

Review Article

Roles of Pro- and Anti-Inflammatory Cytokines in the Pathogenesis of SLE

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Received 30 August 2011; Accepted 27 October 2011

Academic Editor: Marija Mostarica-Stojković

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SLE is an autoimmune inflammatory disease in which various pro- and anti-inflammatory cytokines, including TGF- β , IL-10, BAFF, IL-6, IFN- α , IFN- γ , IL-17, and IL-23, play crucial pathogenic roles. Virtually, all these cytokines can be generated by both innate and adaptive immune cells and exert different effects depending on specific local microenvironment. They can also interact with each other, forming a complex network to maintain delicate immune homeostasis. In this paper, we elaborate on the abnormal secretion and functions of these cytokines in SLE, analyze their potential pathogenic roles, and probe into the possibility of them being utilized as targets for therapy.

1. Introduction

Systemic lupus erythematosus (SLE) is a heterogenic autoimmune inflammatory disease. Though the pathogenesis of SLE is still incompletely deciphered, putative causations are deemed to be environmental factors on a disease-prone genetic background, the former including pathogenic microorganisms which elicit both innate and adaptive immune responses. Unrestricted hyperactivation of the immune system may lead to the overproduction of autoantibodies, immune complex deposition, inflammatory cytokine release, and eventually disease onset. Currently, the treatment for SLE has evolved from conventional drugs such as corticosteroids and immunosuppressants to biologic-targeting therapies, among which cytokines are the most important therapeutic targets.

Cytokines are soluble factors which are mostly generated by immune cells and in turn play crucial roles in the differentiation, maturation, and activation of various immune cells. Abnormal release or functions of diverse cytokines have been identified in SLE patients and animal models both *in vitro* and *in vivo*. These cytokines may exert either pro-inflammatory or anti-inflammatory effects, or both, depending

on specific local microenvironments. They are also critical mediators that bridge innate and adaptive immune systems, constituting a rather complex immune response network. The abnormalities of various cytokines may reflect the imbalance among different immune cell subsets, such as Th1/Th2 and Th17/Treg, thus contributing greatly to SLE pathogenesis. To understand these cytokine abnormalities may be beneficial in figuring out the pathogenesis of SLE and developing effective targeting therapeutics. In this paper, we focus on several hotspot cytokines and introduce some recent advances of these cytokines in SLE.

2. Anti-Inflammatory Cytokines

2.1. TGF- β . Three isoforms of transforming growth factor β (TGF- β) have been identified in mammals, namely, TGF- β 1, TGF- β 2, and TGF- β 3, with TGF- β 1 being predominantly expressed in the immune system [1]. TGF- β can be produced by both innate and adaptive immune cells, such as monocytes/macrophages, dendritic cells (DCs), and T lymphocytes, whereas regulatory T cells (Treg) are demonstrated to be the major source [2]. TGF- β exerts its

regulation of target cell function primarily through a Smad-dependent pathway. By binding to its membrane receptor, TGF- β triggers the activation of TGF- β receptor complex, resulting in nuclear translocation of Smad 2/3 transcriptional factors, subsequently causing transcription of target genes [3].

TGF- β has both immunoregulatory and proinflammatory properties dependent on different microenvironments [4]. In an inflammatory milieu, TGF- β is produced by macrophages upon their phagocytosis of apoptotic cells and exerts an anti-inflammatory effect, reflecting a negative regulation of inflammation processes [5]. Apart from its inhibitory effect on macrophage activation, TGF- β can also suppress other innate immune cells, such as NK cells, mast cells, and granulocytes, and modulate the maturation of differentiated DCs [3, 6, 7].

TGF- β regulates the adaptive immune system mainly through two mechanisms: one is to directly inhibit T-cell proliferation by reducing the production of IL-2 and controlling the expressions of some cell cycle regulators [8]. The other is to regulate the differentiation of naïve CD4⁺ T cells into various effector cell subsets, that is, blocking Th1 differentiation by reducing IL-12 receptor β 2 (IL-12R β 2) and T-bet expression [9], inhibiting Th2 differentiation by decreasing GATA-3 expression and IL-4-mediated STAT6 activity [10], promoting Th17 differentiation by inducing ROR γ t expression [11], and stimulating iTreg generation by eliciting Foxp3 expression [12].

The abnormality of both serum and urinary TGF- β expression or signaling has been investigated in various studies. A recent study which enrolled 42 new-onset SLE patients revealed that the concentration of serum TGF- β 1 was markedly decreased in SLE patients in parallel with reduced peripheral Treg cells, while urinary TGF- β 1 levels were significantly higher in LN patients [13]. Lower TGF- β serum levels were also observed in patients with discoid lupus erythematosus, implicating the role of downregulated TGF- β in tissue injury of lupus patients [14]. Another study on peripheral blood mononuclear cells (PBMCs) from SLE patients demonstrated that resistance to the effects of TGF- β might be present in a good part of SLE patients due to distinct defected TGF- β 1 signaling pathways [15]. A cross-sectional study revealed that patients with SLE had lower levels of TGF- β 1 which were correlated with disease activity and CD4⁺ T, CD8⁺ T, and natural killer cell counts [16], suggesting that TGF- β may be a therapeutic target of interest in SLE. One study on 32 children with active lupus showed that plasma latent and active TGF- β 1 levels were significantly lower and correlated negatively with disease activity, whereas urinary latent and active TGF- β 1 levels were significantly higher and correlated positively with anti-ds DNA titre and negatively with serum C3 levels, indicating a pathogenic role of lowered plasma TGF- β 1 and increased renal production of active TGF- β 1 in lupus nephritis [17].

In MRL/lpr mice, the increased gene expression of TGF- β 1 in lung tissues could be downregulated by mycophenolate mofetil (MMF) treatment, which was correlated with prolonged survival [18], indicating a protective role of TGF- β in SLE lung involvement and the possibility of targeting TGF- β

for treatment of lupus. Intriguingly, one study on lupus-prone NZB/W F1 mice revealed a dual effect of TGF- β in mediating lupus disease. On the one hand, the expression of TGF- β in lymphoid tissues was reduced, which might lead to immune dysregulation and autoantibody production; on the other hand, the expression of TGF- β 1 protein and mRNA as well as TGF- β signaling proteins such as TGF- β receptor type II and phosphorylated SMAD3 increased in target organs such as kidneys, which might exacerbate tissue inflammation and damage [19].

