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Review Article

Inflammatory Cytokines in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin affecting virtually all organ systems. Beyond genetic and environmental factors, cytokine imbalances contribute to immune dysfunction, trigger inflammation, and induce organ damage. The key cytokine that is involved in SLE pathogenesis is interferon alpha. Interferon secretion is induced by immune complexes and leads to upregulation of several inflammatory proteins, which account for the so-called IFN signature that can be found in the majority of SLE PBMCs. Additionally IL-6 and IFN-y as well as T-cell-derived cytokines like IL-17, IL-21, and IL-2 are dysregulated in SLE. The latter induce a T-cell phenotype that is characterized by enhanced B-cell help and enhanced secretion of proinflammatory cytokines but reduced induction of suppressive T cells and activation-induced cell death. This paper will focus on these cytokines and highlights pathophysiological approaches and therapeutic potential.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease of unknown origin affecting virtually every organ in the human body. SLE is primarily caused by autoantibodies and immune complex deposition. Enhanced apoptosis in conjunction with defective clearance of apoptotic cells results in occurrence of high levels of autoantibodies [1]. Deregulated cytokine production contributes to immune dysfunction and mediates tissue inflammation and organ damage. Inflammatory cytokines, like type I and type II interferons and interleukin-6 (IL-6), IL-1, and tumor necrosis factor-alpha (TNF-α) as well as immunomodulatory cytokines like IL-10 and TGF-β, have been identified as important players in SLE. Apart from those IL-21 and IL-17 have been lately identified to play a relevant role in autoimmunity, while recent findings regarding IL-2 brought this cytokine back in focus of SLE research. Beside interferons this paper will highlight some recent advances of IL-6, IL-21, IL-17, and IL-2 research with regard to SLE.

2. Type I Interferons

Type I interferons (IFNs) are important cytokines, whose most prominent function is to mediate the early immune response to viral infections. Viral RNA and DNA are recognized by Toll-like receptors (TLRs) and trigger IFN release of leukocytes. Although all leukocytes produce IFN, plasmacytoid dendritic cells (pDCs) are the main producer [2]. PDCs are a rare cell population. Only 0,2–0,8% of peripheral mononuclear cells (PBMCs) are pDCs, but their capacity to produce IFN is unique and 100–200 times enhanced compared to any other cell type [3, 4]. The ability to release such high amounts of IFN might be caused by the fact that pDCs constitutively express Toll-like receptor 7 (TLR7) and Toll-like receptor 9 (TLR9) [5]. After secretion IFN binds its heteromeric type I IFN receptor on target cells, transduces signals mainly via JAK/STAT pathways, and initiates gene transcription of so-called interferon-stimulated genes [6]. Microarray analysis detected >300 genes induced by interferon [7]. By activation of genes which are responsible for antimicrobial responses, antigen processing, and inflammation, IFNs exert several immunomodulatory effects and are therefore supposed to be key cytokines not only in the innate immune system but also in adaptive immune responses [8]. The central role of IFN in SLE has been confirmed by several observations.

Many of the symptoms that SLE patients develop are congruent with symptoms of patients suffering from influenza or as a side effect of interferon-alpha (IFN-α) therapy. Fever,

fatigue, and leukopenia are some examples. SLE patients often show enhanced IFN-α serum levels [9], and the IFN levels correlate with anti-dsDNA production and disease activity [10]. Furthermore, IFN-α therapy may lead to autoantibody production and an SLE-like syndrome [11, 12]. Genetic association studies of patients with SLE identified several genes, amongst which components of the upstream and downstream pathways of type I interferon are the most frequently found [13] including Signal Transducer and Activator of Transcription 4 (STAT4) and interferon regulatory factor 5 (IRF5) [14–16]. STAT4 interacts with type I interferon receptors and is directly involved in IFN signaling. IRF5 is a transcription factor which induces IFN transcription in response to TLR signaling. In fact the IRF5 risk haplotype in SLE patients is associated with high serum IFN-α activity [17]. These genetic association studies are in accordance with the fundamental observations identified by gene expression profiling of SLE PBMCs in the group of Virginia Pascual. These experiments demonstrate a significant upregulation of interferon-regulated gene transcripts in adult and paediatric SLE PBMCs [18, 19]. This characteristic is referred to as the "interferon signature" and assessed as a new biomarker for disease activity [13].

These observations raised the questions of how the IFN signature in SLE patients develops and how IFNs are involved in pathogenesis of SLE. A hallmark of SLE is the formation of immune complexes (ICs). One cause of immune complex formation is an increased apoptosis and defective clearance of apoptotic material on the one hand and high occurrence of autoantibodies on the other hand [1]. In 1998 Cederblad et al. observed the production of IFN-α by PBMCs when serum samples from SLE patients were used as culture supplement [20]. Further studies showed that immune complexes induce IFN-α production by pDCs [21–24]. Immune complexes are internalized after binding Fc gamma RIIa on the surface of pDCs and activate TLR9 and TLR7 in the endosomal compartment, which induces secretion of IFN-α [25]. Indeed pDC are reduced in SLE blood [20], but this reduction might be related to enhanced recruitment to tissues [26, 27].

