Review

Recovery of the immune balance between Th17 and regulatory T cells as a treatment for systemic lupus erythematosus

Ji Yang1*, Xue Yang2,3*, Hejian Zou2,3*, Yiwei Chu4 and Ming Li1

Abstract

The Th17 lineage, a lineage of effector CD4+ T cells, is characterized by the production of IL-17. Expansion of Th17 cells has been implicated in a growing list of autoimmune disorders. Our studies, as well as others, have shown that Th17 cells play a key role in the pathogenesis of SLE. Therefore, some investigators advocate that Th17 cells are a promising therapeutic target for SLE. However, neutralization of IL-17 in vivo actually aggravated inflammation by inducing infiltration of other effector cells. Thus, the therapeutic effects of antagonizing Th17 cells for the treatment of SLE in the clinic are worth discussing. Moreover, in patients with SLE, the expansion of effector T cells is always closely related to the depletion and dysfunction of Treg cells. Therefore, we hypothesize that for the treatment of SLE, we should focus on therapeutic agents that can regulate the immune balance between Th17 and Treg cells rather than on those that exclusively regulate Th17 cells.

Key words: Th17, Treg, Balance, Therapeutic agents.

Introduction

A fine balance between effector T cells and Treg cells regulates immune homeostasis. However, in autoimmune diseases, the levels and functions of these cells are often disrupted. Th17 cells, a subset of effector CD4+ T cells, are identified based on their ability to produce IL-17A, IL-17F and IL-22 [1, 2]. These cells have become the focus of many immunity studies, with hundreds of studies characterizing their roles in promoting inflammation and autoimmunity [3-6]. Treg cells, in contrast, are capable of modulating the function of effector T cells, maintaining immunological homeostasis, and preventing autoimmunity [7, 8]. Although the immunological mechanism of SLE remains unclear, accumulating studies confirm that the expansion of Th17 cells and the dysfunction or depletion of Treg cells are closely related to the pathogenesis of SLE [6, 9-16].

Evidence that Th17 cells play a role in SLE

Previous studies have confirmed that IL-17 concentrations are elevated in patients with SLE [16-19]. Meanwhile, IL-17 acts in synergy with B-cell-activating factor (BAFF) to promote B-cell differentiation and autoantibody production [20, 21]. Th17 cells can infiltrate the skin, lungs and kidneys of SLE patients [16, 22, 23]. Furthermore, our previous study showed that SLE flares might be linked to the expansion of Th17 cells, as Th17 cells are involved in vascular inflammation. Antagonism of Th17 cells with IL-17-blocking antibodies could relieve the IL-17-mediated vascular inflammation in vitro [16]. The number of Th17 cells is increased in lupus-prone mouse models, including BXD2 [24], SNF1 [25], NZB x NZW F1 [26] and Ro52 knockout mice [27]. Previous studies, including our own, showed expansion of Th17 cells in MRL/lpr mice [16, 28, 29]. Together, these data suggest that Th17 cells may play a key role in the pathogenesis of SLE [19]. Some investigators have suggested that antagonism of Th17 cells is a promising therapeutic method for the treatment of SLE [30, 31]. However, the known therapeutic effects of Th17-cell antagonism for the treatment of SLE in the clinic are minimal.

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Imbalance between Th17 and Treg cells in SLE

Several studies have confirmed decreased numbers and deficient functions of Treg cells in SLE patients [10, 11, 16, 32, 33]. These results suggest that strategies to enhance the number and function of these cells might benefit patients with SLE. In our previous study, we demonstrated that the increase in Th17 cells is directly correlated with the depletion of Treg cells during SLE flares [16]. Previous studies showed that Treg and Th17 cells expand in a mutually exclusive fashion, depending on the activation factors present [34, 35]. TGF-β induces the differentiation of Treg cells, whereas TGF-β in combination with IL-6 results in the differentiation of Th17 cells [36, 37]. The local cytokine environment is a determining factor in the reciprocal development of Th17 and Treg cells [34, 35, 38, 39]. In the steady state, Th17 and Treg cells may remain in a dynamic balance just like the Yin and Yang in traditional Chinese medicine (Fig. 1). This balance is destroyed in autoimmune diseases such as SLE [15, 16, 25]. Thus, it is necessary to repair the immune balance by suppressing the number and function of Treg cells.