The capacity of TGF- β to induce Treg generation can be harnessed in the treatment of autoimmune diseases like SLE. Current data in this respect mainly come from experiments on animal models. MRL/lpr mice with active disease treated with rabbit anti-mouse thymocyte globulin (ATG) and TGF- β 1 acquired decreased proteinuria and improved long-term survival which were correlated with reduced glomerular pathology and protein cast formation. The beneficial effect may be due to augmented CD4⁺ CD25⁺ FoxP3⁺ Tregs induced by ATG + TGF- β 1 treatment in vitro [20]. Antagonizing TGF- β in vivo with an anti-TGF- β antibody could selectively inhibit chronic fibrotic lesions of the kidneys in lupus-prone NZB/W F1 mice but demonstrated no significant effect on circulating autoantibody production [19], implying a complex role of TGF- β in lupus pathogenesis.

2.2. IL-10. Interleukin-10 (IL-10) is a key immunoregulatory cytokine that can be produced by almost all leukocytes, including innate immune cells such as monocytes, macrophages, DCs, mast cells, natural killer cells, eosinophils, and neutrophils, and adaptive immune cells such as Th1, Th2, Treg, Tr1, Th3, $\gamma\delta$ T, CD8⁺ T, and B cells [21, 22], and the recently discovered Th17 and Th22 cells [23, 24], with macrophages, DCs, and Th cells are the major sources. It has now been established that the production of IL-10 can be induced by Toll-like receptor (TLR) or non-TLR signaling in macrophages and myeloid DCs [25].

The activity of IL-10 is mediated by its specific cell surface receptor complex, which is composed of α and β chains and expressed on various cells, in particular immune cells. Engagement of IL-10 with IL-10R activates the tyrosine kinases Jak1 and Tyk2 followed by STAT3 phosphorylation, resulting in target gene activation. IL-10 can inhibit I- κ B kinase (IKK) activity and block DNA binding of NF- κ B already present in the nucleus, thereby blocking NF- κ B nuclear translocation. As NF- κ B controls the transcription of various inflammatory cytokines and chemokines, IL-10 may exert its anti-inflammatory properties by inhibiting this transcription factor [26].

The main targets of IL-10 on immune cells are antigen-presenting cells and lymphocytes. On the one hand, IL-10 inhibited the antigen-presenting capacity of monocytes and macrophages by downregulating cell surface levels of MHC class II, costimulatory molecules such as CD86 and adhesion molecules such as CD58 [27]. IL-10 also inhibited the function of DCs by downregulating the production of IL-12 and expressions of MHC class II and costimulatory molecules

[28]. On the other hand, IL-10 promoted the development of a type 2 cytokine pattern by inhibiting the IFN- γ production of T lymphocytes [29], directly inhibited the proliferation of CD4⁺ T cells and production of cytokines such as IL-2, IFN- γ , IL-4, IL-5, and TNF- α [30], consequently impairing cellular immune responses, and regulates Th1/Th2 imbalance. IL-10 also reduced the secretion of IL-23 by macrophages, which is essential for the existence of Th17 cells [31]. Besides, IL-10 may function as a potent B-cell stimulator that enhances activation, proliferation, and differentiation of B cells [32]. IL-10 decreases apoptosis of autoreactive germinal center B lymphocytes by increasing their bcl-2 expression, thus promoting autoantibody production [33].

Abundant studies have demonstrated that serum IL-10 titers are significantly elevated and correlate with lupus disease activity [34]. The *in vitro* observation that anti-IL-10 antibodies could dramatically inhibit immunoglobulin production by SLE PBMCs corroborated the role of IL-10 in mediating autoantibody production [32]. IL-10-containing SLE PBMC supernatants inhibited IL-12 p35 and IL-12 p40 gene expression, thus restoring normal cellular immune responses by correcting the IL-10/IL-12 imbalance [35]. SLE patients treated with a specific anti-IL-10 mAb were reported to acquire remission in disease activity [36]. That IL-10 neutralization improved cutaneous manifestations of several patients rapidly, which was associated with decreased expression of activation markers on endothelial cells, is consistent with a proinflammatory effect of IL-10 on endothelial cells in SLE [36]. *In vitro* cultured SLE PBMCs administered with an anti-IL-10 antibody could reduce the apoptosis of CD4⁺ and CD8⁺ T cells and the levels of sFas and sFasL in the culture supernatant as well as Fas and FasL mRNA expressions in cultured cells, indicating that IL-10 may trigger apoptosis of CD4⁺ and CD8⁺ T cells via the Fas-FasL pathway, which might partly explain its pathogenic role in SLE [37]. The abnormally generated IL-10 might be partly due to elevated TLR-9 expression on B cells, as experiments showed that TLR-9 level on peripheral blood B lymphocytes from SLE patients was significantly correlated with disease activity, and could induce the production of anti-dsDNA antibody and IL-10 by TLR9-CpG ligation [38].

Experimental data from studies with the NZB/W murine SLE model exhibited beneficial effects of anti-IL-10 antibodies in delaying lupus disease onset, an effect perhaps mediated by upregulation of TNF- α production [39]. However, IL-10-deficient MRL-Fas/lpr mice developed exacerbated disease, associated with augmented production of the Th1 cytokine IFN- γ by CD4⁺ and CD8⁺ T cells and IgG2a anti-dsDNA Abs, suggesting a protective role of IL-10 in lupus pathogenesis. As exacerbated disease was observed particularly in young IL-10-deficient mice, one may hypothesize that IL-10 plays a downregulatory role at an early stage of lupus development, while, at later phases of disease, excessive production of IL-10 may result in enhanced autoantibody production and subsequent formation of pathogenic autoantibody-antigen complexes [40]. Another study on NZB/W mice also found that IL-10 produced by CD4 T cells had a suppressive effect on anti-dsDNA autoantibody production, thus exhibiting a beneficial effect in murine lupus,

even in full-blown disease [41]. The contradictory results of IL-10 may reflect the opposite effects of this cytokine on the two major facets of lupus pathogenesis, namely, B cells and inflammation. One study in a novel congenic model of lupus, B6.Sle1.Sle2.Sle3 (B6.TC), showed that IL-10 overexpression significantly delayed rather than completely abolished autoantibody production and decreased clinical nephritis, with B-cell phenotypes largely unaffected while T-cell activation markedly reduced, demonstrating the immune-regulatory effect of IL-10 on T cells [42].

