of a type I IFN 'gene signature' in the peripheral blood of SLE patients,[31] discovered with the advent of high throughput transcriptional profiling techniques. This signature correlates with increased disease activity and can be modulated by treatment.[31] In addition, elevated serum IFN and IFN-inducible chemokines[32,33] are sometimes observed in SLE patients and genome-wide association studies have identified susceptibility loci in the IFN signaling pathway.[34] IFNα promotes disease and disease is ameliorated with IFNAR deficiency in NZB/W lupus-prone mice.[35–37] IFNα may be the major contributor to SLE pathogenesis: IFN-inducible gene expression upregulated by SLE patient serum in healthy donor peripheral blood mononuclear cells (PBMCs) was comparably neutralized by treatment with either an anti-IFNα mAb or an anti-IFNAR mAb,[38] and SLE serum-induced IFN-upregulated gene expression from a cell line was neutralized by anti-IFNα, but not by anti-IFNβ (or IFNγ) mAbs.[39] Compared with IFNα, there is relatively less data regarding the role of the other type I IFNs in SLE. IFNβ therapy for multiple sclerosis induces genes found in the SLE IFN gene signature,[40] and there is evidence that IFNβ also contributes to the SLE gene signature.[41] IFNω transcripts were found to be elevated in SLE patients compared with healthy controls in microarray studies,[42] and anti-IFNω autoantibodies have been found

in SLE patients.[43] Collectively, these studies demonstrate activation of the type I IFN pathway, particularly IFNα, in both human and murine SLE and raise the possibility of therapeutic blockade of this pathway in SLE.

Several anti-type I IFN therapeutics have undergone evaluation in clinical trials. The anti-IFNα mAbs, sifalimumab and rontalizumab, have completed phase II trials, as has anifrolumab, an anti-IFNAR mAb, which antagonizes all type I IFN subtypes.[44–46] The results of these phase II trials have been promising, with reduction of clinical disease activity measures and suppression of the IFN gene signature. The trials revealed an acceptable safety profile, although a signal suggesting a higher rate of herpes zoster reactivation was observed. Interestingly, a small study in Japanese patients indicated that neutralization of IFNAR rather than IFNα alone may be more efficacious, with superior suppression of a 21 IFN gene signature seen with anifrolumab compared with sifalimumab.[47] To date, only anifrolumab has progressed to a phase III trial, which is currently recruiting patients (NCT02446899).

Alternate therapies that target type I IFN are the anti-IFNα mAb, ASG-009, which was well tolerated and effective in neutralizing a 27 IFN gene signature in a phase I trial,[48] and an IFNα kinoid (IFN-K) vaccine composed of IFNα2b coupled to a carrier protein, that induces polyclonal anti-IFNα neutralizing antibodies. Recently reported results of a phase I/IIa trial of IFN-K showed induction of anti-IFNα antibodies that were associated with decreased expression of both IFN-induced and B-cell activation-associated gene transcripts, without significant adverse events.[49] A larger phase IIb trial is currently recruiting (NCT02665364).[50]

ROLE OF OTHER IFNS IN SLE

Although the strongest evidence exists for the contribution of type I IFN to SLE, other IFN types may contribute. Type II IFN, or IFNγ, signals through a different receptor complex, the IFNγ receptor (IFNGR), which is expressed by most cell types. Activation of IFNGR leads to phosphorylation of STAT1 homodimers and subsequent expression of genes containing IFNγ-activated sites (GASs). Although the receptor for IFNγ is distinct to type I IFNs, the downstream signaling pathways overlap (Figure 3). Like type I IFN, the administration of IFNγ in humans can induce an SLE-like disease,[51] and there are a number of murine studies, and *in vitro* human studies, that support a pathogenic role for this cytokine in SLE. Administration of IFNγ to NZB/W F_1 mice augmented disease, while neutralization ameliorated disease and improved survival.[52] Similarly, IFNγ receptor deletion inhibited autoantibody production and nephritis. In a different murine model of SLE, resulting from the genetic deletion of Lyn kinase, IFNγ deletion reduced BAFF production, myeloid proliferation and T-cell hyperactivation, reducing glomerular disease.[52] In human SLE, elevated serum IFNγ levels[52] and IFNγ transcripts in PBMCs have been observed compared with healthy controls. Both NK cells and T cells from SLE donors produce more IFNγ, which can induce BAFF production by monocytes.[52] A recently published phase I clinical trial of an anti-IFNγ mAb, AMG811, showed that it was well tolerated and reduced IFNγ-related gene expression.[51]

