CLINICAL INVESTIGATION

IL-17 in systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies and the formation of immune complexes that can damage multiple tissues, organs and systems. IL-17 is a proinflammatory cytokine that plays an important role in several autoimmune diseases including SLE. The expression of IL-17 is elevated in both SLE patients and in lupus-prone mice, and it is positively correlated with disease activity. IL-17 also appears to participate in the development of several SLE complications. In this article, we provide an overview and an update of the role of IL-17 in SLE.

Keywords: autoimmunity • cytokines • IL-17 • mouse models • RORγt • systemic lupus erythematosus • T cells

Systemic lupus erythematosus (SLE) is an autoimmune disease that most frequently affects women during childbearing age and significantly impacts patients' quality of life. The pathogenesis of SLE is multifactorial and involves genetic and environmental factors, in addition to abnormalities of both the innate and adaptive immune systems.

In SLE, various organs are affected with varying degrees of severity. The production of autoantibodies by B cells and the activation of autoreactive T cells represent central players in the pathogenesis of the disease, by providing pathogenic factors that are ultimately responsible for the clinical manifestations of disease and organ damage. Upon activation, naive $CD4^+$ T cells differentiate into different functional cell subsets that include T helper (Th)1, Th2, Th17 cells. In addition to their signature cytokine IL-17, Th17 cells also produce IL-21, IL-22 [1] and the CCR6 chemokine ligand CCL20 [2]. The differentiation of Th17 cells can require the contribution of TGF-β, IL-6, and involves RORC/RORγt (in humans/mice, respectively) [1].

$CD4^+$ Th17 cells are not the only producers of IL-17, as this cytokine can also be expressed by activated $CD8^+$ lymphocytes and γδ T cells, as well as natural killer T cells [3].

IL-17 has six family members (IL-17A to IL-17F). IL-17A and IL-17F share the highest homology in amino acid sequence but display different functions: IL-17A has important roles in host defenses against bacterial and fungal infections and can participate in autoimmunity, inflammation and tumors; IL-17F appears mainly involved in mucosal host defense mechanisms, although many effects of IL-17 on inflammation and immune responses appear as secondary to the modulation of other cytokines, chemokines and adhesion molecules [4]. Other members of the IL-17 family include IL-17B, -17C, -17D and -17E (also called IL-25). All members of the IL-17 family have a similar protein structure and are all well conserved in mammals, with as much as 62–88% of amino acids conserved between human and mouse homologs [4].

This review describes the mechanisms of action of IL-17 in SLE, together with the effects of IL-17 blockade in the disease.

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Increased IL-17 & Th17 cells in SLE

In a study of 50 SLE patients, the frequency of circulating Th17 cells was increased in active SLE patients (n = 25) as compared with patients with inactive disease (n = 25) [5]. Serum IL-17A was also higher in active patients than in controls [5–8]. In another study of 34 SLE patients, Th17 cells were numerically increased in patients with active disease as compared with healthy individuals [9]. Most of the IL-17 producing T cells in the SLE were confined to the $CCR6^+$ T-cell subset that expressed high levels of CD80 and CD134 (a costimulatory molecule expressed by a T cell following activation that promotes cell survival and cytokine production) [9].

Of interest, it has been shown that in addition to $CD4^+$ T cells, double negative (DN; $CD3^+CD4^-CD8^-$) T cells can also produce IL-17 [10]. This is interesting because an increased frequency of DN T cells has been observed in the peripheral blood and kidneys of SLE patients [10,11]. Similar observations have been found in lupus-prone $MRL^{lpr/lpr}$ (MRL/lpr) mice [12].

In the kidneys of lupus nephritis (LN) patients, IL-17 levels were also elevated [10]. Kidney biopsies from LN patients showed significant amounts of IL-17 where inflammatory cellular infiltrates were observed [9]. Patients with LN expressed the highest levels of CD134 on Th17 cells when compared with controls, and $CD134^+$ T cells were found in renal biopsies of LN patients [9].

In mice, IL-23-induced Th17 (primarily DN T) cells provided conspicuous help to B cells for the promotion of immunoglobulin deposition in kidneys and a subsequent activation of complement – likely leading to nephritis [12].

Association between IL-17 levels & clinical manifestations of SLE

SLE clinical manifestations are variable and can include erythematous rash, oral ulcers, arthritis, polyserositis, hematologic, renal, neurologic, pulmonary and cardiac abnormalities. Active disease, infection, LN and neuropsychiatric lupus are usually associated with higher morbidity and mortality in SLE. IL-17 might participate in the progression of clinical SLE manifestations in the CNS, vasculitis and LN, as described below.

CNS

In a study of 108 patients grouped as neuropsychiatric SLE (n = 54), SLE with CNS infection (n = 16), SLE controls (n = 20), and non-inflammatory neurological disease (n = 18), IL-17 was higher in SLE with CNS infection as compared with SLE controls and neuropsychiatric SLE [13].