3. Proinflammatory Cytokines

3.1. IL-6. IL-6 is a pleiotropic cytokine mainly produced by monocytes, fibroblasts, and endothelial cells, but its secretion may also be found in keratinocytes, mesangial cells, and T and B lymphocytes [43]. IL-6 receptor consists of two subunits, IL-6R and gp130. Binding of IL-6 to IL-6R leads to dimerization of gp130, subsequent activation of gp130-associated kinase JAK1, and then tyrosine phosphorylation of gp130, thereof accomplishing the transmission of intracellular signals [44]. The predominant function of IL-6 is to stimulate the final stages of B-cell maturation, causing B cells to differentiate into mature immunoglobulin- (Ig-) secreting plasma cells [44]. It has also been shown recently that IL-6 can induce antibody production indirectly by promoting the B-cell helper properties of CD4⁺ T cells through IL-21 production [45]. IL-6 can also induce T-cell growth and cytotoxic T-cell differentiation through the increase of IL-2 receptor expression and IL-2 production [44]. Besides, in the presence of TGF- β , IL-6 induces naïve CD4⁺ T cells to develop into Th17 cells through activation of STAT3 and induction of the transcription factor ROR γ t [46].

The abnormality of IL-6 has been found in various lupus-prone mouse models. In MRL/lpr mice, serum IL-6 and soluble IL-6R levels were elevated with age [47]. In IL-6-deficient MRL/lpr mice, the infiltration of macrophages and deposition of IgG and C3 in kidney were reduced significantly, indicating the stimulating role of IL-6 in lupus nephritis [48]. In NZB/W mice, while IL-6 promoted lupus manifestations [49], blockade of IL-6R could modulate the age-related increase of anti-dsDNA, reduced proteinuria, and significantly improved mortality [50]. Exogenous administration of recombinant IL-6 to female NZB/W mice resulted in accelerated proteinuria and dose-dependent increases in mortality [51].

Abnormal IL-6 levels were observed in patients with SLE in serum and local tissues. Serum levels of IL-6 were significantly elevated and correlated with disease activity and anti-dsDNA titres [52]. In patients with active lupus nephritis, the urinary level of IL-6 was higher than that of normal controls and patients with quiescent renal disease [53]. The *in situ* expression of IL-6 gene was also enhanced along the glomeruli and tubules in lupus nephritis kidneys [54]. In patients with neuropsychiatric involvement, the levels of IL-6 in the cerebrospinal fluid were elevated [55]. The raised serum IL-6 presented an inverse correlation with hemoglobin level, indicating that IL-6 may involve

in the development of anemia in lupus patients [56]. Moreover, Lupus patients with pulmonary involvement had higher serum IL-6 levels compared with those without pulmonary involvement [57]. A latest study also revealed that SLE patients with ongoing synovitis and joint deformities had increased IL-6 which correlated with ESR and anti-dsDNA levels [58]. Altogether, IL-6 may play most important pathogenic role in SLE and mediate multiple organ damages.

The dominant role of IL-6 in SLE pathogenesis is to accelerate autoantibody production by promoting the proliferation of autoreactive B cells. It has been established by *ex vivo* experiments that B cells from lupus patients could secrete heightened quantity of immunoglobulin and IL-6 blockade significantly abolished this spontaneous immunoglobulin synthesis which was restored with exogenous IL-6 administration [59], indicating the pivotal role of IL-6 in autoantibody production. Among various subtypes of B lymphocytes, low density B cells are primarily responsible for the production of the majority of autoantibodies, and IL-6 can facilitate these low density B cells from active lupus patients to differentiate directly into Ig-secreting cells [60]. At gene level, the aberrant production of IL-6 by SLE B cells upregulated the positive regulator of recombination-activating genes (RAG2), namely, p27(Kip1), causing SLE B cells to become prone to secondary immunoglobulin gene rearrangements and autoantibody production [61].

The sources and mechanisms of IL-6 overproduction are multiple. Heightened IL-6 production by SLE B lymphocytes was observed in various *in vitro* experiments [52, 59, 61]. Autoreactive T cells in lupus may also produce high levels of IL-6 [62]. Excessively produced anti-dsDNA autoantibodies could upregulate the expression of IL-6 in endothelial cells and stimulate the release of IL-6 from resting mononuclear cells in a paracrine way [63]. In lupus nephritis, the main source of IL-6 in the kidney is infiltrating monocytes and macrophages [64], while mesangial cells also produce some [65]. Studies both in mice and human SLE showed that IL-6 overexpression could be induced by deregulation of JunB expression in the epidermis and was sufficient to induce autoantibody production and SLE-like disease [66]. Studies in the B6.TC mice models of lupus revealed that DCs could overproduce IL-6 which is necessary for the blockade of Treg activity [67].

Apart from stimulating autoantibody production by SLE B cells, the abnormally elevated IL-6 could also contribute to the pathogenesis of SLE through several other mechanisms. Studies in one mouse model displayed that *Ifi202* gene is a major genetic contribution to the development of SLE. IL-6 may stimulate its transcription and expression through STAT3 activation and may contribute to increased susceptibility to the development of lupus by retarding cell cycle progression and inhibiting apoptosis of immune cells [68]. In the B6.TC lupus-prone mice, increased IL-6 production was associated with an inhibition of Treg functions, and neutralizing of IL-6 significantly increased suppressive effect of Treg, suggesting that IL-6 may promote autoimmunity through interfering with the regulatory functions of Treg cells [67].