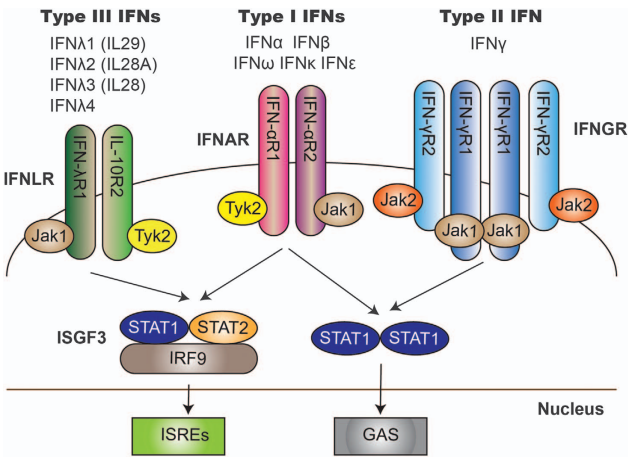

Figure 3 Overlapping type I, II and III IFN signaling pathways. Type I, II and III IFNs signal via distinct receptors (IFNAR, IFNGR and IFNLR, respectively) with signal transduction mediated through JAK/STAT activation. The downstream signaling pathways of the different IFNs overlap, resulting in the production of IFN-stimulated genes following activation of transcriptional response elements in the nucleus (ISREs, IFN-stimulated response elements; GAS, IFNγ activated site). Figure adapted from Amezcua-Guerra *et al*.[53]

Type III IFNs are the most recently discovered IFN type and include IFNλ1 (IL29), IFNλ2 (IL28A), IFNλ3(IL28B) and IFNλ4.[53] Unlike type I IFN, which is produced mainly by pDCs, type III IFNs are produced by a variety of cell types, including pDCs, regulatory T cells, macrophage and hepatocytes. Type III IFNs signal through a heterodimeric receptor comprising IFNλR1 (IL28RA) and IL10R2 subunits, with subsequent activation of the JAK/STAT cascade, similar to that seen with type I IFNs (Figure 3). Thus, type III IFNs may share biological activities with type I IFNs through the induction of the ISGF-3 transcriptional complex, and have been postulated as a potential explanation for partial responses to type I IFN blockade.[53] However, type III IFNs have a narrower range of effects, due to the limited expression of its receptor on epithelial, and some hematopoietic cells,[53] and therefore may contribute less to the peripheral blood IFN gene signature in SLE.[15]

To date, there are limited data suggesting dysregulation of the type III IFN pathway in SLE. Serum IFNλ2 was found in a greater percentage of SLE patients compared with healthy donors (65 vs 34%);[54] and serum IFNλ1 levels were associated with disease activity, the presence of anti-dsDNA antibodies, glomerulonephritis and arthritis.[55] Elevated IFNλ2 mRNA transcripts were found in activated CD4+ T cells from lupus patients compared with healthy controls.[54] Currently, there are no therapeutics that specifically target type III IFNs in clinical trials for autoimmune diseases, although the dual blockade of type I and type III IFNs, for example, by the depletion of pDCs (which produce both), may reduce type III IFNs. Blockade of the IFNAR or type I IFN itself may also reduce type III IFN, as reduced type III IFN production has been observed in IFNAR-deficient mice[56] and type III IFN has been shown to be induced by type I IFN *in vitro*.[57]

UPSTREAM TARGETING OF THE PDC-IFN PATHWAY

The therapeutics so far described inhibit only the type I IFNs or type II IFN. However, there is significant overlap in the signaling pathways of the different IFN subtypes and gene expression analyses suggest that the IFN signature is driven by both type I and type II IFNs in many patients,[51] although type III IFN may also contribute. Therefore, the therapeutic targeting of IFN producing cells, or inhibition of common components of the signaling cascade utilized by the different IFN types, such as the JAK-STAT pathway, may confer a therapeutic advantage by more complete suppression of IFN-related processes.