The overproduction of IFNs in SLE exerts wide effects, which result in the above-mentioned IFN signature. We would like to accent a few of these effects which were intensively observed and papered by Obermoser and Pascual [13].

First IFN-α promotes feedback loops by induction of TLR7 in pDCs, mDCs, and monocytes which enhance synthesis of IFN [28]. Secondly IFNs contribute to disruption of peripheral tolerance by promoting DC maturation (mDC) and thereby reducing numbers of immature DCs. Immature DCs are important to keep up immune tolerance by induction and maintenance of regulatory T cells. In addition immature DCs promote anergy and deletion of self-reactive T cells by presenting self-peptide MHC complexes in the absence of costimulatory signals to self-reactive T cells [29]. Activated and self-reactive T cells provide help for B cells. Thirdly mDCs can also directly enhance selection and survival of autoreative B cells by producing B-cell activating factor (BAFF) [30]. This cytokine belongs to the family of B-lymphocyte stimulators (BLySs) and contributes to survival of B cells [31]. Finally IFN-α drives disease activity by enhancing cytotoxicity of CD8 T cells [32] and also directly increases numbers of autoreactive CD4 T cells by upregulation of the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APCs) [13]. Therefore, activation of the IFN system by ICs as endogenous IFN inducers in SLE patients generates a self-reinforcing trial which Rönnblom and Alm describe as a vicious circle (Figure 1) [8].

Therapeutical targets which disrupt this circle are subjects of intensive research. The widely used and old drug resochin changes the pH of the endosomes and therefore the affinity of TLR7 and TLR9 towards ICs. Specific inhibitors of TLR7 and TLR9 have already been tested in animal models [33]. Antibodies to block IFN-alpha (Sifalimumab, Rontalizumab) are currently being tested in clinical trials [34]. In a phase I trial treatment of SLE patients with an anti-IFN-α monoclonal antibody influenced interferon signature and skin lesions of these patients [35].

3. Interleukin-6

IL-6 is produced in many cell types, like monocytes, fibroblasts, endothelial cells, and also T and B lymphocytes [36] and has a range of biological activities on various target cells. IL-6 serves as a differentiation factor for several haematopoetic cells. Differentiation of B cells in plasma cells and induction of IgG production is induced by IL-6 [37] as well as differentiation and proliferation of T cells [38] and macrophages [39]. Further effects of IL-6 are bone marrow stem cell maturation, activation of neutrophils, and stimulation of the production of platelets from megacaryocytes and osteoclast differentiation [40]. IL-6 is the major hepatocyte stimulation factor and induces acute-phase proteins [41].

IL-6 signaling occurs via its heteromeric receptor complex, which consists of two glycoproteins, an IL-6-specific binding chain (IL-6R) and a signal transducing chain (gp130) [42]. Binding of IL-6 on IL-6R triggers dimerisation of gp130, which results in activation of JAK1 and tyrosine phosphorylation of gp130. This activates the ERK/MAPK signaling pathway and p-STAT3-mediated pathways [43]. IL-6R expression is limited to several cells, but a so-called gp130 transsignaling occurs when IL-6 binds a soluble IL-6R form and then interacts with the more unique expressed gp130 (Figure 2) [44].

Murine lupus models indicate the involvement of IL-6 in B-cell hyperactivation and onset of autoimmune disease. In Mrl/lpr mice IL-6 and soluble IL-6R serum levels are increased related to age [45, 46]. IL-6-deficient Mrl/lpr mice show a delayed onset of lupus nephritis and prolonged survival [47]. IL-6 receptor blockade suppressed IgG antibody production in NZB/W F1 mice and development of autoimmune disease [48, 49], whereas exogenous administration of IL-6 accelerates glomerulonephritis in NZB/W F1 mice. Recent investigations suggest that IL-6 blockade not only targets autoreactive B cells but also inhibits autoreactive T cells in NZB/W F1 mice [50]. Next to its effects on B cells IL-6 is a key cytokine that determines T-cell differentiation of naïve T cells into so-called regulatory