Based on the crucial role of IL-6 in SLE pathogenesis, biological monoclonal antibodies-antagonizing IL-6 or its receptor has been developed to treat the disease. Tocilizumab is a humanized monoclonal antibody against the α -chain of the IL-6 receptor and prevents the binding of IL-6 to membrane bound and soluble IL-6 receptor. In an open-label, phase I study of tocilizumab in SLE, 16 patients with mild to moderate disease activity were treated with escalating doses of tocilizumab. At the 8th week of followup, decreases in circulating plasma cells and serum anti-dsDNA antibody levels were observed, together with disease activity improvement, suggesting a specific effect of tocilizumab on autoantibody producing cells and a promising aspect of this drug for SLE treatment, though further studies are still warranted to establish the optimal dosing regimen and efficacy [69].

3.2. BAFF. BAFF (B-cell-activating factor) and APRIL- (a proliferation-inducing ligand), which belong to members of the TNF superfamily, play crucial roles in the survival and proliferation of peripheral B lymphocytes and plasma cells [70]. BAFF, also called Blys (B lymphocyte stimulator), is a type transmembrane glycoprotein which is mainly synthesized by myeloid cells, such as macrophages, monocytes, DCs, and basophils, and can also be expressed by stromal cells, activated T cells, activated and malignant B cells, and epithelial cells [71]. APRIL is closely related with BAFF. They are firstly synthesized as transmembrane proteins and then cleaved into soluble forms by a furin transferase, with BAFF cleaved on cell surface while APRIL in the Golgi apparatus [72]. They present as both homo- and heterotrimers in the serum and signal by binding with specific receptors.

There are three types of receptors for soluble BAFF and APRIL, namely, BR3/BAFF receptor (BAFFR), transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and B-cell maturation antigen (BCMA), which are expressed on different stages of B cells. BR3/BAFFR is expressed on nearly all stages of B cells (pro-B, pre-B, transitional B) in the bone marrow to primary and activated follicular and marginal zone B cells in peripheral lymphoid organs, as well as GC and memory B cells [73]. BCMA and TACI expressions can only be detected on mature B cells, GC B cells, memory B cells, and plasma cells, but not on immature B cells [74]. While BAFF binds to and signals through all the three receptors, APRIL only signals through TACI and BCMA [75]. Therefore, BAFF neutralization alone does not affect the plasma cell pool as they may receive overlapping signals through BCMA and TACI by APRIL. This is confirmed by studies on mice which indicate that simultaneous blockade of BAFF and APRIL is necessary for the decrease of plasma cell numbers [76].

By binding to its receptors which interact with TNF receptor-associated factors (TRAFs) and activate NF- κ B signal pathways, BAFF can upregulate the expression of antiapoptotic genes including Bcl-2 and Bcl-XL [77, 78], downregulate the proapoptotic gene Bim [79], and block the nuclear translocation of PKC δ in c-myc-dependent manner [80], thereby protecting self-reactive B cells from apoptosis.

As B-cell abnormality is essential in autoantibody production in SLE, BAFF/APRIL and their receptors are believed to be involved in SLE pathogenesis. In mice, transgenic overexpression of BAFF is associated with the development of lupus-like manifestations, including high levels of circulating anti-dsDNA, proteinuria, and Ig deposition in the kidneys [81]. Treatment of NZB/W F1 mice with BAFFR-Ig reduced the circulating levels of anti-dsDNA antibody titres in parallel with clinical improvement [82]. Patients with SLE have elevated serum levels of BAFF which are correlated with increased levels of autoreactive antibodies [83]. Elevated levels of BAFF and APRIL in the cerebral spinal fluid (CSF) of SLE patients have also been reported, and, compared with patients without CNS involvement, the CSF level of APRIL was markedly augmented in NPSLE patients [81]. BCMA expression was substantially higher on SLE B cells, especially on memory cells and plasmablasts, which might contribute to the production of IgG autoantibodies [84].

The mechanism of the aberrant BAFF production in SLE is not fully elucidated. In addition to monocytes and DCs, which are the main sources of BAFF, SLE T cells can produce elevated BAFF through signal transduction pathways triggered by antigens compared to normal T cells [85]. Both CD4⁺ and CD8⁺ T cells from patients with active SLE expressed intracellular BAFF, whereas those from normal subjects did not, suggesting a pathogenic role of T-cell-derived BAFF in SLE [86]. BAFF production can be induced by pathogen-associated molecular pattern (PAMP) stimuli such as peptidoglycan, CpG dsDNA, and lipopolysaccharide (LPS) [87] and enhanced by IFN- α , IFN- γ , and IL-10 [88]. Furthermore, CpG dsDNA and LPS can induce the expression of BAFF receptors in B cells by interacting with Toll-like receptor (TLR) 9 and 4, respectively [89]. In vitro experiments demonstrated that SLE B cells released BAFF/APRIL upon activation, thus initiating a vicious cycle in which enhanced levels of BAFF and APRIL act in an autocrine manner to reinforce the systemic activation of the humoral immune system [90].

Compelling evidence has demonstrated that SLE is associated with an increased risk of lymphoma, predominantly diffuse large B-cell lymphoma (DLBCL) [91]. Smedby et al. found consistent expression of APRIL in the DLBCL from all SLE patients and a strong association between APRIL expression and presence of EBV in the lymphoma tissue [87]. EBV upregulates the expression of APRIL and BAFF on B cells, which in turn contributes to the persistence of EBV-infected B cells [92]. Though the exact functional role of APRIL in DLBCL remains unclear, researchers have found that endogenous BAFF and APRIL on non-Hodgkin's lymphoma (NHL) B cells may prompt them to escape apoptosis and result in overproliferation [93]. There is also substantial evidence in support of a role for IL-10 in B-cell lymphomagenesis [94], and IL-10 serum levels have been shown to be prognostic factors for NHL, particularly the DLBCL subtype [95].

