

# Interleukin 23 as a Treatment Target in Systemic Lupus Erythematosus

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Although the etiology of systemic lupus erythematosus (SLE) remains largely unknown, several studies have described the mechanisms that mediate tissue injury [1]. Both immune cell tissue infiltration and immune complex deposition lead to the severe and sometimes permanent organ damage. T cells, both helper and cytotoxic T cells, play a central role in this process as they fail to properly regulate the immune response while at the same time provide inappropriate help to autoreactive B cells and infiltrate target tissues [2]. Hence, SLE T cells represent a proper therapeutic target. Classically, T helper (Th) cells were thought to fall into two categories Th1 or Th2, based on the type of cytokines they produce once activated. Th1 cells provide a milieu for cell mediated toxic responses whereas Th2 favor antibody driven humoral immunity. Beyond this strict Th1/Th2 paradigm, T cells can acquire several pro- or counter-inflammatory (regulatory) phenotypes. Th17 cells represent such a committed T cell subset that is characterized by the expression of the transcription factor ROR $\gamma$ t and the production of the signature cytokine IL-17. IL-22, IL-21, IL-10, GM-CSF are also produced by Th17 cells, making these cells potent mediators of the inflammatory responses [3]. Several studies have established that Th17 cells are essential for the propagation of the immune response in preclinical models of autoimmune diseases. Moreover, studies from humans with autoimmune diseases have shown that Th17 cells may play a significant role in a variety of diseases such as psoriasis [4], Crohn's [5], multiple sclerosis [6] and rheumatoid arthritis [7].

Recent studies have implicated Th17 in the pathogenesis of SLE. Crispin et al. [8] found IL-17 producing T cells in kidney biopsies of patients with lupus nephritis. Of note, many of these IL-17+ CD3+ T cells were CD4-CD8-, part of the expanded double negative T cell population in SLE. Circulating CD4+ as well as CD4-CD8- cells from SLE patients were capable of producing IL-17 when tested *in vitro*, suggesting that Th17 cells home to the kidney of patients with lupus nephritis. Several other studies have confirmed the increased presence of IL-17+ T cells [9] and increased levels of IL-17 [10] in the peripheral blood of SLE patients. The mechanisms that lead to the overproduction of IL-17 by T cells in SLE as well as their exact role remain unclear to date. Th17 cells differentiate from naïve Th0 cells in the presence of conditioning cytokines, most notably IL-6, transforming growth factor (TGF)- $\beta$ , IL-1 $\beta$  and IL-23. New evidence suggests that Th17 phenotype may differ depending on whether TGF- $\beta$  or IL-23 are present; more precisely, Th17 cells may acquire a more "regulatory" profile in the presence of TGF- $\beta$  vs, a more "inflammatory" profile in the presence of IL-23 [11]. Pro-inflammatory Th17 cells produce besides IL-17, IFN- $\gamma$ , IL-22 and GM-CSF that mediate inflammatory tissue damage. Hence we asked the question whether interleukin-23 is increased in SLE and whether it plays a role in disease pathogenesis by supporting a pro-inflammatory Th17 population. Indeed MRL/lpr lupus prone mice, that develop spontaneously nephritis, were found to have a significant population of both CD4+ and CD4-CD8- T cells in the spleen and lymph nodes that produce IL-17 and express the receptor for IL-23 [12]. Similarly to patients with SLE IL-17+ T cells were also found in the kidneys of these mice that had already developed nephritis. To assess the pathogenicity of these Th17 cells, we then took splenocytes from MRL/lpr mice and injected them in otherwise

healthy lymphopenic mice. Only MRL/lpr splenocytes activated and conditioned *in vitro* with IL-23, were able to cause nephritis upon transfer to healthy mice, suggesting that IL-23 supported Th17 cells play a role in the pathogenesis of murine lupus nephritis. To study the pathogenic importance of IL-23 driven Th17 cells, we crossed lupus prone B6/lpr mice with B6 mice that lacked the IL-23 receptor (IL-23R) [13]. These B6/lpr IL23R-/- mice did not develop lymphadenopathy, splenomegaly, pathogenic autoantibodies and nephritis as the wild type B6/lpr mice did. Of note, in the absence of IL-23R, the double negative T cell population did not expand, suggesting that IL-23 may play a role in the generation and/or maintenance of this T cell population. The aforementioned observational studies in patients with SLE and the experiments using murine lupus models suggest that Th17 cells are important instigators of tissue damage. IL-23 is a key cytokine in the generation and commitment of Th17 cells and therefore represents an attractive treatment target. Nevertheless, although IL-23 is key in the initiation of the disease, at least in murine lupus, its role once the inflammation is established is less well understood. As new drugs targeting IL-23 are being developed, it is imperative to clarify the exact role of IL-23 in SLE pathophysiology in order to design appropriately clinical trials.

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