pDCs as a therapeutic target

Although type I IFN can be produced from a number of different cell types, the main producer (on a per cell basis) is the pDC,[58] a rare and

specialized dendritic cell type that is capable of rapid production of type I IFN. This usually occurs in response to viral infection, with viral nucleic acids triggering endosomal TLR7 and TLR9 activation. In SLE, TLR7 and TLR9 can be triggered by self-nucleic acids in immune complexes or NETs.[59]

Many *in vitro* human studies have indirectly implicated the pDC in SLE pathogenesis, with reports of altered circulating pDC numbers,[60–62] abundant pDCs producing IFNα/β found in lupus skin lesions[60,63] and TLR9-mediated pDC activation by DNA-containing immune complexes.[64,65]

Recently, experimental murine lupus models have clarified a central role for pDCs in SLE pathogenesis.[66,67] Haploinsufficiency of *Tcf4*, which encodes the transcription factor E2-2 that is critical for pDC development from bone marrow progenitors, impairs innate immune function of pDCs in mice and humans.[68] In one study, *Tcf4* haploinsufficiency ameliorated disease in two different lupus mouse models.[66] In the *Tlr7-tg* mouse, which overexpresses *Tlr7*, global and DC-specific *Tcf4* haploinsufficiency abolished splenomegaly and myeloid cell expansion and decreased anti-RNA autoantibody levels. In the second model, B6.*Sle1.Sle3*, which contains the genomic regions of two susceptibility loci from the lupus-prone NZM2410 strain crossed on to a C57BL/6 background,[69] there was a significant decrease in anti-DNA antibody levels and glomerulonephritis. Transient depletion of pDCs (with diphtheria toxin) in other murine models showed beneficial effects on autoantibody production and the development of glomerulonephritis.[67,70]

Therapeutic targeting of pDCs is still in early stage development. A mAb targeting BDCA2, which is a pDC-specific cell surface receptor, increased internalization of BDCA2 and CD32 (FcγRIIa) *in vitro*, which resulted in inhibition of both TLR and SLE immune complex stimulated type I IFN production.[71] This antibody, known as BIIB059, is now in a phase I clinical study (NCT02106897). Selective depletion of pDCs has been explored. Inhibition of Bcl-2, an anti-apoptotic protein, was shown to deplete pDCs, but not conventional DCs, in lupus-prone NZB/NZW mice, and *in vitro* in human SLE samples, which decreased IFNα production. Interestingly, the depletion of pDCs was enhanced by co-exposure to glucocorticoids.[72] A clinical trial of Bcl-2 inhibitor ABT-199 has completed a phase I trial in SLE (NCT01686555). We have recently shown that a humanized therapeutic mAb against the IL-3Rα (CD123) depletes pDCs from SLE donors *in vitro* and inhibits TLR9-induced IFNα production.[73]

TLRs as therapeutic targets

Several TLRs are relevant to the IFN signaling pathway in SLE. Immune complexes containing nucleic acids are internalized upon binding Fc receptors and stimulate IFN production by activating intracellular TLRs 3, 7/8 and 9.[74] TLRs signal through two main pathways. All except TLR3 signal through the MyD88-dependent pathway, whereas TLR3 (and TLR4) signals through the TRIF (TIR domain-containing adaptor protein inducing interferon beta)-dependent pathway. Recruitment of downstream signaling molecules, such as IRAK1/4 and tumor necrosis factor receptor-associated factor 6 (TRAF6), and the IFN regulatory factors (IRF3, IRF5 and IR57), subsequently leads to transcription of type I IFNs.[74]

As with the other components of the IFN signaling pathway, data from both human and murine studies support the role of TLRs in the pathogenesis of SLE. In humans, SLE PBMCs have upregulated TLR7 and TLR9 mRNA expression, which correlates with IFNα expression. Male BXSB lupus-prone mice, which harbor the Y-linked autoimmune acceleration (*Yaa*) cluster that includes a *TLR7* gene duplication, showed decreased autoantibody production when TLR7 signaling was ablated.[75] Reduced IFNα and IL-6 levels were seen in murine TLR7$^{-/-}$ pDCs stimulated with ribonucleoprotein containing immune complexes.[76] IL-6 is also implicated in the pathogenesis of SLE, with elevated serum levels seen in SLE patients with active disease;[77] and IL-6 deficiency has been shown to ameliorate disease activity in murine lupus models.[78] Blockade of IL-6 in SLE is currently being explored in clinical trials (NCT01273389). Decreased autoantibody and immunoglobulin levels and lymphocyte activation were seen in the MRL/*lpr* murine lupus model lacking TLR7.[79] Additionally, in the pristane-induced murine lupus model, which is highly IFN dependent, TLR7-deficient mice developed lower autoantibody levels and less glomerulonephritis.[80]