Currently, three types of monoclonal antibodies targeting BAFF or/and APRIL have been developed for clinical trials of treating SLE, including belimumab, briobcept, and ataccept. Belimumab is a recombinant fully humanized

monoclonal IgG1 antibody that binds to soluble BAFF and inhibits binding of BAFF to its receptors. The Phase I clinical trial which enrolled 70 patients suffering from mild-to-moderate SLE corroborated belimumab's biologic activity of reducing peripheral B-cell numbers and serum anti-dsDNA antibody level with adequate tolerability and safety [96]. Though the subsequent Phase II randomized, double-blind, placebo-controlled study of 449 SLE patients did not meet its primary clinical endpoints of an improvement in Safety of Estrogen in Lupus: National Assessment and Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and "time to flare" endpoints at 24 weeks, there was a marked reduction in circulating naive, activated, and plasmacytoid B cells [97]. Long-term observation of this trial showed significant decrease in IgG anti-dsDNA titers and increases in C4 and C3 by week 52 [98]. In two Phase III trials, namely, BLISS-52 and BLISS-76, which treated 865 and 819 SLE patients, respectively, significantly reduced SLE disease activity (measured using SLE Responder Index, SRI), SLE flare rates, and the need for prednisone therapy have been reported at 52 weeks [99, 100].

Briobcept (BR3-Fc) is a recombinant glycoprotein with two BAFF receptors linked to Fc domain of human IgG1. As BR3-Fc specifically binds to BAFF but not APRIL, it uniquely targets BAFF. Studies on cynomolgus monkeys revealed that BR3-Fc decreased B-cell numbers in the periphery and lymphoid organ [101], but data on clinical trials are still lacking.

Ataccept is a fully human chimeric molecule composed of the extracellular domain of TACI integrated with a human IgG1 Fc domain. Mimicking a soluble receptor, ataccept binds to both APRIL and BAFF and inhibits signaling through BAFFR (BR3), BCMA, and TACI, consequently having effect on a broader spectrum of B-cell lineages, including circulating mature B cells, follicular B cells, marginal zone B cells, as well as bone marrow plasma cells [102, 103]. In a multicenter, phase Ib clinical trial, SLE patients treated with ataccept displayed decreased circulating B cells and reduced serum immunoglobulin levels [103]. A Phase II trial in LN with ataccept in combination with mycophenolate mofetil (MMF) was discontinued for the sake of increased risk of serious infections [104]. A Phase II/III trial in SLE is still ongoing.

3.3. IFN. The interferon (IFN) cytokine family is composed of type I IFNs (13 species including IFN- α , IFN- β , IFN- ω , and IFN- κ), type II IFN (IFN- γ), and the recently described type III IFNs (IFN- λ) [105]. Extensive data have suggested an important pathogenic role for IFN- α and IFN- γ in SLE.

3.3.1. IFN- α . The main producers of IFN- α in peripheral blood are plasmacytoid dendritic cells (pDCs). Viral DNA or RNA, which are the classical activators of type I IFN production, can trigger type I IFN gene transcription via either Toll-like receptors (TLRs) or the retinoic acid-inducible gene I(RIG-I)-like receptors [106]. By binding to its receptor, a heterodimer of IFNAR1 and IFNAR2, IFN- α activates STATs transcription and promotes increased expression of MHC

I, DC maturation, T-cell survival, and antibody production [107].

Extensive studies have revealed a crucial role for IFN- α in the etiopathogenesis of SLE [108]. An SLE syndrome can develop during long-term IFN- α treatment of patients with chronic infections and malignant disease [109] and discontinuation results in remission of symptoms, supporting a causal relationship between IFN- α and SLE. It has been established that elevated serum levels of IFN- α positively correlate with SLE disease activity and the generation of autoantibodies [110]. Plasmacytoid DCs (pDCs) are the primary sources of IFN- α in lupus patients, which are abundant in skin and lymph nodes but sometimes reduced in number in the peripheral blood [111]. On one hand, pDCs can be triggered to produce IFN- α by immune complexes; on the other hand, IFN- α can promote activation of DCs and antibody-secreting cells, augment production of autoantibodies, whereas suppressing regulatory T-cell development [112]. In the progress of the above-mentioned vicious cycle, CD4⁺ T cells are necessary for IFN- α -driven induction of anti-dsDNA antibodies and clinical manifestations of SLE [113].

CSF from neuropsychiatric SLE can induce significantly higher production of IFN- α in a culture system containing pDC and a source of Ag, compared with CSF from patients with other autoimmune diseases, indicating an important pathogenic role of IFN- α in NPSLE [114]. Vasculitis is believed to be a fundamental pathological change in SLE. IFN- α may interfere with vascular repair in SLE through repression of IL-1-dependent pathways and promote loss of renal function [115]. Activation of the IFN- α signaling pathway may also be linked to the risk of atherosclerosis by affecting plaque formation in patients with SLE [116].

The role of IFN- α has now been confirmed in lupus-prone mouse strains. Lupus-prone NZB mice lacking type-I IFN receptor display significantly reduced autoimmunity, kidney disease, and mortality [117]. However, MRL/lpr mice that lack the same receptor have accelerated lymphoproliferation, autoantibody production, and end organ disease, suggesting a converse role of IFN- α in the two lupus models [14]. Exposure to IFN- α in vivo induces lupus in preautoimmune lupus-prone NZB/NZW F1 (NZB/W) but not in BALB/c mice [118]. IFN- α may play different roles in different autoimmune background, so data derived from these strains cannot be readily compared with SLE patients.

Dysregulation of IFN- α in SLE is also evident in gene expression profiles, including genes that regulate type I IFN pathway and IFN-inducible genes (IFIGs). Genome-wide association studies (GWASs) have identified multiple novel genes that impact on type I IFN pathway associated with SLE, including variants of interferon regulatory factor 5 (IRF5), STAT4, and interferon regulatory factor 7 (IRF7) [119]. Recent studies have demonstrated a close morphological association between the expression pattern of IFN-inducible chemokines (MxA, CXCL10) and typical histological features of cutaneous lupus erythematosus [120].

IFIGs correlating with the production of autoantibodies and the clinical manifestations of SLE are thought to be responsible for the immunomodulatory properties of IFN.