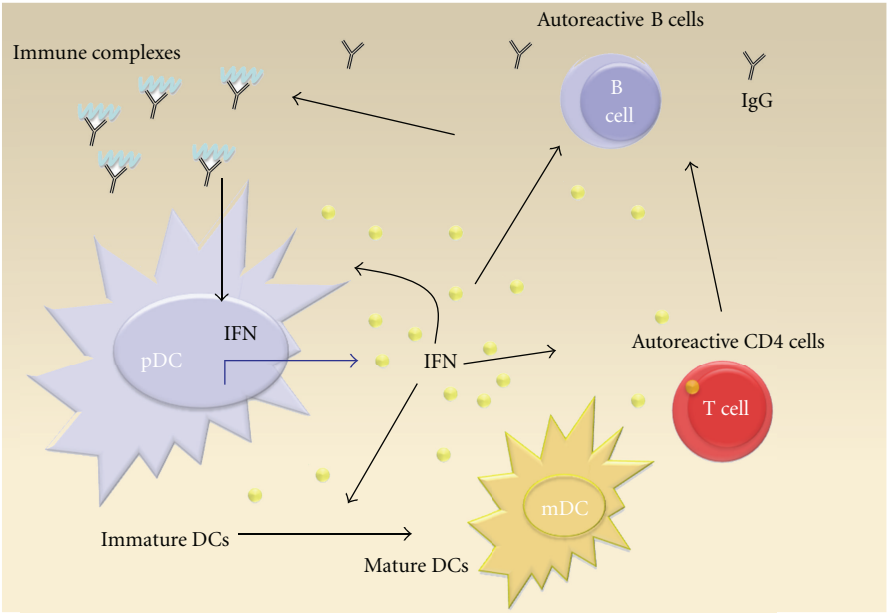

Figure 1: The vicious circle of IFN signaling in SLE: ICs bind to Fc gamma RII receptors on pDCs and reach the endosomes where they are recognized by TLRs. TLRs transduce signals to the nucleus which induce transcription of IFN. IFN secretion enhances expression of its own receptor on pDCs, mDCs, and monocytes. Furthermore, IFN promotes maturation of DCs which leads to disruption of peripheral tolerance and activation of autoreactive CD4 T helper cells. The appearance of autoreactive CD4 T cells is further amplified by upregulation of CD80 and CD86 on APCs. This results in enhanced B cell help by autoreactive CD4 cells, which is again sustained by an upregulation of BAFF. The increased formation of autoreactive B cells triggers appearance of ICs and further IFN release.

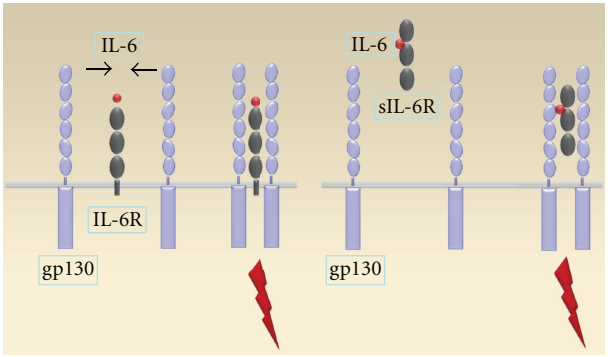

Figure 2: Model of gp130 transsignaling. IL-6 signaling occurs by binding its membrane bound receptor (IL-6R) in target cells and subsequent dimerization of gp130 (Figure on the left). Cells which do not express IL-6R can also be susceptible to IL-6 via soluble IL-6 receptors that dimerize with membrane bound gp130 (Figure on the right).

T cells with a suppressive phenotype or into T cells with a proinflammatory Th17 phenotype. Since IL-6R blockade in mouse model of arthritis inhibited the differentiation of Th17 cells [51], effects of IL-6 blockade on T-cell responses and therefore benefits for autoimmune diseases should also be taken into consideration [52].

Patients with active SLE have increased IL-6 serum levels [53, 54] which in some studies correlated with disease activity [53] or anti-DNA levels [40, 54]. Elevated IL-6 levels are associated with B-cell hyperactivity and autoantibody production [40] and secretion of IgG anti-DNA antibodies were reduced by neutralizing IL-6 and restored by adding exogenous IL-6 *in vitro* [40, 53]. In addition to its systemic effects IL-6 also has a role in local inflammation, for example, in lupus nephritis and is supposed to be involved in mesangial cell proliferation, one of the hallmarks of proliferative lupus nephritis [40]. Patients with active lupus nephritis show elevated urinary IL-6 secretion [55, 56], and the expression of IL-6 is increased along glomerular and tubulus tissue in lupus nephritis kidneys *in situ* [57]. IL-6 is increased during cardiopulmonary complications of SLE [58], and SLE patients with neuropsychiatric syndromes show elevated IL-6 levels in the cerebrospinal fluid [59]. Current investigations also indicated the involvement of IL-6 in joint damage in SLE patients [60].

As IL-6 exerts systemic effects and also mediates local inflammation, IL-6 targeting therapy, which has been shown to be efficacious in inflammatory autoimmune diseases [61], might also be promising in the treatment of SLE patients. Tocilizumab is a humanized monoclonal antibody, which inhibits IL-6 signaling by binding IL-6R and soluble IL-6 receptors. It was recently tested in an open label-phase 1 dosage escalation study in SLE patients. The results are promising regarding decreased levels of anti-dsDNA antibodies and of acute-phase reactants in Tocilizumab treated patients [62].

