Published in final edited form as:

Curr Opin Rheumatol. 2011 September ; 23(5): 444–448. doi:10.1097/BOR.0b013e328349a255.

Effector T cell subsets in systemic lupus erythematosus: update focusing on Th17 cells

Min Sun Shin^a, Naeun Lee^a, and Insoo Kang^{a,*}

^aDepartment of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520, USA

Abstract

Purpose of review—The discovery of T helper (Th) 17 cells that produce the proinflammatory cytokine IL-17 has substantially advanced our understanding of T cell biology and autoimmunity. We will review recent findings on effector T cells, in particular Th17 cells, in lupus.

Recent findings—Studies reported increased IL-17 levels in the circulation and tissues in human and murine lupus. Patients with systemic lupus erythematosus (SLE or lupus) had an increased frequency of Th17 cells in peripheral blood which correlated with disease activity. However, the frequency of IFN- γ -producing Th1 cells did not change in the same patients, suggesting a selective dysregulation of Th17 cells in SLE. In addition, patients with SLE had an increased frequency of IL-17-producing CD3+CD4–CD8– (double negative or DN) T cells in the peripheral blood and kidneys. Similar findings were noticed in lupus-prone MRL/*lpr* mice. A recent study demonstrated that IL-17 could promote B cell survival and differentiation into antibody-producing cells. This raises the possibility that IL-17 is implicated in the pathogenesis of SLE by promoting humoral immunity against self antigen.

Summary—Emerging data show a body of evidence that IL-17 and Th17 cells may play a role in the pathogenesis of SLE. Further studies are warranted to dissect the mechanism for increased IL-17 production and the therapeutic implication of targeting this cytokine in SLE.

Keywords

Th17 cells; IL-17 and systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE or lupus) is an autoimmune disease of unknown etiology that affects multiple organs [1]. The pathologic hallmarks of SLE are dysregulated immune responses to autoantigens, with autoantibody production and subsequent inflammatory tissue injury. In the pathogenesis of lupus, innate immune cells such as dendritic cells (DCs) as well as adaptive immune cells including B and T cells are involved. Patients with SLE have increased production of cytokines such as IL-10 and B lymphocyte stimulator (BLyS; also known as BAFF or B cell activation factor of the tumor necrosis family) [2]. These cytokines could contribute to aberrant B cell immunity by promoting B cell maturation, survival and differentiation into plasma cells [2]. Immune complexes containing dsDNA or ssRNA (molecules in the target antigens of lupus) can activate autoreactive B cells and induce the production of IFN- α from innate immune cells such as

*Correspondence: Insoo Kang, Department of Internal Medicine, Section of Rheumatology, S525C TAC, 300 Cedar Street, New Haven, CT 06520, Telephone: (203) 785-6678, Fax: (203) 785-7053, Insoo.kang@yale.edu.

The authors have no conflicts of interests.

plasmacytoid DCs via the activation of Toll-like receptors (TLRs) [3]. CD4⁺ T cells with the capacity to help B cells are a critical component of lupus pathogenesis. Studies indicate that pathogenic autoantibody production by autoreactive B cells in murine and human lupus is promoted by CD4⁺ T cell help in a cognate and contact-dependent manner, resulting in an immune-complex mediated end-organ disease [1]. Over the past decade, our knowledge of T cell biology has substantially increased through the discovery of new T cell subsets including T helper (Th) 17 cells [4]. Emerging data now provide new insights on the role of T cell immunity in lupus pathogenesis. In this paper, we will review the biology of Th17 cells and update the potential role of these cells in the pathogenesis of SLE.

New Th cell paradigm

Mature but naïve CD4⁺ T cells from the thymus migrate to secondary lymphoid tissues (e.g. spleen and lymph nodes) where they survey antigens presented by antigen presenting cells in the context of the major histocompatibility complex (MHC) molecules. After encountering with antigen in T cell zones in secondary lymphoid tissues, naïve CD4⁺ T cells become activated and proliferate with differentiation into effector Th cells. The latter cells are critically involved in controlling the source of the antigen, including pathogens in infections and self-tissues in autoimmunity, via the induction of B cell differentiation and macrophage activation or through cytokine production and co-stimulation.