The interferon signature is associated with active disease and the presence of renal and CNS involvement. Global profiling of gene expression in PBMCs has consistently shown upregulation of IFIGs in SLE patients which are correlated with disease activity [121]. Data from a recent research indicates that IFN-induced protein with tetratricopeptide repeats 4 (IFIT4) might contribute to the pathogenesis of SLE by inducing monocytes to differentiate into DCs. Data from murine lupus models have also supported a genetic contribution of IFN-regulated genes to lupus susceptibility. Ifi202, a chromosome 1q-encoded gene that is induced by both IFN- α and IFN- γ , is polymorphic and differentially expressed in lupus and control mice [122].

Current data suggested there exists a reciprocal regulation between TNF- α and IFN- α in human autoimmune diseases like SLE. RA patients undergoing therapy with TNF- α antagonists had increased titer of anti-dsDNA antibodies and developed lupus-like syndrome [123], which indicated that TNF- α might act as an antagonist of IFN- α . Palucka et al.'s study showed that TNF- α might regulate IFN- α production in vitro by inhibiting the generation of plasmacytoid dendritic cells (pDCs) from CD34⁺ hematopoietic progenitors and IFN- α release by immature pDCs [124]. Therefore, TNF- α blockade might result in increased production and bioavailability of IFN- α in SLE and in patients receiving anti-TNF- α therapy, leading to elevated titers of antinuclear antibodies (ANAs) and anti-dsDNA antibodies, mainly restricted to the nonpathogenic IgM and IgA isotypes, but no IgG anti-dsDNA antibodies [125].

TNF- α and IFN- α induce differentiation of distinct types of dendritic cells, namely, TNF-DCs or IFN-DCs, which present different antigens and produce distinct autoimmune responses. TNF- α may drive IL-23/IL-17 axis inflammation by promoting monocytes to differentiate into TNF-DCs [126]. TNF-DCs have been termed as semimature as they were unable to produce mRNA or proteins of proinflammatory cytokines such as IL-12. They could protect mice from EAE via the MHC II/peptide presentation to CD4⁺ T cells but induced killing of CD8⁺ T cells via MHC I/peptide presentation [127]. In SLE patients, circulating IFN- α may induce monocytes to differentiate into IFN-DCs, which then potently capture apoptotic cells and nucleosomes and then present these autoantigens to CD4⁺ T cells, thus initiating the expansion of autoreactive T cells, followed by differentiation of autoantibody-producing B cells [128]. IFN-DCs also proved to be effective in inducing a Th1 type of immune response and CD8⁺ T-cell responses against defined antigens in different models [129]. TNF- α , together with IFN- γ , IL-6, IL-1, and IL-18, are currently recognized as important factors in the pathogenesis of macrophage activation syndrome (MAS), which is a life-threatening complication of various rheumatic diseases including SLE [130, 131], while elevated levels of TNF- α and IL-6 and a trend to lower IFN- γ were found in patients with definite antiphospholipid syndrome (APS) [132].

In view of the accredited important role of IFN- α in the pathogenesis of SLE, therapeutic agents targeting this cytokine are theoretically feasible. From the production source of IFN- α to its binding receptor complex and

downstream signaling pathway, various points can be utilized as therapeutic targets. High-dose steroids are deemed to be the most effective approach to inhibiting production of IFN- α by inducing the death of the major producers of IFN- α , pDCs [133]. Currently, at least three monoclonal antibodies specific for different IFN- α isoforms are in clinical development. Recent data from MedImmune have demonstrated inhibition of the IFN signature in PBMC and in skin biopsies from some lupus patients treated with MEDI-545 [134]. Considering the essential role of type I IFN in host defense against virus infection, monoclonal anti-IFN- α antibodies which block the interaction of IFN- α with IFNAR seem to be safer and more feasible, as antibodies blocking the IFN receptor might completely inhibit downstream gene expression and cause more risk of viral infection and malignancy.

3.3.2. IFN- γ . IFN- γ is generated by both innate and acquired immune cells, particularly T cells and NK cells. IFN- γ receptor (IFN- γ R), which is widely distributed on all karyocytes, is composed of two subunits, IFN- γ R-1 and -2, and transduces signals through JAK/STAT pathway [135]. It is commonly accepted that IFN- γ can promote Th1 polarization, facilitate specific cytotoxicity by increasing the expression of MHC class-I and -II molecules, and boost antigen processing and immunoglobulin switching.

IFN- γ has long been categorized as a typical Th1 cytokine, and its production was demonstrated to be decreased in SLE patients [136]. However, enhanced level of IFN- γ has been recently reported in SLE patients, which might contribute to SLE pathogenesis by inducing BAFF production [137]. While the ratio of IFN- γ -producing cells are found to be higher in SLE patients which are correlated with elevated serum level of IFN- γ [138], *in vitro* experiments also indicate that PBMCs from SLE patients may produce larger amount of IFN- γ in response to anti-CD3 plus costimulating mAb stimulation [22]. During exacerbation of SLE, IFN- γ is synthesized in larger amount which may result in the tissue damage observed [139]. On genetic level, the mRNA levels of T-bet and IFN- γ as well as the relative expression levels of T-bet/GATA-3 and IFN- γ /IL-4 are significantly higher in SLE patients than those of normal controls [140]. Lupus nephritis (LN) patients show a predominant Th1 phenotype with a high IFN- γ expression in peripheral blood and glomerular that parallels the severity of renal damage [141]. The serum levels of C3, C4, and anti-dsDNA antibody exhibit a significantly positive correlation with glomerular expression of T-bet and IFN- γ [142].