4. Interferon-Gamma

Interferon-gamma (IFN-γ) activates macrophages at the site of inflammation, contributes to cytotoxic T-cell activity,

has antiviral capacities, and is strongly associated with Th1 responses. It induces differentiation of naïve T cells into Th1 cells and triggers Th1 differentiation in an autocrine manner. IFN-γ signaling induces phosphorylation of STAT1 which leads to expression of the Th1-lineage-specific transcription factor T-bet and subsequent expression of IFN-γ [63].

Due to the fact that Th1-mediated effects can explain many features of autoimmune diseases, IFN-γ became an archetypical inducer of organ-specific autoimmunity [64]. IFN-γ might contribute to autoimmune disease by inducing production of IgG2a and IgG3 isotype antibodies that activate complement and furthermore by activating macrophages and promoting tissue inflammation. However, in autoimmune models like experimental autoimmune encephalomyelitis [65] and collagen-induced Arthritis [64, 66], IFN-γ-deficient mice are more susceptible; therefore, the role of IFN-γ is not proinflammatory per se. Recent studies detected diverse mechanisms via which IFN-γ might counteract inflammatory pathways (review in [67]). One important mechanism might be that IFN-γ inhibits the development of autoimmune-related Th17 cells [67, 68].

The role of IFN-γ in SLE was analyzed in several mouse models. T-helper cells expressing IFN-γ correlate with age and development of disease in NZB/W F1 mice [69]. Additionally treatment of NZB/W F1 mice with recombinant IFN-γ accelerated development of disease, while administration of monoclonal antibodies against IFN-γ resulted in remission of disease [70]. Furthermore, IFN-γR-deficient NZB/W F1 mice show reduced glomerulonephritis and reduced serum concentration of anti-dsDNA antibodies [71].

IFN-γ-deficient Mrl/lpr mice are prevented from early death and have reduced lymphadenopathy and reduced glomerulonephritis [72]. Treatment with a cDNA encoding IFN-γR/Fc reduces disease manifestations [73]. However, treatment of Mrl/lpr mice with recombinant IFN-γ leads to dichotomic effects. While treatment at an early age proves to be protective, treatment later in life accelerates disease manifestations [74]. In a pristine-induced lupus model IFN-γ deficient BALB/c mice are protected from renal disease [75]. Several studies on lupus models suggest that an imbalance towards Th1 dominance plays a role in acceleration of disease [76–78]. In human patients with SLE a disbalance in mechanisms that regulate Th1 and Th17 cells with an enhanced expression of Th17 cells was observed [79], which was partially aggravated by the use of glucocorticoids [80]. Recent studies detected unusual IFN-γ and IL-17 double-positive T cells [81] which indicates a quite complex and not yet understood plasticity of Th1 and Th17 cells [82]. The complex role of IFN-γ in SLE is underscored by contradictory clinical studies that find a correlation between serum IFN-γ level and disease activity and a correlation between IFN-γ expression and severity of lupus nephritis while others show decreased IFN-γ levels in lupus nephritis [83, 84]. Nevertheless, AMG-811, a human monoclonal antibody to IFN-γ, is under investigation in a phase Ib study in SLE patients [34].

5. Interleukin-2

T cells are the main producer and responder cells of interleukin-2 (IL-2). IL-2 production is induced after T-cell receptor (TCR) activation, induces itself in paracrine and autocrine loops, and also upregulates surface expression of its receptor. IL-2 was initially discovered as a cytokine which drives clonal expansion of T cells, but the phenotypes of IL-2-deficient or IL-2-receptor- (IL-2R-) deficient mice expand the tasks and impact of IL-2 [85].

Mice with IL-2 or IL-2R deficiency show an enlargement of peripheral lymphoid organs (lymphadenopathy and splenomegaly) and impaired activation-induced cell death (AICD) and develop autoimmune disorders [86, 87]. In addition to this, a defective production of IL-2 is observed in several murine models of autoimmune diseases [88] including three well-established lupus models. In all of these models the production of IL-2 is reduced once disease starts to appear [89–91].