Vasculitis

In SLE, cardiovascular disease is very common, together with accelerated atherosclerosis, intravascular thrombosis associated with antiphospholipid syndrome, and hypertensive cardiomegaly. Importantly, vasculitis with superimposed thrombosis may lead to critical blood reduction to vital organs such as the heart and brain. Patients with active SLE and vasculitis had significantly higher amounts of Th17 cells as compared with active SLE patients without vasculitis, suggesting that IL-17 may take part in the pathogenesis of vasculitis in active SLE [5].

LN

Autoantibodies to self-antigen can form immune complexes that can deposit in tissues and organs, such as kidneys, causing glomerular damage and LN. LN has a poor prognosis and a high risk of developing into end-stage renal failure.

Th17 cells and IL-17 levels are increased in SLE patients' LN [14]. In a study that divided 60 SLE patients into patients with nephritis (LN group) and patients without nephritis (SLE group), Th17 cell frequency was higher in the LN group as compared with both the SLE group and a healthy control group (n = 28), and both the SLE group and the LN group had higher levels of IL-17 as compared with healthy individuals [15]. In another study that included 23 subjects with active LN, 25 subjects with a history of LN in remission and 30 SLE patients with no history of renal disorder, the urinary expression of Th17-related cytokines was higher in all three groups as compared with controls [16]. Other groups also showed that plasma IL-17 levels and circulating Th17 cells were higher in SLE patients than in healthy subjects [17].

Histologically, $IL\text{-}17^+$ T cells were found to infiltrate glomerular and interstitial areas in SLE patients with class III/V, IV/V and V nephritis [18]. In the glomeruli, IL-17 levels weakly correlated with urine protein, activity index score, chronicity index and blood urea nitrogen, and there was a significant positive association between IL-17 expression and hematuria and SLE Disease Activity Index (SLEDAI) score. In the interstitia, IL-17 levels had a weakly positive correlation with blood urea nitrogen, serum creatinine, activity index score, chronicity index, and creatinine clearance, and a good association with hematuria and SLEDAI score [18].

Skin involvement

Cutaneous lupus erythematosus includes lesions that may be refractory to therapy. Discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) represent common lesions in the clinical

practice. DLE typically causes scarring, particularly on the scalp, whereas lesions of SCLE heal without scarring.

In a study of 26 patients with DLE, 23 patients with SLE and 17 with SCLE, IL-17A expression was higher in DLE, SLE and SCLE patients as compared with normal subjects [19]. Of interest, serum anti-Ro antibodies correlated with IL-17A$^+$ T cells in the SCLE lesions [19].

Elevated IL-17 positively correlates with disease activity in SLE

In 60 new-onset SLE patients divided according to their SLEDAI scores, there was a positive association between IL-17A and RORγt mRNA, erythrocyte sedimentation rate, IgG, IgA and SLEDAI score [20]. Also, RORγt mRNA showed a positive correlation with erythrocyte sedimentation rate, IgG and SLEDAI score [20]. The polyclonal stimulation *ex vivo* of lupus peripheral blood mononuclear cells (PBMCs) increased the numbers of CD4$^+$ and CD8$^+$ IL-17$^+$ T cells as compared with healthy controls [21], and IL-17 concentration positively correlated with anti-dsDNA antibody titers and Th17 cells positively correlated with disease activity in multiple studies [13,15,18,21]. IL-17$^+$CD4$^+$CCR4$^+$CCR6$^+$ T-cell frequency was also positively associated with SLE disease activity [9].

Another marker in lupus synovial fluid cell-derived CD4$^+$IL-17$^+$ T cells was CD45RO [22]. It has been reported that the elevated serum concentration of IL-17 might not change during pregnancy [23], suggesting a lack of correlation between those aspects in SLE.

IL-17 in lupus-prone mice

MRL/lpr mice

MRL/lpr mice showed that an expansion of Th17 cells and higher expression of IL-17A mRNA closely correlated with disease activity, when compared with age- and sex-matched C57Bl6 (B6) mice [15]. Also, lymphocytes from LN of MRL/lpr mice had significantly higher levels of IL-17 than lymphocytes from control MRL/MPJ mice [12]. Moreover, IL-17A-expressing splenocytes were numerically increased in MRL/lpr mice as compared with MRL/MPJ mice, and DNT cells had significantly more IL-17A than CD4$^+$ T cells [12].

B6/lpr mice

B6/lpr T cells had significantly more IL-17 and Th17 cells than control wild-type mice, and their kidneys contained Th17 cells in the tubulointerstitial areas [12]. Conversely, B6/lpr deficient in the IL-23 receptor were protected against the development of lupus-like disease [24].

BXD2 mice

Autoimmune BXD2 mice had more IL-17 than wild-type mice, and displayed a spontaneous development of germinal centers (GCs) before their increased production of pathogenic autoantibodies. Blocking IL-17 signaling disrupted the interactions between CD4$^+$ T cells and B cells that were required for the formation of GCs, and IL-17 receptor-deficient mice showed reduced B-cell development in GCs and decreased humoral responses [25].

IL-17 in SLE: mechanisms

As mentioned previously, there is a positive association between IL-17 and SLE disease activity, particularly with the development and progression of CNS disease, nephritis, vasculitis and skin disorders. Possible underlying mechanisms are described below.

