

# T helper cells: Top targets for systemic lupus erythematosus treatment?

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In the original research article, Parisa R et al. demonstrated that the induction of lupus-like autoimmune syndrome in BALB/c Mice caused disturbance in splenic T cell subpopulations. This study also elucidated those other mechanisms, apart from disturbance in T cells balance, may be responsible for the development of the disease's symptoms [1].

The underlying mechanisms of systemic lupus erythematosus (SLE) are not clearly known [2]. SLE is a complex relapsing-remitting autoimmune disease characterized by impaired clearance of apoptotic cells, an interferon (IFN) gene expression signature in peripheral lymphocytes, and the breakdown of the peripheral tolerance mechanisms [3]. Notably, failure of immunological tolerance results in the generation of autoantibodies that damage tissues and organs, including the kidneys [4].

Excellent reports were provided covering a wide spectrum of research that show T cells play a major role in SLE pathogenesis; by amplifying inflammation via the secretion of pro-inflammatory cytokines, supporting autoantibodies production by B cells, and sustaining the disease through the accumulation of autoreactive memory T cells [5-7]. Therefore, in recent years the role of T cell subsets in SLE pathology has come into the limelight and the molecular pathways involved in their aberrant differentiation, as well as their varied metabolic needs have gained prominence [8-11].

T cells can be divided into lineages; T helper cells, including Th1 (IFN- $\gamma$ ), Th2 (IL-4, IL-6, and IL-10), Th17 (IL-17), and regulatory T cells (Tregs) which produce IL-10 and TGF- $\beta$  [12]. T-cell subsets are vital cell populations in the immune system, and there is an interplay amongst different subsets [13]. It is important to note that coordinated interaction of T cell subsets, fine tune immune responses in various conditions [14]. Accordingly, deregulated levels of Th1, Th2, Th17, and Tregs cytokines have been associated with autoimmune inflammation [15-18]. Of note, different subsets of T cells have been shown to be involved in the pathogenesis of SLE, including Th1, Th2, Th17, and CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> (so-called "double-negative" T cells [6,12,19]. In addition, the regulatory role of Tregs is widely accepted in the SLE disease context [6,12,20]. In Parisa R et al. study, in order to draw a correlation between the distribution of T cell subpopulation and SLE disease activity, SLE-like syndrome was induced in BALB/c mice. As previously mentioned, the hallmark of SLE is plentiful supply of nuclear antigens from different apoptotic cells. During this process dsDNA is exposed on the surface of apoptotic blebs, which could activate autoreactive T cells [21]. Hence, in order to modify DNA and induce SLE in mice, Concanavalin A (Con A) and/or polyamines were used. To evaluate SLE disease activity, proteinuria, anti-dsDNA, and antinuclear antibody (ANA) levels were measured as a standard protocol. Interestingly, in comparison to the control group, all mice groups revealed significant manifestations of SLE disease (as shown by single-up arrow in the Figure 1).; however, the mice group received Con A and polyamines simultaneously (PA group), manifested more conspicuous signs of the disease (as shown by double-up arrow in the Figure 1). This indicates that a combination of polyamines and Con A procured a more potent immunogenic DNA. A feasible explanation for this might be structural changes in DNA by polyamines [22,23], in addition to DNA hypomethylation caused by Con A [24].

Next, T cell subpopulations were assessed in mice splenocytes. Results revealed that the expression of Foxp3 mRNA level was down-regulated in all groups and this decrease was particularly significant in the Con A- group [1].