These observations are somewhat inconsistent with the view of IL-2 as growth factor for T cells and raise the question of how loss of IL-2 is connected with loss of immunotolerance. Interestingly, IL-2 deficiency in mouse models is paralleled by reduced levels of regulatory T cells (Tregs). Therefore, the uncontrolled activation of B and T cells in the absence of IL-2 might be caused by deficiencies of regulatory T cells in these mice. Direct evidence that regulatory T cells depend on IL-2 comes from experiments which show that IL-2 is required for homeostatic maintenance of regulatory T cells [92] as well as for their thymic development and IL-2 also directly affects suppressive function of regulatory T cells [93]. In addition to its effect on regulatory T cells, it was very recently discovered that IL-2 also affects Th17 cells. This highly proinflammatory T-cell subset is linked to many autoimmune diseases. IL-2 limits production of IL-17 *in vivo* and *in vitro*, and low levels of IL-2 favour occurrence of Th17 cells [94]. IL-2-deficient mice show enhanced serum levels of IL-17 and a higher number of IL-17 producing T cells in peripheral lymph nodes. Laurence et al. showed by adoptive transfer experiments that the IL-17 overproduction is not caused by a secondary manifestation of disease, but directly due to deficiency of IL-2 [95].

It is therefore currently accepted that IL-2, beyond its role as a growth factor, is important to maintain functionality and homeostasis of regulatory T cells on the one hand and to inhibit production of IL-17 on the other hand. As a consequence IL-2 appears to be a crucial cytokine to prevent formation of autoimmunity.

In accordance with this SLE T cells show reduced IL-2 production [96–98] and IL-2 deficiency is also paralleled by low numbers of regulatory T cells in SLE patients [99]. The molecular mechanism of the IL-2 defect in SLE is caused amongst others by overexpression of cAMP response element modulator alpha (CREMα), a transcription factor which binds to the IL-2 promoter and inhibits IL-2 transcription. Anti TCR/CD3 antibodies present in SLE sera induce expression of CREMα, which leads to an increased CREMα binding to the IL-2 promoter and decreased IL-2 production [100]. We recently showed that increased CREMα expression is the

result of enhanced CREMα promoter activity in SLE T cells and CREMα promoter activity correlates with disease activity [101]. Interestingly the defective IL-2 production of SLE T cells can be restored by introducing a plasmid encoding antisense CREMα into these cells [102]. The IL-2 activating transcription factor CRE-binding protein (CREB) shares the same binding site on the IL-2 promotor and is displaced by CREM in SLE cells possibly because of high levels of CREM [103]. Furthermore, diminished activity of CREB, caused by increased levels of the serine/threonine phosphatase PP2a, the phosphatase that is responsible for dephosphorylation of CREB, contributes to reduced production of IL-2 [104]. It is not clear whether lower IL-2 levels in SLE also contribute to enhanced IL-17 levels, but the ratio of Treg to Th17 cells in SLE patients with active disease is significantly lower than that in healthy controls and inversely correlates with the severity of active SLE [105]. IL-2 is also involved in activation-induced cell death (AICD). AICD is a controlled apoptotic mechanism by which excess effector cells are eliminated and it is regulated by CD95 and TNFR1 [106–108]. This process is affected in SLE patients, in whom T cells are more resistant to AICD [109, 110] resulting in persistence of autoreactive T cells. Furthermore, IL-2 is also important for the development of CD8 T-cell cytoxicity. Cytotoxic T cells (CTL) destroy virus-infected T cells and are important to defend infections. Some SLE patients develop cytotoxic defects, while a lot of SLE patients suffer from increased mortality and morbidity during infections [109].

Altogether defective IL-2 production in SLE T cells seems to contribute to several immune alterations including reduced numbers and function of regulatory T cells, decreased AICD, decreased CTL responses and to upregulation of IL-17 production [109]. This raised the question whether compensation of low IL-2 levels by adding exogenous IL-2 would result in lower disease activity [111].

Humrich et al. treated lupus prone mice with IL-2. In the IL-2 treated mice the homeostatic balance of Treg and T effector cells was re-established and impeded disease progression [112]. However, the half live of exogenous cytokines *in vivo* is quite short, while IL-2 in complexes with an antibody is more functional [111]. These complexes can prevent type 1 diabetes [113] and suppress experimental myasthenia [114]. Furthermore *in vivo* expansion of regulatory T cells with IL-2/IL-2mAB complexes induces resistance to experimental autoimmune encephalomyelitis [115].

Therefore IL-2 seems to have a therapeutic potential to treat autoimmune diseases, but the activity of IL-2 as growth factor bears a risk. IL-2 has been used as adjuvant for treatment of patients with renal cancer albeit with considerable side effects. The effect of IL-2 seems to depend on the administered dose, it is possible that low doses favour Tregs, while high doses favor memory/effector cell function [111].

Recently published data from Liao et al. further expand the impact of IL-2 to a cytokine that in addition to its influence on regulatory T cell and Th17 cells broadly regulates T helper cell differentiation [116]. Further investigations is needed to understand the several and sometimes ambivalent roles of IL-2. It should be taken into consideration to therapeutically influence mechanisms upstream from IL-2, which are responsible for reduced IL-2 expression in SLE.