Effector Th cells are not a single population and can be categorized into Th1, Th2 and Th17 cells with unique functions based on the cytokines they dominantly produce; *e.g.*, IFN- γ , IL-4 and IL-17 for Th1, Th2 and Th17 cells, respectively [5,6]. The concept of Th1 and Th2 cells was developed by Robert Coffman and Tim Mosmann more than 20 years ago. Th1 cells promote cell-mediated immune responses via the secretion of IFN- γ with the capacity to activate macrophages. In fact, Th1 cells are essential for controlling intracellular microorganisms. In contrast, Th2 cells produce IL-4, IL-5 and IL-13 but not IFN- γ . Cytokines from Th2 cells are involved in controlling parasites and allergens through the activation of eosinophils and the induction of IgE. Although the Th1/Th2 dichotomy has provided reasonable explanations for how distinct subsets of Th cells are involved in controlling pathogens and developing some immune-mediated diseases such as allergies, it still has limitations in interpreting the results of various immune phenomena in infections and autoimmunity. For instance, IFN- γ blocking or a genetic deficiency of IFN- γ made the disease worse in mice with experimental allergic encephalitis (animal model of multiple sclerosis) which was thought to be a Th1 cell-mediated disease [4]. Indeed, this led to the discovery of a new subset of Th cells called Th17 cells that produce the pro-inflammatory cytokine IL-17 (reviewed in [4–6]).

Differentiation of Th cell subsets

The proper activation and differentiation of naïve CD4⁺ T cells into effector Th cells require multiple signals through T cell receptor (TCR), co-stimulatory molecules and cytokines (reviewed in [5,6]). In addition to presenting antigen to TCR, antigen-presenting cells like DCs provide the co-stimulation and cytokines for T cell activation and differentiation. Cytokine milieu is a critical factor in determining the fate of effector Th cells in humans and mice [5–7]. IL-12 and IFN- γ promote the development of Th1 cells whereas IL-4 enhances the differentiation of Th2 cells. For Th17 cells, multiple cytokines are involved in promoting Th17 cell development. These cytokines include IL-1 β , IL-6, IL-21, IL-23 and TGF- β . Each of these cytokines appears to have a different role in optimally regulating the Th17 cell differentiation. IL-1 β , IL-6 and TGF- β participate in initially differentiating Th17 cells from naïve CD4⁺ T cells [8–11]. IL-23 is likely involved in expanding the committed Th17 cells

in that naïve CD4⁺ T cells do not express the receptor for IL-23 [11,12]. In contrast, IL-21 that can be self secreted by Th17 cells stabilizes and auto-amplifies Th17 cells [11,13].

The cytokines involved in the Th cell differentiation work closely with transcription factors including T box transcription factor T-bet, GATA3 and retinoid orphan receptor (ROR) γ t (reviewed in [6,14]). These transcription factors serve as the master regulators in the development of each Th cell subset. T-bet is essential for Th1 cell differentiation whereas GATA3 and ROR γ t are critical for Th2 and Th17 cell differentiation, respectively [6,14]. The master transcription factors are tightly linked to the signaling transducer and activator of transcription (STAT) proteins that are activated by cytokines. IFN- γ and IL-12 induce activation (phosphorylation) of STAT1 and STAT4, respectively, leading to the development of Th1 cells by increasing the expression of T-bet [6,14]. IL-4 enhances GATA3 expression via activating STAT6 while IL-6 induces activation of STAT3, which results in increased expression of ROR γ t [11,14]. The cytokines and master transcription factors involved in Th cell differentiation appear to have reciprocal relationships [6]. T-bet can suppress GATA3 expression and ROR γ t [15,16]. IFN- γ and IL-4 can suppress Th17 cell differentiation [17]. In addition to ROR γ t, the transcription factors ROR α , interferon regulatory factor (IRF)-4 and runt-related transcription factor (Runx)1 can increase Th17 cell differentiation through working in cooperation with ROR γ t [14]. Taken together, the differentiation of Th cell subsets including Th17 cells are critically regulated by a complicated network of transcriptional factors in association with cytokine milieu.