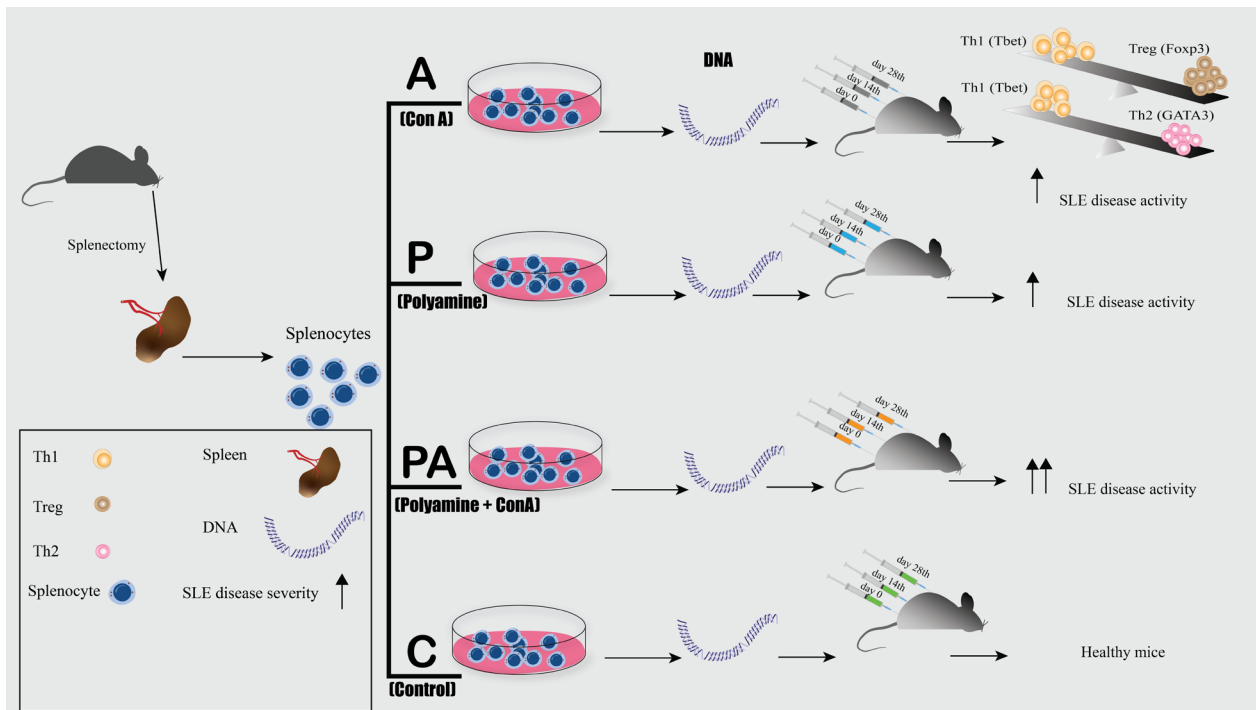
Normally, to maintain immune tolerance, the development of effector T cells is in balance with

that of Tregs [25]. An imbalance among cell populations engenders autoimmune response as observed in SLE patients [13]. Evidence from patients have shown that SLE has an impact on both the Th1/Th2 and the Th17/Treg paradigm [7,26,27]. Consequently, this imbalance may contribute to immune pathology [28]. Consistent with the previous reports, Parisa R et al. also observed an imbalance in T cell ratios. Most notably, their results maintained that the ratio of T-bet/GATA3 and T-bet/foxp3 mRNA levels were increased in Con A group in comparison to other groups indicating a disequilibrium in favor of Th1 subsets [1] (Figure 1). Parisa R et al. findings are in accordance with previous data that show T-bet<sup>hi</sup>Foxp3<sup>lo</sup> non-suppressor cells (IFN- $\gamma$ -producing) are abundant in SLE and T-bet<sup>hi</sup>Foxp3<sup>hi</sup> activated Treg cells (non-IFN- $\gamma$ -producing) have insufficient levels [29].

Prominently, Con A by stimulating the differentiation of T cells leads to an alteration in the secretion of inflammatory mediators in mice, including IL-4, IFN- $\gamma$ , IL-17A, and TGF- $\beta$ . Consequently, changes in the expression levels of these cytokines could lead to the imbalance of Th1, Th2, Th17, and Treg immune cells [13]. Therefore, it can be speculated that reduction of Foxp3-expressing T cells might influence the level of Tbet-expressing T cells, and thereby Th1/Th2 and Th1/Treg ratios. Accordingly, alteration in the Th1/

Th2 and Th1/Treg ratios might results from a significant decrease in the Tregs level, concomitant with an increase in Th1 subsets in group A. Another possible mechanism might be the alteration of T cell metabolic pathways in SLE patient [30]. In fact, the balance between Th and Treg cells, and the mechanisms controlling their balance, including immune-metabolism, is currently of great importance. Above all, Iwata et al. investigated fatty acid synthesis in T cells from SLE patients, and identified alterations in Th1 subsets of SLE patients and their involvement in disease pathology [29]. Notably, metabolic changes have significant repercussions on the number of these subsets, which means, in SLE, metabolic abnormalities, such as enhanced fatty acid synthesis, contribute to the overproduction of IFN- $\gamma$  by Th1 cells and an imbalance of Th1 subsets [6, 30].