6. Interleukin-21

IL-21 is produced by a range of differentiated $CD4^+$ T cell subsets and natural killer (NK)T cells [117]. IL-21 signals through a heterodimeric receptor, which is formed by common gamma chain (shared with IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15 receptors) and an IL-21 specific receptor (IL-21R) [118, 119]. Since IL-21R is expressed on $CD4^+$, $CD8^+$ T cells, B cells, NK cells, dendritic cells, macrophages and keratinocytes [118], IL-21 acts on a range of lymphoid lineages and exerts pleiotropic effects. We will give a short numeration of its effects on immune cells. IL-21 is a stimulator of $CD8^+$ T cell proliferation. In synergy with IL-15 and IL-7 it promotes $CD8^+$ T cell expansion [117, 120, 121]. IL-21 drives differentiation of naïve T cells into Th17 cells [122]. IL-21 is induced by IL-6 and RORγt and stabilizes and maintains Th17 cells by upregulating its own expression and the expression of IL-23R [117, 121]. Induced regulatory T cells are negatively regulated by IL-21, as IL-21 downregulates FoxP3 induction in TGF-β stimulated cells [122]. Furthermore IL-21 counteracts suppressive effects of Tregs, however it is not known if IL-21 acts on Tregs or $CD4^+$ T cells in this circumstances [123]. Furthermore IL-21 plays a role in follicular T helper cell (Tfh) development and is necessary for germinal center (GC) formation [124, 125]. GCs can be the origin of autoantibodies and abnormalities in GCs can lead to aberrant selection of autoreactive B cells and might contribute to autoimmunity [126]. IL-21 effects on B cells are context-depended. IL-21 has a role in B cell activation and differentiation of plasma cells that produce IgG [127], but also induces apoptosis of resting and activated B cells [128]. IL-21 without antigen or in the presence of a non-specific polyclonal signal induces deletion of autoreactive B cells. IL-21 in context of a specific antigen and T cell interaction leads to expansion of responding cells [118]. IL-21 can also act anti-inflammatory, it inhibits dendritic cell maturation and stimulates IL-10 production [129, 130].

SLE patients have higher serum levels of IL-21, while IL-21 and IL-21R polymorphisms are associated with susceptibility to SLE [131, 132]. A subset of patients with SLE shows increased numbers of circulating $CD4^+$ $CXCR5^+$ cells (Tfh cells) [133]. The sanroque mouse bears a mutation in a gene that negatively regulates Tfh cell development. These mice develop lupus-like symptoms, paralleled by an overproduction of IL-21 and increased levels of Tfh cells [134]. Mrl/lpr mice show increasing numbers of Tfh cells and extrafollicular T helper cells with age and disease development [135]. Mrl/lpr mice treated with IL-21R/Fc to block IL-21 signaling displayed reduced level of autoantibodies and SLE-like symptoms [136]. The lupus mouse BXSB.B6-Yaa+ shows increased IL-21 mRNA levels compared to wildtype mice [125] and disease was prevented by genetic deletion of IL-21R in these mice [137]. Notably treatment of BXSB.B6-Yaa+ mice with an IL-21R/Fc fragment negatively influenced

survival early on and positively influenced survival at later stages of disease [138]. Because of these pleiotropic effects, it remains debatable if IL-21 blockade might be useful to treat SLE.

7. Interleukin-17

IL-17 is produced by several T-cell subsets including T helper cells ($CD4^+$ T cells), cytotoxic T cells ($CD8^+$ T cells), double-negative ($CD4^-CD8^-CD3^+$) T cells, gamma-delta T cells but also by natural killer (NK) cells and neutrophils [139]. A new $CD4^+$ T-cell subset, which preferentially produces IL-17 but not IL-4 or IFN-γ, is termed Th17 cells. Beyond IL-17a and IL-17f these cells produce IL-22 and IL-21. Important factors for the differentiation of murine as well as human Th17 cells include IL-6, IL-21, and IL-1β together with TGF-β [122, 140–146]. In addition to these cytokines, IL-23 is crucial for expansion and maintenance of Th17 cells [147]. Th17 cells are involved in the immune response against bacteria, like *Citrobacter*, *Klebsiella pneumoniae*, and *Borrelia burgdoerferi* and against fungi like *Candida albicans* [64]. Some of these infections cannot be cleared by Th1 or Th2 cells. Beyond these protective roles, IL-17 and Th17 cells contribute to tissue inflammation and organ damage in autoimmune diseases by triggering chronic inflammation [148].

IL-17 exerts several effects and affects several cell types (Table 1). IL-17 receptors are broadly expressed not only on immune cells but also on epithelial and endothelial cells [139, 149–151]. IL-17 signaling through these receptors increases production of chemokines (interleukin-8 (IL-8), monocyte chemoattractant protein-1, growth-related oncogene protein-alpha), which leads to recruitment of monocytes and neutrophils into the inflamed tissue [152–154]. Moreover, IL-17 also induces T-cell infiltration by upregulating the expression of intercellular adhesion molecule 1 (ICAM-1) [155]. IL-17 induces secretion of many proinflammatory proteins, among them prostaglandin E2, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony stimulating factor [155–157], and also cytokines which induce a positive feedback loop and lead to further IL-17 production like interleukin-6 (IL-6), IL-1β (interleukin-1 beta) and IL-21 (interleukin-21) [148]. Recent experiments provide evidence that IL-17 alone or in synergy with BAFF also promotes B-cell differentiation and autoantibody production [158, 159].