Data regarding the pathological role of TLR9 in SLE are conflicting. Deletion of TLR9 in a number of TLR9-dependent murine lupus models led to disease exacerbation, rather than abrogation.[79,81] In humans, despite increased TLR9 expression in DCs and B cells from SLE patients with severe disease, B cells are less activated and hyporesponsive to ODN-CpG (a TLR9 agonist) stimulation.[82] TLR8 is phylogenetically similar to TLR7 and also recognizes ssRNA and synthetic ligands. There are few studies of TLR8 in SLE, with conflicting evidence to date regarding the contribution of TLR8 to SLE. For example, TLR8 deletion augmented disease in lupus-prone mice through a TLR7-dependent mechanism.[83] TLR8 has been postulated to contribute to the gender differences in SLE, because it is located on the X chromosome. The 564Igi murine model is an Ig-transgenic mouse strain in which B cells express an Ig receptor specific for the lupus antigen SSB/LA.[84] In this model, decreased autoantibody production was seen in female mice with only one copy of the *Tlr8* gene on a *Tlr7/9*$^{-/-}$ background.

The antimalarial drug HCQ is a TLR7/8/9 antagonist. The activity of HCQ has been attributed to reduced endosomal acidification, which is required for TLR activation. More recent evidence suggests that HCQ binds directly to nucleic acids, causing structural modifications that prevent ligand binding to TLRs.[85] HCQ is a mainstay of SLE treatment: its benefits include decreasing overall disease severity, preventing disease flares and disease progression and altering lipid profiles favorably. These benefits are seen without clinically significant immunosuppression, and vindicate the concept of therapeutically targeting TLR7 and TLR9.

There are a number of other therapeutics in development that target TLRs, or their downstream molecules, including oligonucleotides and small-molecule inhibitors. Several oligonucleotides act as TLR antagonists. In a phase Ib/IIa study, DV-1179, a TLR7/9 dual antagonist, was well tolerated, but did not achieve its pharmacodynamic end point of reducing IFNα-regulated genes.[86] Preclinical studies with another dual TLR7/9 antagonist, IRS-954, showed inhibition of IFNα production by pDCs in response to DNA/RNA viruses and isolated SLE immune complexes[87] and showed efficacy in murine models.[88] Interestingly, resistance to glucocorticoid-induced pDC death mediated by TLR7 and TLR9 was also reversed by IRS treatment in lupus-prone mice.[89] Another compound, IMO-3100, was shown to not only inhibit IFNα, but TNFα and IL-17 production from human PBMCs.[90] A TLR7/8/9 antagonist, IMO-8400, showed efficacy in mouse models,[91] and is proceeding to a phase I trial in SLE.[92] Both IMO-3100 and IMO-8400 have been well tolerated and interestingly, were effective in phase II trials in psoriasis, another IFN-associated disease.[93,94]

Small-molecule inhibitors have the potential advantage of oral availability, and compounds have been designed to target TLRs and downstream signaling proteins, such as MyD88. The quinazoline derivative, CpG-52364, a small-molecule inhibitor of TLR7/8/9, was shown to be safe and more effective than HCQ in preclinical animal studies.[85,95] It has completed a phase I clinical trial in SLE (NCT00547014), although no results have been reported. The

MyD88 dimerization inhibitor, ST-2825, interferes with recruitment of IRAK4 and IRAK1 via MyD88, and inhibits pro-inflammatory cytokine production and TLR9-induced B-cell proliferation and differentiation.[96,97]