In murine lupus, the important role of IFN- γ has been highlighted [143]. Th1 cells help in the production of IgG2a antibodies, the major subclass of pathogenic anti-DNA autoantibodies eluted from the murine renal lesions. IFN- γ upregulates IgG autoantibody production and accelerates nephritis *in vivo*, while treatment with anti-IFN- γ antibody and soluble IFN- γ receptors can delay lupus disease onset [144]. Gene deletion of IFN- γ or IFN- γ receptor in both NZB and MRL/lpr lupus-prone mice result in improvement of renal disease and survival rate [145]. Administration of

IFN- γ R-Ig fusion protein to MRL/lpr mice may significantly decrease plasma concentration of IFN- γ and reduce autoantibody production and lymphadenopathy [146]. Diffuse proliferative glomerulonephritis in MRL/lpr mice similar to that in human LN (WHO class IV) is associated with autoimmune responses dominated by IFN- γ [147].

Several polymorphisms in the interferon-gamma gene (IFNG) are associated with susceptibility to SLE, including single-nucleotide polymorphism SNP (rs2430561) located in an NF- κ B binding site [148]. The expressions of other IFN- γ inducible genes, such as IP-10 or Mig, are increased in SLE monocytes [149]. STAT-1 is a critical component in both IFN- α and IFN- γ signaling pathways. STAT-1 expression is increased in PBMCs from SLE patients and correlated significantly with disease activity and with the IFN-inducible expression of CD95 and HLA-DR. A lately described gene polymorphism in the 3' Repair exonuclease (Trex1) induced by IFN- γ was reported to be associated with SLE [150].

Targeting therapy for IFN- γ has been successfully applied to lupus mice [138], and treatment with humanized anti-IFN- γ mAb or recombinant IFN- γ -Ig fusion protein may provide a novel therapeutic strategy for this intractable disease in human.

3.4. IL-23/IL-17. IL-23 is a heterodimeric cytokine composed of a unique p19 subunit and a common p40 subunit shared with IL-12, mainly secreted by antigen presenting cells, and activates the transcription factor STAT4. The IL-23 receptor, IL-23R, is present on NK cells, DCs, T cells, monocytes, and macrophages [151]. IL-23 affects IFN- γ production, stimulates Th1-cell responses, activates memory T cells, and enhances inflammation by stimulating the production of proinflammatory cytokines. IL-23 is also essential to promote the expansion and survival of IL-17-producing cells, including Th17, $\gamma\delta$ T, and double negative T (CD3⁺ CD4⁻ CD8⁻, DNT) cells [152].

Though IL-23 is generally regarded as a critical pathogenic factor in some organ-specific autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA) [153], its abnormality has been recently reported in SLE patients too. mRNA expressions of p40 and p19 subunits are increased in PBMCs of untreated SLE patients compared with immunosuppressor-treated ones and higher in active SLE patients (SLEDAI >10) than in inactive ones, indicating that IL-23 is responsive to the therapy and might be a good marker for SLE remission [154]. IL-23 can stimulate CD4⁺ T cell to produce IL-17 and IFN- γ , which is related to the development and maintenance of the disease process in SLE [155]. Clinical and pathologic measures of lupus nephritis were thoroughly abrogated in IL-23R-deficient MRL/lpr mice, suggesting an indispensable part of IL-23 in kidney involvement. Despite the above findings, IL-23R polymorphisms do not appear to play an important role in the susceptibility or severity of SLE [156].

IL-17, commonly known as IL-17A, is a proinflammatory cytokine with multiple functions in the regulation of tissue inflammation. So far, six different IL-17, namely, IL-17A

TABLE 1: Cytokine functions in different development phases of SLE.

Phases of SLE development	Involved cytokines	Main functions
Susceptibility	IFN- α	Increase MHC-I expression, upregulate Ifi202 gene
Initiation	IFN- α	Promote DC maturation, inhibit Treg
	IFN- γ	Increase BAFF, MHC-I/II, initiate Th1 cell response
Propagation	IL-6	Promote Th17 and plasma cells, inhibit Tregs differentiation, reduce apoptosis of T, B lymphocytes
	BAFF	Stimulate B-cell expansion and antibody production
Regulation/resolution	IL-23, IL-17	Promote T and B cell activation, stimulate Th17 differentiation
	IL-10	Downregulate IFN- γ and IL-23, reduce apoptosis of T, B lymphocytes
	TGF- β	Inhibit Th1 and Th2 response, induce Treg and Th17 differentiation