Inflammatory molecules induced by IL-17

Th17 cells produce cytokines including IL-17 (IL-17A), IL-17F, IL-21 and IL-22. IL-17 and IL-17F belong to the IL-17 family cytokines [4–6]. IL-17 and IL-17F form homodimers or heterodimers [18]. IL-17 and IL-17F bind the heterodimers of IL-17 receptor A and C subunits [18]. Although IL-17 and IL-17F can drive inflammation and autoimmunity, their functions and potencies may not be equal [19]. IL-17 can induce the production of chemokines and cytokines from multiple cells including epithelial cells and fibroblasts (reviewed in [20,21]). IL-17 can promote the proliferation, maturation, and recruitment of neutrophils through inducing G-CSF, GM-CSF, CXCL1, CXCL2 (MIP2a) and IL-8 (CXCL8) [20,21]. IL-17 can also stimulate the production of the chemokines CCL2 (MCP1), CCL3 (MIP-1 α), CCL7 (MCP3) and CCL20 (MIP-3a) that can recruit inflammatory cells including macrophages and lymphocytes [20,21]. The proinflammatory cytokines IL-6 and TNF- α can be induced by IL-17 [20,21]. IL-17 can cause tissue damage by up-regulating matrix metalloproteinases (MMPs) [20,21]. These findings indicate that IL-17 is a potent pro-inflammatory cytokine with the capacity to induce the production of inflammatory and tissue-damaging molecules. Of interest, increased levels of IL-17 have been found in various immune-mediated inflammatory diseases including SLE, multiple sclerosis (MS) and psoriasis, suggesting the potential role for IL-17 in autoimmunity [21].

Cell surface molecules associated with human Th17 cells

Human Th17 cells have unique cell surface molecules. Human Th17 cells express high levels of the chemokine receptors CCR4 and CCR6 as well as CD161, a natural killer (NK) cell-associated molecule in humans [22,23]. Also, an increased expression of IL-1 receptor I (IL-1RI) on human Th17 cells has been reported [24]. Human memory CD4⁺ T cells with the expression of CCR4 and CCR6 selectively produced IL-17 and expressed the transcription factor RORC (human ortholog of ROR γ t) [23]. CCR6 binds to CCL20 produced by Th17 cells [25]. This suggests that Th17 cells could further increase Th17 cell response via producing this chemokine. Human CD161⁺ memory CD4⁺ T cells had increased production of IL-17 compared to CD161[–] memory CD4⁺ T cells although it is

unknown whether this molecule has any physiologic function in inducing Th17 cell response [23]. Of interest, human memory CD4⁺ T cells with the expression of IL-1RI produced increased levels of IL-17 in response to TCR triggering and IL-1 β compared to memory CD4⁺ T cells without the expression of IL-1RI [24]. Similarly, human naïve CD4⁺ T cells with the expression of IL-1RI produced IL-17 in response to a combination of IL-1 β and TCR triggering while the same cells without the expression of IL-1RI could not produce this cytokine. This is an intriguing observation since previous studies reported the requirement of multiple cytokines including TGF- β for the induction of IL-17 from human and mouse naïve CD4⁺ T cells [26]. Although these cell surface molecules are useful in identifying Th17 cells, none of them could identify a pure population of Th17 cells.