SLE patients have raised serum levels of IL-17. Enhanced percentages of IL-17 producing cells [160–164] and plasma IL-17 levels correlate with disease activity [162]. One source of IL-17 in SLE patients is double-negative T cells (DNTs) [164]. SLE patients have expanded numbers of double-negative T cells (DNTs) compared to healthy individuals [165]. IL-17 producing cells infiltrate skin, lung, and kidneys of SLE and lupus nephritis (LN) patients [160, 165–167] and most likely contribute to organ damage by exerting-above-mentioned effects. Evidence that IL-17 also contributes to B cell activation in LN comes from *in vitro* experiments with PBMCs [168]. These experiments document that IL-17 induces induction of IgG and anti-dsDNA production.

Table 1: IL-17 exerts effects on several cell types and tissues.

T cells	Induces production of proinflammatory IL-6, IL-1beta, and IL-21, providing a feedback loop [148]
	Enhances recruitment of T cells to inflamed tissue [155]
B cells	Drives B-cell differentiation into plasma cells and production of autoantibodies [158, 159]
Monocytes	Enhances migration to inflamed tissue [173]
Epithelial/ endothelial cells	Induces increased production of chemokines and upregulation of adhesion molecules [152]
Neutrophils	Enhances migration to inflamed tissue [154]

In the last years the Mrl/lpr mice model provided some evidence for the functional contribution of IL-17 to disease progression and organ damage. Mrl/lpr mice have increased numbers of double-negative T cells (DNTs), which produce high amounts of IL-17 and expression of IL-17, and IL-23 receptor (IL-23R) increases with disease progression [169]. Lymphoid cells from Mrl/lpr mice can induce nephritis in nonautoimmune species after IL-23 *in vitro* treatment [169]. After ischemic reperfusion of the gut, enhanced IL-17-mediated tissue injury was observed in Mrl/lpr mice [170]. Splenocytes from SNF1 (New Zealand Black x SWR F1) mice secrete higher levels of IL-17 than nonautoimmune B6 mice [171]. In congruence with observation from the Mrl/lpr model IL-17-producing T cells are detected in kidneys affected by nephritis [171]. BXD2 mice express high levels of IL-17 in serum and increased numbers of IL-17^+ cells in the spleen [172], which form spontaneous autoreactive germinal centers in concert with IL-17R expressing B cells. These features could be blocked by inhibition or deletion of the IL-17 receptor [172].

Although these data indicate that IL-17 plays a role in pathogenesis of autoimmune diseases, it is not clear whether targeting IL-17 is suited to treat SLE. Next to Th17 cell other T-cell subsets like Th1 cells crossregulate each other [158]. In a graft-versus-host-disease model the absence of donor Th17 cells leads to an exacerbated disease by augmented Th1 differentiation [174]. More importantly there is a reciprocal relationship between regulatory T cells and Th17 cells. Recent studies showed that increases in Th17 cells are directly correlated with the depletion of Treg cells during SLE flares [160]. It is therefore suggested to consider possibilities to recover the balance between Th17 and regulatory T cells to treat SLE and other autoimmune diseases [148, 175]. In fact Tregs and Th17 cells can be generated from the same cell. TGF-beta induces the differentiation of Treg cells from naïve T cells; however, the addition of IL-6 or IL-21 results in Th17 differentiation [140, 176, 177]. The lineage transcription factors of Th17 and Treg cells, RoRγT/RORα and FoxP3, respectively, bind each other and inhibit each other's function [178, 179]. IL-2 is an indispensable growth