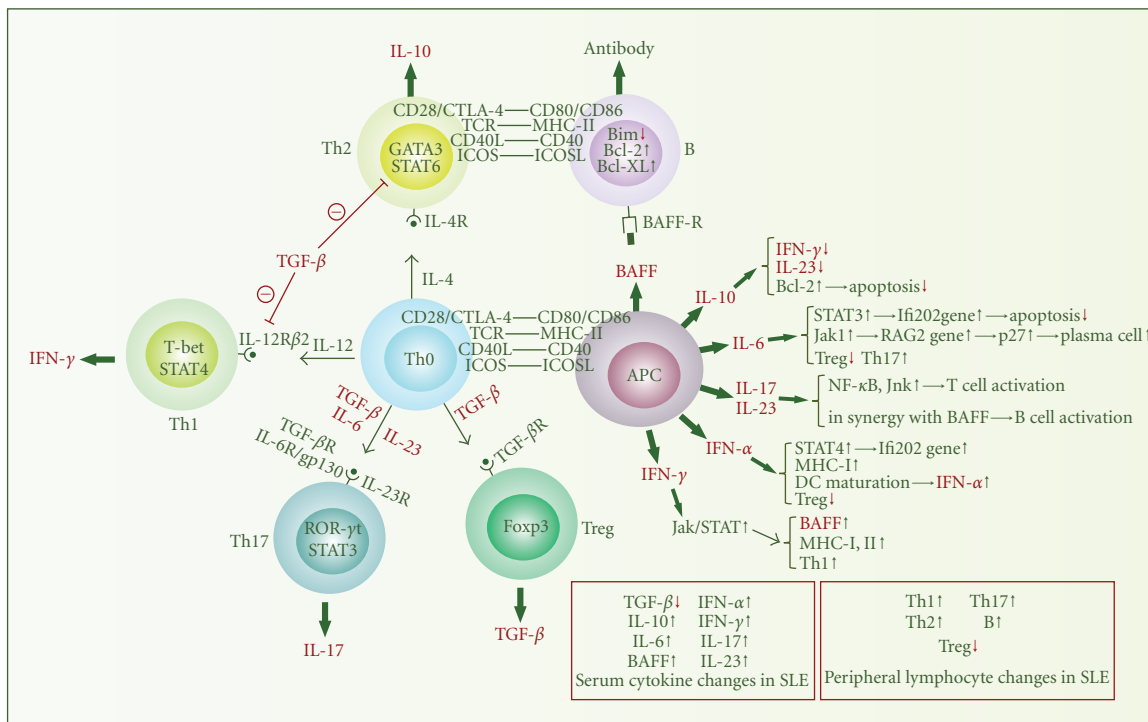


FIGURE 1: Cytokine network that links innate and adaptive immunity. This figure illustrates the functions of some key cytokines secreted by several most important types of immune cells. APC refers primarily to monocytes, macrophages, and dendritic cells. In SLE, TGF- β and IL-10 mainly exhibit anti-inflammatory effects, while IL-6, BAFF, IFN- α , IFN- γ , IL-17, and IL-23 function as proinflammatory cytokines. These cytokines have cross-talks by affecting one another, thereafter constituting a complex network.

to F, have been described and are structurally homologous to each other. The IL-17 receptor (IL-17R) is distributed ubiquitously in various tissues, and its engagement activates both transcription factor NF- κ B and kinase Jnk pathways [157]. IL-17 has a key role in tissue neutrophil recruitment and helps the clearance of pathogens such as extracellular bacteria. IL-17 is produced by several cell types including activated T-cell subsets (CD4⁺, CD8⁺, CD4⁻ CD8⁻, γ δ T cells), natural killer cells, and neutrophils [158].

The pathogenic role of IL-17 has been observed in EAE, CIA, inflammatory bowel disease (IBD), and SLE [159]. IL-17 facilitates T-cell activation and infiltration into tissues

by upregulating the expression of intercellular adhesion molecule-1 (ICAM-1) [160]. It can also act in synergy with BAFF to influence B-cell proliferation and antibody secretion [161]. IL-17 may promote autoantibody production, and IL-17-producing cells are found in afflicted organs in human SLE patients and lupus-prone mice [162]. Th17 and DNT cells are expanded in the peripheral blood of SLE patients and account for the increased production of IL-17 [163]. The urinary expressions of Th17-related genes (ROR- γ t, IL-17, and IL-23) are increased in SLE patients and are inversely correlated with kidney biopsy as well as systemic and renal lupus activity [164]. Migration of IL-17-producing

T cells into the kidneys of MRL/lpr mice is driven by locally produced chemokines such as CXCR3. Genetic silencing of genes involved in the increased production of IL-17 in lupus-prone mice and treatment of those mice with biologic agents that result in decreased IL-17 production leads to disease mitigation [165]. Th17 cells mediate accelerated ischemia/reperfusion-induced intestine injury in MRL/lpr mice, while IL-23-deficient mice display significantly less intestinal damage [166].

IL-23 is essential to promote the expansion and survival of IL-17-producing cells. Rapid IL-23/IL-17-mediated neutrophil responses might be important for initial control of the infection, but dysregulation of the pathway can break tolerance and lead to severe autoimmune pathologies such as multiple sclerosis, rheumatoid arthritis, psoriasis, and Crohn's disease [167]. The importance of IL-23/IL-17 axis in human lupus and lupus model mice has been validated. Plasma IL-12, IL-17, IL-23, and CXCL10 concentrations and the number of Th17 cells are significantly elevated in SLE patients than those of control subjects, and proinflammatory cytokine IL-23, can promote the disease severity by activating pathogenic Th17 cells [168]. There is a strong correlation between IL-17, and IL-23 levels in lupus patients [169]. IL-23/IL-17A pathway is activated in lupus-prone mice and is associated with increased Ig deposition and complement activation in the kidney [162]. DNT cells from MRL/lpr mice express high amounts of IL-17 and, as disease progressively worsens, the expressions of IL-17, and IL-23 receptor (IL-23R) in lymphocytes from these mice are increased. IL-23R-deficient lupus-prone MRL/lpr mice display decreased numbers of DNT cells and IL-17A-producing cells in the lymph nodes and produce less anti-DNA Abs. In addition, clinical and pathologic measures of lupus nephritis are abrogated when IL-23R is deficient [170].

A number of key points discussed here constitute a definitive rationale for the development of novel drugs or biologics to block the IL-23/IL-17 axis to limit autoimmunity and organ damage of SLE. The presented experiments document the importance of IL-23R-mediated signaling in the development of lupus nephritis and urge the consideration of proper biologics for the treatment of the disease [171]. The IL-23/IL-17 axis of inflammation and related molecules may rise as therapeutic targets for treating autoimmune diseases such as SLE [172].

4. Concluding Remarks

The cytokines discussed above are mostly generated by innate immune cells upon stimulation by invading pathogens, which then induce the activation and proliferation of adaptive immune cells to perform a joint protective immune function. A local inflammatory milieu will elicit the production of anti-inflammatory cytokines in a negative feedback, as well as the generation of regulatory T and B cells, to prevent overactivation of immune response and subsequent autoimmune disease. However, there exist various abnormalities of multiple cytokines in number and function in SLE patients, which play crucial roles in disease pathogenesis

(Table 1). These cytokines are downstream products of activated immune cells and can also exert different effects on the proliferation and function of immune cells. They may act directly or indirectly on each other, thereby constituting a complex network (Figure 1).

Currently, the treatment for SLE has evolved from conventional drugs to biologic agents. Various therapeutic agents targeting different cytokines have been developed to treat SLE, such as belimumab targeting BAFF, tocilizumab targeting IL-6, and IFN- γ -Ig fusion protein targeting IFN- γ . All these biologic agents can improve lupus disease to different extent in both animal models and SLE patients, but they cannot inhibit the disease progression completely. The efficacy of these agents is believed to depend on specific disease condition, different organs involved, and timing of medication, indicating a spatial and temporal variety of cytokine expression in SLE, which provide challenge for cytokine-targeted therapy for SLE and necessitate further investigation.

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