IL-17 and Th17 cells in lupus

Although CD4⁺ T cells appear to be essential in the development of lupus in mice and humans, it is still unresolved which type of Th cells plays a dominant role. Before the era of Th17 cells, the overproduction of Th1 and Th2 including IFN- γ and IL-4 was reported in patients with SLE [27–30]. However, recent data from human and murine studies clearly suggest the role of IL-17 and Th17 cells in lupus pathogenesis. Patients with SLE, including those with new-onset SLE, had increased plasma or serum levels of IL-17 [27,31–36]. In some studies, levels of this cytokine in the circulation correlated with disease activity [31,34]. Also, such cytokine levels were even higher in lupus patients with nephritis than in those without nephritis [36]. Different types of immune cells can produce IL-17. These cells are CD4⁺ T cells, CD8⁺ T cells and $\gamma\delta$ -T cells as well as CD3⁺CD4[−]CD8[−] (double negative or DN) T cells and NK cells [37–40]. Thus, it is possible that increased IL-17 levels in the blood of patients with SLE could be secondary to enhanced IL-17 production from different types of immune cells. In fact, several independent studies reported that patients with SLE had an increased frequency of IL-17-producing CD4⁺ T cells in peripheral blood which correlated with disease activity [36,41,42]. Also, the frequency of CD4⁺ T cells that expressed the Th17-associated chemokine receptors CCR4 and CCR6 was higher in lupus patients compared to healthy controls [41]. Furthermore, the frequency of CCR4⁺CCR6⁺ CD4⁺ T cells correlated with disease activity [41]. In addition to CD4⁺ T cells, lupus patients had expansion of DN T cells and CD3⁺CD8[−] T cells that produced high amounts of IL-17 compared to healthy controls [40,43]. In consistence with human studies, increased expression of IL-17 was found in DN T cells from lupus-prone MRL/*lpr* mice [44]. Taken together, patients with SLE have increased IL-17 production from different T cell subsets including CD4⁺ and DN T cells.

It is still unknown why lupus patients have an increased frequency of IL-17-producing T cells. This could be secondary to enhanced Th function in general. In a study where lupus patients were found to have an increased frequency of CD3⁺CD8[−]IL-17⁺ T cells in blood, the patients also had increased *IFNG* gene expression in peripheral blood mononuclear cells (PBMCs) and higher serum levels of the same cytokine compared to healthy controls [43]. However, it was not clear whether this finding was secondary to increased IFN- γ production from CD4⁺ T cells and/or other immune cells in that IFN- γ are produced by different types of immune cells. We recently measured the frequency of Th1 and Th17 cells in the peripheral blood of lupus patients and healthy controls. In this study, lupus patients had an increased frequency of Th17 cells but not Th1 cells compared to healthy controls [41]. Of interest, the frequency of IL-17-producing Th17 cells directly correlated with the frequency of IFN- γ -producing Th1 cells in healthy controls. However, a similar correlation was not found in lupus patients. We also analyzed the ratio of CD4⁺ T cells producing IL-17 to the same cells producing IFN- γ since patients with SLE could have an increased frequency of both cell subsets without an alteration in the Th17/Th1 ratio [41]. Indeed, the ratio of Th17 to Th1 cells was higher in patients with SLE than in healthy controls. These findings

indicate that an aberrant CD4⁺ T cell response occurs in lupus, resulting in a propensity toward an increased frequency of Th17 cells [41]. The cytokine environment is essential for Th17 cell differentiation. Thus, it is possible that the increased Th17 cell response in lupus is driven by enhanced Th17 cell-polarizing cytokines such as IL-23. Recent studies reported hyperproduction of IL-23 and expansion of IL-23 receptor-positive CD4⁺ T cells in the peripheral blood of lupus patients [31,45]. In lupus prone MRL/*lpr* mice, increased IL-23 receptor expression was found in lymph node T cells [44]. Furthermore, lymph node cells from these mice treated with IL-23 induced nephritis upon the transfer to non-autoimmune lymphocyte-deficient Rag-1 mice [44].

Although patients with SLE have increased IL-17 production, the role for this cytokine in lupus pathogenesis is yet to be defined. As discussed above, IL-17 can induce the production of an array of inflammatory molecules (e.g. cytokines, chemokines and MMP) from immune and non-immune cells, leading to the recruitment and activation of inflammatory cells with tissue damage. Studies with murine lupus models reported the presence of IL-17-producing T cells including DN T cells and CD4⁺ T cells in the kidneys [43,44,46]. The deficiency of the receptor for IL-23 that promoted Th17 cell differentiation prevented the development of nephritis in lupus mice [46,47]. Similarly, lupus patients had increased expression of IL-17 and DN T cells in the kidneys [40,48]. In the urine sediments from lupus patients, increased expression of the *IL17* gene was found [49]. These findings suggest that IL-17 could be responsible for inflammatory tissue damage in lupus nephritis. IL-17 can promote humoral immunity that plays a major role in lupus pathogenesis. IL-17 alone or in combination with BAFF increased the survival and proliferation of human B cells as well as the differentiation of B cells into antibody-producing cells [32]. In autoimmune BXD mice, blocking IL-17 signaling reduced the development of germinal center B cells and production of autoantibodies including anti-dsDNA antibodies [50]. Thus, IL-17 could promote inflammation in lupus by affecting both cellular and humoral immunities.