Host nucleic acids as therapeutic targets

Nucleic acids may also activate TLR-independent pathways to stimulate type I IFN production. One of these pathways involves the cytosolic RNA helicases RIG-I (retinoic-acid-inducible gene I), MDA5 (melanoma differentiation-associated gene 5) and LGP2 (laboratory of genetics and physiology 2), also known as RLRs (RIG-I-like receptors). Binding of RNA to RLRs leads to their association with adaptor protein IPS-1 (IFNβ promoter stimulator 1), located in the mitochondria, which activates TBK1 (TANK-binding kinase) and IκB kinase. Subsequently, IRF3, IRF7 and NFκB activation leads to type I IFN and pro-inflammatory cytokine production.[98] The adaptor protein STING (stimulator of IFN genes) mediates signal transduction following sensing of cytosolic DNA. Its downstream signaling pathway overlaps with that of the RLRs, as it translocates to perinuclear regions to interact with TBK1. Variants or mutations in components of these signaling pathways have been identified as predisposing factors to the development of SLE in murine models, and in humans.[99–102] However, so far attempts to decrease DNA and RNA levels have met with inconclusive results. Recombinant DNAse 1 slowed the progression of disease in a murine lupus model.[103] However, a phase Ib human study showed no change in relevant serum markers, although the drug was well tolerated.[104] TLR7 × RNase double transgenic (Tg) mice (with higher concentrations of serum RNase) had increased survival compared with TLR7 Tg mice, associated with reduced T- and B-cell activation and less IgG and C3 deposition in the kidneys.[105] A phase I trial of a RNase-Fc fusion protein, RSLV-132, has recently been completed, following preclinical studies showing efficacy in degrading circulating immune complexes, thereby preventing renal IFN production and kidney damage.[106] A phase IIa study of RSLV-132 has commenced (NCT02660944).

JAK/STAT inhibition as a therapeutic target

There are four JAKs—JAK1, JAK2, JAK3 and TYK2, each of which is involved in the signaling cascade of various cytokines. Therefore, a theoretical advantage of modulating the JAK/STAT pathway in SLE is the potential to inhibit other pathogenic cytokines, such as IL-6.[107] Small-molecule inhibition of the JAK/STAT pathway has already been successful in other autoimmune diseases.[108–110]

In SLE, genome-wide association studies have linked TYK2 and STAT4 to SLE.[111] Evidence from murine models shows that JAK2 inhibitors prevented or improved established disease. The administration of trophostin AG490 in MRL/*lpr* mice decreased expression of IFNγ, as well as serum dsDNA levels, proteinuria, T cell and macrophage infiltrates and deposition of IgG and C3 in the kidneys.[112] Another JAK2 inhibitor, CEP-33779, prevented the development of nephritis in mice and was superior to dexamethasone, and cyclophosphamide, in treating established nephritis.[113,114] In this model, mice treated with the JAK2 inhibitor had improved survival, reduced proteinuria, decreased dsDNA antibodies and a decrease in autoantibody producing plasma cells in the spleen. Importantly, several pro-inflammatory cytokines, including IL-4, IL-6, IL-12, IL-17A and TNF-α, were decreased after treatment with CEP-33779. These pro-inflammatory cytokines have also been implicated in SLE, with altered serum levels in SLE patients.[115,116] Interestingly, IL-17 was found to augment glomerulonephritis in a poly I:C induced type I IFN-dependent lupus murine model.[117] The role of TNF-α in SLE is controversial. As mentioned earlier, therapeutic blocking of TNF-α can induce SLE autoantibodies and rarely, a SLE-like syndrome; however, in a small pilot study, the TNF inhibitor infliximab was safe and well tolerated in SLE patients with active disease.[118]

The first JAK inhibitor developed for autoimmune disease treatment in humans was tofacitinib, which inhibits JAK1, JAK3 and to a lesser extent JAK2.[111] Tofacitinib has been shown to have an acceptable safety profile and was effective in treating rheumatoid arthritis, a disease in which type I IFN also has a pathogenic role. Tofacitinib is approved for clinical use in rheumatoid arthritis and is currently undergoing a phase I clinical trial in SLE (NCT02535689). A phase II trial (NCT01777256) of a specific JAK1 inhibitor, GSK2586184, in SLE was terminated early due to lack of efficacy and development of this drug in SLE has been halted.[119] In this trial, two patients who had received the drug also developed the DRESS syndrome (a rare but serious idiosyncratic drug reaction causing rash, eosinophilia and systemic symptoms) and severe, but reversible, abnormalities in liver function.[120] Although mild liver function abnormalities are a recognized side effect of other JAK inhibitors, such as tofacitinib, DRESS has not previously been reported with JAK inhibitors. The development of a JAK/SYK inhibitor, R333, has also been terminated,[121] after failing to meet its primary end point of a 50% decrease in active skin lesions in a phase II trial of treatment in discoid lupus (NCT01597050).