Most importantly, growing evidence has shown deregulated levels of Th and Tregs cytokines in SLE patients associated with disease activity and severity [28]. Foxp3 is essential for Treg suppressive and regulatory function [31]. These cells play crucial roles in restraining effector function of T cells and controlling inflammation and autoimmune diseases [32-34]. Treg suppress SLE and effectively induce autoimmune tolerance [35,36]. It is generally believed that defective regulatory mechanisms of Tregs might allow harmful Th1-driven immune response develops [37-39]. In tandem, in



**Figure 1: Schematic overview of the research process.** Mice splenocytes cultured in four conditions. The first condition involved stimulation with Con A (5  $\mu$ gr/mL) for 48 hr (group A), the second with 20  $\mu$ mol/L of each of Polyamines (Putrescine, Spermine, and Spermidine) for 18 h (group P), the third group was stimulated with both Con A and Polyamines at the same concentration level and time as mentioned (group PA) and the fourth group was left without stimulation as the control group. Then, splenocytes were harvested and DNA was extracted. Syngeneic BALB/c mice were divided into four groups (n=7) and were actively immunized by subcutaneous injection on the back with an emulsion containing 50  $\mu$ gr of DNA in 100  $\lambda$  phosphate-buffered saline PBS plus 100  $\lambda$  complete Freund's adjuvant. Initial immunization was performed on day 0. Mice were boosted on day 14 and 28. Two weeks after their last immunization, the mice were sacrificed. SLE development and T cells distribution were assessed in mice. To evaluate SLE disease activity, proteinuria, anti-dsDNA, and antinuclear antibody (ANA) levels were measured as a standard protocol. The level of proteinuria in PA, P, and A groups were significantly higher than in the control group (SLE activity indicated by single-up arrow). SLE disease activity was significantly higher in the PA group (shown by double-up arrow); however, T cell disturbance was observed more in the group A (As shown by balance scale diagram). All groups were compared to the control group (splenocytes only).

accordance to various studies on the imperative role of Th1 cells in SLE development and progression, we expected to have more signs of SLE disease in Con A group; however, our finding differed from those studies. This suggests that mechanisms other than disturbance in T cells balance may have contributed to the development of disease symptoms. Noteworthy is that most researchers believe that active SLE is characterized by decreased function of Th1 [3]. This means that Th1 may play a protective role in the pathogenesis of SLE. Consistent with the above-mentioned statement, the presence of anti-interferon- $\gamma$  autoantibodies was associated with higher clinical SLE disease activity [40,41], which underestimate the role of Th1 and IFN- $\gamma$  in SLE development.

In contrast with other studies that have demonstrated important role of Th17 in SLE activity [42], Parisa et al. revealed that PA group had the lowest Th17/Treg (ROR  $\gamma$ t/ FOXP3) ratio amongst different groups and Th17/Treg ratio was increased in group A and B, though the differences were statistically insignificant. A possible explanation for this might be the generation of non-pathogenic Th17 cell generation [43].

Consistent with this IL-17A-deficient lupus-prone mice and animals treated with anti-IL-17A antibodies still developed lupus [6].

In general, these results show controversy regarding the role of Th1 and Th17 in SLE development and warrant further study in order to uncover specific therapeutic targets for controlling SLE. For this reason, care must be taken while applying therapies that target T cells.

### Author Contributions

HN and FP wrote the first draft of the commentary. This was revised by FR with valuable comments and suggestions. All authors contributed to the article and approved the submitted version.

### Conflict of Interest

The authors declare no conflict of interest.

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