Conclusions

Th17 cells are a recently identified subset of CD4⁺ T cells. Having the capacity to produce potent pro-inflammatory cytokines including IL-17, this cell subset likely has an important role in autoimmunity. Studies provide a body of evidence that lupus patients have increased Th17 cell response that correlates with disease activity. In addition, IL-17 is shown to induce inflammation, tissue damage and production of autoantibodies which are essential components of lupus pathogenesis. These findings clearly raise the possible pathogenic role for IL-17 in lupus. However, additional studies are needed to find out the mechanisms for increased Th17 cell response and the therapeutic implication of targeting IL-17 in SLE.

Acknowledgments

This work was supported in part by grants from the National Institutes of Health (U19 AI082713, AT 005241, AI082713, AG028069, AG030834 all to IK; UL1 RR024139 to Yale Center for Clinical Investigation). Insoo Kang is a participant in the World Class University Program of Republic of Korea.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

*of special interest

**of outstanding interest

1. Kang, I.; Craft, J. The immunology of systemic lupus erythematosus in the autoimmune diseases. In: Rose, NR.; MacKay, IR., editors. *The Autoimmune Diseases*. 4. Elsevier; 2006. p. 357-368.
2. Ahmed S, Anolik JH. B-cell biology and related therapies in systemic lupus erythematosus. *Rheum Dis Clin North Am*. 2010; 36:109–130. [PubMed: 20202594]
3. Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol*. 2006; 6:823–835. [PubMed: 17063184]
4. Palmer MT, Weaver CT. Autoimmunity: increasing suspects in the CD4+ T cell lineup. *Nat Immunol*. 2010; 11:36–40. [PubMed: 20016508]
5. Dong C. TH17 cells in development: an updated view of their molecular identity and genetic programming. *Nat Rev Immunol*. 2008; 8:337–348. [PubMed: 18408735]
6. Murphy KM, Stockinger B. Effector T cell plasticity: flexibility in the face of changing circumstances. *Nat Immunol*. 2010; 11:674–680. [PubMed: 20644573]
7. Chen Z, O'Shea JJ. Regulation of IL-17 production in human lymphocytes. *Cytokine*. 2008; 41:71–78. [PubMed: 17981475]
8. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat Immunol*. 2007; 8:942–949. [PubMed: 17676045]
9. Mangan PR, Harrington LE, O'Quinn DB, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature*. 2006; 441:231–234. [PubMed: 16648837]
10. Sutton C, Brereton C, Keogh B, et al. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J Exp Med*. 2006; 203:1685–1691. [PubMed: 16818675]
11. Zhou L, Ivanov, Spolski R, et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol*. 2007; 8:967–974. [PubMed: 17581537]
12. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med*. 2005; 201:233–240. [PubMed: 15657292]
13. Nurieva R, Yang XO, Martinez G, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature*. 2007; 448:480–483. [PubMed: 17581589]
14. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol*. 2010; 28:445–489. [PubMed: 20192806]
15. Usui T, Preiss JC, Kanno Y, et al. T-bet regulates Th1 responses through essential effects on GATA-3 function rather than on IFNG gene acetylation and transcription. *J Exp Med*. 2006; 203:755–766. [PubMed: 16520391]
16. Lazarevic V, Chen X, Shim JH, et al. T-bet represses T(H)17 differentiation by preventing Runx1-mediated activation of the gene encoding RORgammat. *Nat Immunol*. 2011; 12:96–104. [PubMed: 21151104]
17. Harrington LE. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nature Immunol*. 2005; 6:1123–1132. [PubMed: 16200070]
18. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol*. 2009; 9:556–567. [PubMed: 19575028]
19. Ishigame H, Kakuta S, Nagai T, et al. Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses. *Immunity*. 2009; 30:108–119. [PubMed: 19144317]
20. Gaffen SL. An overview of IL-17 function and signaling. *Cytokine*. 2008; 43:402–407. [PubMed: 18701318]
21. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. *Immunology*. 2010; 129:311–321. [PubMed: 20409152]
22. Cosmi L, De Palma R, Santarlasci V, et al. Human interleukin 17-producing cells originate from a CD161+CD4+ T cell precursor. *J Exp Med*. 2008; 205:1903–1916. [PubMed: 18663128]
23. Acosta-Rodriguez EV, Rivino L, Geginat J, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol*. 2007; 8:639–646. [PubMed: 17486092]