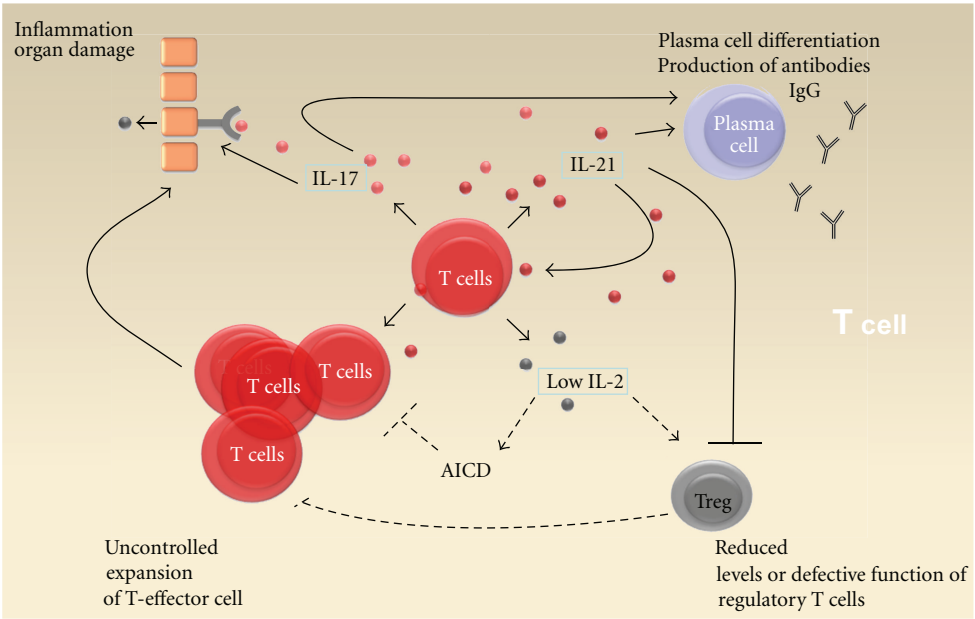

Figure 3: Dysregulated cytokine expression by T cells contributes to pathogenesis of SLE. SLE T cells secrete enhanced levels of IL-17 and IL-21 compared to healthy persons. IL-17 induces secretion of chemokines and other proinflammatory cytokines and therefore participates in tissue inflammation and organ damage. IL-21 and IL-17 both promote differentiation of B cells into plasma cells and production of IgG antibodies. IL-21 further maintains and expands occurrence of Th17 cells. In contrast SLE T cells have a defective production of IL-2, which leads to reduced level of regulatory T cells and defective function of T cells, which might also be caused by IL-21. Since IL-2 is crucial for AICD, low levels of IL-2 might be responsible for reduced AICD leading to expansion of autoreactive T cells, which further trigger B-cell activation and tissue inflammation.

factor for Tregs but inhibits Th17 differentiation [94, 95], and IL-21 promotes Th17 differentiation and inhibits the induction of regulatory T cells [122]. Finally Tregs treated with IL-6 can produce IL-17 [180–182] and can convert into IL-17 producing autoimmune effector cells [183]. The balance of Th17 and Treg cells is regulated by several transcription factors which are activated in a context-dependent manner depending on external cytokines. The cytokine environment in SLE is ideal for the generation of Th17 cells [184]. Low levels of IL-2, enhanced production of IL-21 and IL-6 [53, 185] might lead to enhanced IL-17 levels. We do not know if Tregs lose expression of FoxP3 and become IL-17-producing cells during SLE flares. But the cytokine milieu apparent in SLE patients could theoretically facilitate this phenomenon.

Future investigations might shed light on the question whether IL-17 blockade or blockade of cytokines or transcription factors that regulate Th17-Treg homeostasis will be useful to treat SLE.

8. Concluding Remarks

Cytokines are important mediators of intercellular communication and orchestrate the interaction of immune cells during immune responses. In SLE several cytokines are involved in general immune dysregulation and also in local inflammation which leads to tissue injury and organ damage. Here we summarized recent advances in the studies of some cytokines, which contribute to SLE pathogenesis. It is widely accepted that interferons have a crucial role in the pathogenesis of SLE. The therapeutic blockade of the IFN driven vicious circle might be one of the most promising anti-cytokine therapies in the future. Furthermore, an aberrant SLE T-cell phenotype which is characterized by a dysregulated production of IL-17 and IL-21 and low production of IL-2 also aggravates disease pathology (Figure 3). These cytokines exert pleiotropic pathogenic effects, which make them potential targets in SLE.

Abbreviations

AICD: Activation-induced cell death
APCs: Antigen-presenting cells
BAFF: B-cell activating factor
BLyS: B-lymphocyte stimulator
CREB: cAMP response element binding protein
CREM: cAMP response element modulator
CTL: Cytotoxic T cells
DNTs: Double-negative T cells
GC: Germinal center
IC: Immune complex
IFN: Here referred as interferone type I
IFN-α: Interferon-alpha
IFN-γ: Interferon-gamma
IL: Interleukin
IL-...R: IL-...receptor
IL-21R: IL-21 receptor
IRF5: Interferon regulatory factor 5

JAK: Janus kinase
LN: Lupus nephritis
NK: Natural killer cell
NKT: Natural killer T cell
PBMC: Peripheral mononuclear cells
pDCs: Plasmacytoid dendritic cells
SLE: Systemic lupus erythematosus
STAT: Signal transducer and activator of transcription
TCR: T-cell receptor
Tfh: Follicular helper cell
TLR: Toll-like receptor
TNF-α: Tumor necrosis factor-alpha
Tregs: Regulatory T cells.

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