Induction of adhesion molecules

Adhesion molecules, consisting of cell surface cadherins, integrins, selectins and members of the immunoglobulin gene superfamily, such as ICAM-1 and VCAM-1, play an important role in inflammation and autoimmune diseases. In patients with active SLE, PBMCs secreted increased levels of IL-17A as compared with healthy controls after stimulation, and the supernatants of cultured PBMC promoted mRNA expression of E-cadherin, ICAM-1 and VCAM-1 in human umbilical vein endothelial cells [5]. This aspect could facilitate interactions between lymphocytes and antigen-presenting cells in the development of autoimmune responses.

IL-17 & B cells

In SLE patients, self-reactive B cells can undergo somatic hypermutation and class switch, and can produce pathogenic autoantibodies that form immune complexes depositing in different organs. IL-17 is increased in B cells, where it promotes nuclear translocation of the NF-κB and c-Rel, activating the canonical NF-κB pathway [8]. It was found that the combination of IL-17 and BAFF more efficiently protected B cells from apoptosis in an NF-κB-dependent way [8]. Thus, IL-17 – alone or in combination with BAFF – could promote the survival, proliferation, differentiation and hyperactivity of self-reactive B cells.

Production of IgG, anti-dsDNA autoantibodies & IL-6

IL-17 was found to be able to stimulate PBMCs to produce IgG, anti-dsDNA autoantibodies and IL-6 in a dose-dependent manner in SLE patients with nephritis [26]. This finding is interesting because IL-6 is a pleiotropic cytokine, with a wide range of biological

activities that plays a relevant role in inflammation and autoimmune diseases by inducing the differentiation of T cells into effector cells and the differentiation of B lymphocytes into antibody-forming cells.

■ Reciprocal relation between Th17 cells & regulatory CD4+ T cells

An additional mechanism by which IL-17 could favor SLE could be the inhibition of regulatory $CD4^+$ T-cell development and activity [27]. Since regulatory $CD4^+$ T cells seem to have quantitative and/or qualitative defects in their capacity to suppress the proliferation and proinflammatory cytokine production in effector immune cells in SLE, it is possible that IL-17 may contribute to their inhibition because of the reciprocal control in the generation and maintenance of Th17 cells versus regulatory T cells [27].

Effects of SLE therapy on IL-17 levels

■ Glucocorticoids

In patients with SLE, glucocorticoids have an important and critical role in the therapy of the disease by reducing the hyperactive immune responses that characterize SLE. In patients with active disease treated with glucocorticoids, the ratio of regulatory T cells to Th17 cells increased, suggesting that corticosteroids could affect the balance between regulatory T cells and Th17 cells [28].

■ $H47_{1–94}$ peptide

$H4_{71–94}$ is a nucleosomal histone peptide that encompasses an autoantigen involved in the pathogenesis of the autoimmune responses in lupus mice. Low doses of $H4_{71–94}$ injected into lupus-prone mice induced functional regulatory T cells that could suppress nuclear autoantigen-specific T and B cells and block renal inflammation, and also cause reduced Th17-cell activity [29].

■ Apigenin

Apigenin, a dietary flavonoid, can activate normal human T cells to apoptose by inhibiting NF-κB-regulated Bcl-xL, COX-2, and c-FLIP expression [30]. Lupus mice injected with apigenin or vehicle daily were analyzed for Th17 responses. After 2 months of treatment with apigenin, autoantibodies to dsDNA, ssDNA, nucleosomes and histones, were reduced in the apigenin-treated mice, and the Th17 responses to nucleosomes were markedly reduced in apigenin-treated mice as compared with vehicle-treated controls [30].

■ Dipyridamole

Dipyridamole, an oral anti-platelet drug, is widely prescribed for the secondary prevention of vascular events, including stroke. Lupus T cells treated with dipyridamole significantly inhibited IL-17, CD154, IFN-γ and IL-6 production [31].

Future perspective

The biological properties of IL-17 in the defense of the host from infection can be subverted when an excessive production and/or unabated control of IL-17 can fuel inflammation and autoimmune responses. IL-17 properties may impact significantly the development and/or perpetuation of chronic inflammation in SLE through several mechanisms that have been discussed above, and that might represent possible targets of intervention in the disease. While additional work is required to better understand the contribution of IL-17 to the pathogenesis of SLE, the finding that the inhibition of IL-17 associates with reduced inflammatory responses envisions the possibility of IL-17-targeted therapeutic intervention in this debilitating disease.

Executive summary

- IL-17 is elevated in lupus-prone mice and in systemic lupus erythematosus (SLE) patients, where it positively correlates with disease activity.
- IL-17 seems to play a role in CNS disease, vasculitis, nephritis and skin involvement in SLE, although the mechanisms responsible for the contribution of this cytokine to these complications, remain elusive.
- The mechanisms by which IL-17 seems to promote SLE include the induction of adhesion molecules, the promotion of survival, differentiation and activity of B cells, including the production of (auto)antibodies.
- Several therapeutic agents reduce proinflammatory Th17 responses in SLE.

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