- 24*. Lee WW, Kang SW, Choi J, et al. Regulating human Th17 cells via differential expression of IL-1 receptor. *Blood*. 2010; 115:530–540. Naive and memory CD4+ T cells with and without the expression of IL-1 receptor I were found in the circulation of healthy humans. Cells with the expression of IL-1 receptor I produced increased levels of IL-17 compared to cells without the expression of this cytokine receptor. [PubMed: 19965648]
25. Hirota K. Preferential recruitment of CCR6-expressing TH17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J Exp Med*. 2007; 204:2803–2812. [PubMed: 18025126]
26. Manel N, Unutmaz D, Littman DR. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgamma. *Nat Immunol*. 2008; 9:641–649. [PubMed: 18454151]
27. Wong CK, Ho CY, Li EK, Lam CW. Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. *Lupus*. 2000; 9:589–593. [PubMed: 11035433]
28. Masutani K, Akahoshi M, Tsuruya K, et al. Predominance of Th1 immune response in diffuse proliferative lupus nephritis. *Arthritis Rheum*. 2001; 44:2097–2106. [PubMed: 11592372]
29. Csiszar A, Nagy G, Gergely P, et al. Increased interferon-gamma (IFN-gamma), IL-10 and decreased IL-4 mRNA expression in peripheral blood mononuclear cells (PBMC) from patients with systemic lupus erythematosus (SLE). *Clin Exp Immunol*. 2000; 122:464–470. [PubMed: 11122256]
30. Akahoshi M, Nakashima H, Tanaka Y, et al. Th1/Th2 balance of peripheral T helper cells in systemic lupus erythematosus. *Arthritis Rheum*. 1999; 42:1644–1648. [PubMed: 10446863]
- 31*. Wong CK, Lit LC, Tam LS, et al. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: Implications for Th17-mediated inflammation in auto-immunity. *Clin Immunol*. 2008; 127:385–393. Patients with SLE had increased levels of IL-17 and IL-23, a cytokine known to promote Th17 polarization, in plasma compared to healthy controls. [PubMed: 18373953]
- 32*. Doreau A, Belot A, Bastid J, et al. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. *Nat Immunol*. 2009; 10:778–785. This work that demonstrated the promotion of humoral immunity by IL-17 provides a possible explanation of how IL-17 could be involved in lupus pathogenesis. [PubMed: 19483719]
33. Zhao XF, Pan HF, Yuan H, et al. Increased serum interleukin 17 in patients with systemic lupus erythematosus. *Mol Biol Rep*. 2010; 37:81–85. [PubMed: 19347604]
34. Chen XQ, Yu YC, Deng HH, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. *J Clin Immunol*. 2010; 30:221–225. [PubMed: 20107878]
35. Cheng F, Guo Z, Xu H, et al. Decreased plasma IL22 levels, but not increased IL17 and IL23 levels, correlate with disease activity in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2009; 68:604–606. [PubMed: 19286907]
36. Xing Q, Wang B, Su H, et al. Elevated Th17 cells are accompanied by FoxP3+ Treg cells decrease in patients with lupus nephritis. *Rheumatol Int*. 2011 Epub ahead of print.
37. Louten J, Boniface K, de Waal Malefyt R. Development and function of TH17 cells in health and disease. *J Allergy Clin Immunol*. 2009; 123:1004–1011. [PubMed: 19410689]
38. Ortega C, Fernandez AS, Carrillo JM, et al. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. *J Leukoc Biol*. 2009; 86:435–443. [PubMed: 19487306]
39. Kondo T, Takata H, Matsuki F, Takiguchi M. Cutting edge: Phenotypic characterization and differentiation of human CD8+ T cells producing IL-17. *J Immunol*. 2009; 182:1794–1798. [PubMed: 19201830]
- 40*. Crispin JC, Oukka M, Bayliss G, et al. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J Immunol*. 2008; 181:8761–8766. This study reported the expansion of IL-17-producing CD3+CD4–CD8– (double negative) T cells in patients with SLE. In addition, the infiltration of this cell subset was found in the kidneys of patients with SLE. [PubMed: 19050297]