Other data supporting the potential benefit of JAK inhibition in IFN-driven diseases include studies in patients with rare, monogenic interferonopathies. A compassionate use study of baricitinib (a JAK1/2 inhibitor) in CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures) found decreased disease manifestations and steroid requirements.[122] *In vitro*, JAK inhibitors—tofacitinib, baricitinib and ruxolitinib (a JAK1/2 inhibitor)—reduced constitutive upregulation of phosphorylated STAT molecules in lymphocytes from patients with SAVI (STING-associated vasculopathy

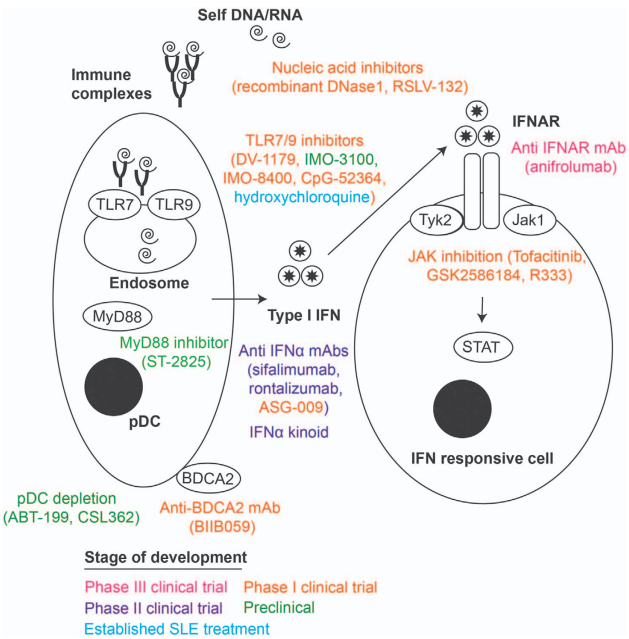

Figure 4 Therapeutics in development target the IFN pathway in SLE. Therapeutics targeting various aspects of the IFN pathway are in different stages of development, ranging from those that target the IFN producing cell, the pDC, to various parts of the IFN signaling machinery, IFN itself, or its receptor.

with onset in infancy), and a dose-dependent blockade of some IFN-responsive genes was seen.[123] A phase II trial of baricitinib in SLE is planned (NCT02708095).

PERSPECTIVE AND FUTURE DIRECTIONS

SLE is a prototypical autoimmune disease, which remains challenging in terms of understanding pathogenesis and improving treatment. In most patients, SLE appears to be a complex, multifactorial disease, with multiple aberrant immunological pathways. There are important unmet clinical needs in SLE—traditional intensive immunosuppression can be effective, but causes many toxicities—and there is great interest in new targets and more selective intervention. Surprisingly, to date, B cell-directed therapies have been relatively disappointing and patients with SLE have not enjoyed the breakthroughs that have been seen with biologic agents in other autoimmune diseases, such as rheumatoid arthritis. The IFN pathway has emerged as a strong contributor to SLE, and promising results have been seen in early phase trials of therapeutics that dampen the activity of this pathway (Figure 4). The strategy of type I IFN blockade is most advanced, with a phase III trial of the anti-IFNAR mAb, anifrolumab, currently underway (Table 1). Although trials of novel SLE therapeutics involve patients with a variety of disease manifestations such as rash, arthritis, serositis and cytopenias, patients with more severe disease, such as lupus nephritis and central nervous system lupus, have generally been excluded. As a consequence drugs with proven efficacy for these more severe and sometimes life-threatening manifestations are lacking. More recent studies have begun to address this issue, with a phase II study of anifrolumab specifically recruiting patients with recently diagnosed active lupus nephritis (NCT02547922).

As with other therapeutics, however, there is a population of SLE patients who have not apparently responded to therapeutics targeting type I IFN. It may be that blockade of common components of the different IFN signaling pathways, and thereby inhibition of multiple IFN types, would be more effective. However, as SLE is a highly heterogeneous disease, biomarkers that predict which patients may benefit from particular therapeutic approaches are an important objective. For example, those with higher expression of a panel of IFN-inducible genes at baseline were found to have a greater response rate to anifrolumab in a phase II trial. The use of more than one therapeutic agent in order to suppress overlapping pathogenic processes in SLE may be a better therapeutic approach. There are some data to support combining B cell-targeted therapies from murine lupus models. The use of an anti-CD20 mAb, together with a plasma-cell depleting agent[124] or anti-BAFF agent[125] in NZB/W F_1