- 41*. Shah K, Lee WW, Lee SH, et al. Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. *Arthritis Res Ther*. 2010; 12:R53. Patients with SLE had an increased frequency of IL-17-producing Th17 cells but not IFN- γ -producing Th1 cells in blood compared to healthy controls, suggesting a dysregulated balance of Th17 and Th1 cells in lupus. Furthermore, the frequency of Th17 cells correlated with disease activity and the frequency of CD4+CCR4+CCR6+ T cells. [PubMed: 20334681]
42. Dolff S, Quandt D, Wilde B, et al. Increased expression of costimulatory markers CD134 and CD80 on interleukin-17 producing T cells in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2010; 12:R150. [PubMed: 20653937]
- 43*. Yang J, Chu Y, Yang X, et al. Th17 and natural Treg cell population dynamics in systemic lupus erythematosus. *Arthritis Rheum*. 2009; 60:1472–1483. Patient with SLE had an increased frequency of CD3+CD8– T cells that produced IL-17 compared to healthy controls. The frequency of this cell subset correlated with disease activity. [PubMed: 19404966]
44. Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. *J Immunol*. 2009; 183:3160–3169. [PubMed: 19657089]
- 45*. Puwiprom H, Hirankarn N, Sodsai P, et al. Increased interleukin-23 receptor(+) T cells in peripheral blood mononuclear cells of patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2010; 12:R215. This study showed an increased frequency of IL-23 receptor-positive T cells in lupus patients. [PubMed: 21110900]
- 46*. Kyttaris VC, Zhang Z, Kuchroo VK, et al. Cutting edge: IL-23 receptor deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice. *J Immunol*. 2010; 184:4605–4609. This work demonstrated that IL-23 receptor-deficient lupus-prone C57BL/6-lpr/lpr mice had decreased numbers of IL-17-producing cells in the lymph nodes, with improved nephritis. [PubMed: 20308633]
47. Kang HK, Liu M, Datta SK. Low-dose peptide tolerance therapy of lupus generates plasmacytoid dendritic cells that cause expansion of autoantigen-specific regulatory T cells and contraction of inflammatory Th17 cells. *J Immunol*. 2007; 178:7849–7858. [PubMed: 17548623]
48. Wang Y, Ito S, Chino Y, et al. Laser microdissection-based analysis of cytokine balance in the kidneys of patients with lupus nephritis. *Clin Exp Immunol*. 2010; 159:1–10. [PubMed: 19807734]
49. Kwan BC, Tam LS, Lai KB, et al. The gene expression of type 17 T-helper cell-related cytokines in the urinary sediment of patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2009; 48:1491–1497. [PubMed: 19773408]
50. Hsu HC, Yang P, Wang J, et al. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. *Nat Immunol*. 2008; 9:166–175. [PubMed: 18157131]

Key points

- Th17 cells produce IL-17 that can induce the production of inflammatory molecules and promote humoral immunity.
- Th17 cells and IL-17 may play a role in the pathogenesis of SLE in that patients with SLE have increased levels of IL-17 and expansion of IL-17-producing T cells in the circulation and target organs like the kidneys.
- Further studies are required to determine the mechanisms for increased Th17 cell response and therapeutic benefits of blocking IL-17 in SLE.