Table 1 Therapeutics targeting the interferon pathway in SLE

Target	*Drug name*	*Progress*	*Trial number/references*
Type I IFN			
Anti-IFNAR mAb	Anifrolumab	Phase III—recruiting	NCT02446899[46]
Anti-IFNα mAb	Sifalimumab	Phase II—completed	[45]
Anti-IFNα mAb	Rontalizumab	Phase II—completed	[44]
Anti-IFNα mAb	ASG-009	Phase I—completed	[48]
IFN-kinoid vaccine	IFN-K	Phase IIb—recruiting	NCT02665364[49]
Type II IFN			
Anti-IFNγ mAb	AMG811	Phase I—completed	[51]
pDCs			
Anti-BDCA2 mAb	BIIB059	Phase I—recruiting	NCT02106897[71]
Bcl-2 inhibitors	ABT-199, ABT-737	Phase I trials in SLE and chronic lymphocytic leukemia completed	NCT01686555[72,127]
Anti-CD123 mAb	CSL362/JNJ-473	Preclinical, phase I completed in acute myeloid leukemia	[73,128]
DNA/RNA			
RNase-Fc fusion protein	RSLV-132	Phase IIa—recruiting	NCT02660944[105]
Recombinant DNAse 1		Phase Ib—completed	[104]
TLRs			
TLR7/9 oligonucleotide inhibitor	DV-1179	Phase Ib/IIa—completed	[86]
TLR7/9 oligonucleotide inhibitor	IRS-954	Preclinical	[87–89]
TLR7/9 oligonucleotide inhibitor	IMO-3100	Preclinical in SLE Phase II completed in psoriasis	[90,92]
TLR7/8/9 oligonucleotide inhibitor	IMO-8400	Preclinical in SLE Phase II completed in psoriasis	[91,93,94]
TLR7/8/9 small-molecule inhibitor	CpG-52364	Phase I—completed	[95]
MyD88			
MyD88 dimerization inhibitor	ST-2825	Preclinical	[97,96]
JAK/STAT			
JAK1/3 inhibitor	Tofacitinib	Phase I—recruiting	NCT02535689
JAK1 inhibitor	GSK2586184	Phase II—terminated	NCT01777256[119,120]
JAK/SYK inhibitor	R333	Phase I—completed	[121]
JAK2 inhibitor	CEP-33779	Preclinical	[114,113]

Abbreviations: pDCs, plasmacytoid dendritic cells; IFN, interferon; mAb, monoclonal antibody; SLE, systemic lupus erythematosus; TLR, toll-like receptor.

mice resulted in greater improvements in disease compared with B-cell depletion alone. In the human setting, clinical trials of the combined use of rituximab and belimumab in lupus nephritis (NCT02260934 and NCT02284984) are currently underway.

Interestingly, there are data to suggest that targeting the IFN pathway early in the course of disease may be more efficacious. In pre-autoimmune BXSB mice, the development of autoantibodies, hypergammaglobulinemia and glomuleronephritis was decreased with pDC depletion, which was associated with decreased IFN-inducible gene transcription.[67] Another study showed that an anti-IFNα/β receptor blocking antibody had a protective effect, but only in young BXSB mice.[126] Additionally, a rise in anti-RNP autoantibodies and proteinuria was prevented in young MRL/Fas^{lpr} that had been treated with prophylactic IFN receptor blockade.[126] It may be that the best results from IFN targeting therapeutics will occur in patients with early disease.

In conclusion, the IFN pathway has emerged as a promising therapeutic target in SLE, with strong evidence for its central role in pathogenesis and encouraging results from early trials of therapeutic agents that target various aspects of the pathway. The final results of these trials, and the discovery of biomarkers that may streamline the use of targeted therapies in this highly heterogeneous disease, are eagerly awaited.

CONFLICT OF INTEREST

Author NJW is an employee of CSL Limited. IW's laboratory receives research funding from CSL for work on SLE.

ACKNOWLEDGEMENTS

IW is supported by an NHMRC Clinical Practitioner Fellowship (#1023407) and NHMRC Program Grant (#1016647). SO is supported by an NHMRC Postgraduate Scholarship (#1039026). IW's laboratory is supported by the John T Reid Charitable Trusts.

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