Regulation of Th17-cell differentiation by cytokines

The differentiation of Th17 cells is initiated by TGF-β and IL-6 and requires IL-23 [35]. Specifically, TGF-β and IL-6 function together to induce Th17-cell differentiation from naive precursors, as both cytokines are necessary for the up-regulation of IL-23R expression [39]. Subsequently, IL-23 induces the expansion of previously differentiated Th17 cell populations [40]. Additionally, TNF-α, IL-1 and IL-9 can further enhance Th17 cell differentiation in the presence of TGF-β and IL-6 [41-44]. IL-21 is not only expressed by Th17 cells, but can also regulate the differentiation of Th17 cells [45, 46]. Although these cytokines can induce the differentiation of Th17 cells, other cytokines in the immune system can negatively regulate Th17 cells, including IL-27, IL-2, IL-25, IL-4 and INF-γ [1, 2, 47-49]. Although there are cytokines that positively or negatively regulate Th17-cell differentiation, little is known about therapeutic agents that can modulate Th17-cell differentiation based on the regulation of these pro- or anti-inflammatory cytokines.

Regulation of Th17-cell differentiation by transcription factor

It was previously demonstrated that neither Th1-cell- nor Th2-cell-associated transcription factors are required for Th17-cell differentiation [50]. However, great progress has been made in identifying positive and negative regulatory transcriptional factors required for the differentiation of Th17 cells (Table 1). Retinoic acid-receptor-related orphan receptor-γt (RORγt), signal transduction and activator of transcription 3 (STAT3), aryl hydrocarbon receptor (AHR), INF regulatory factor 4 (IRF4), B-cell-activating transcription factor (BATF), epidermal fatty acid-binding protein (E-FABP) and src-homology 2-containing inositol 5’ phosphatase (SHIP) can positively mediate Th17 lineage commitment [51-59]. IL-6 and TGF-β together induce RORγt expression and Th17-cell differentiation [53]. At low concentrations, TGF-β synergizes with IL-6 to promote Th17-cell differentiation. However, high concentrations of TGF-β favour forking box p3 (Foxp3) Treg cells and up-regulation of Foxp3 might further inhibit RORγt activity [39] (Fig. 2). AHR activation by its ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces functional Treg cells that suppress experimental autoimmune encephalomyelitis (EAE).

![Fig. 1 Schematic representation of the immune balance between Treg and Th17 cells.](image)

**TABLE 1** Positive and negative regulatory transcription factors of Th17-cell generation

<table>
<thead>
<tr>
<th>Transcription factor</th>
<th>Primary activators</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive transcription factors</td>
<td>TGF-β + IL-6</td>
<td>[53]</td>
</tr>
<tr>
<td>RORγt</td>
<td>TGF-β + IL-21</td>
<td>[57]</td>
</tr>
<tr>
<td>STAT3</td>
<td>TGF-β + IL-2</td>
<td>[63]</td>
</tr>
<tr>
<td>AHR</td>
<td>FICZ</td>
<td>[52]</td>
</tr>
<tr>
<td>IRF4</td>
<td>Not determined</td>
<td>[59]</td>
</tr>
<tr>
<td>BATF</td>
<td>Not determined</td>
<td>[55]</td>
</tr>
<tr>
<td>E-FABP</td>
<td>Not determined</td>
<td>[56]</td>
</tr>
<tr>
<td>SHIP</td>
<td>Not determined</td>
<td>[58]</td>
</tr>
<tr>
<td>Negative transcription factors</td>
<td>IFN-γ</td>
<td>[60]</td>
</tr>
<tr>
<td>T-bet</td>
<td>IL-2</td>
<td>[62]</td>
</tr>
<tr>
<td>Ets-1</td>
<td>IL-2</td>
<td>[63]</td>
</tr>
<tr>
<td>STAT5</td>
<td>IL-27</td>
<td>[47]</td>
</tr>
<tr>
<td>STAT1</td>
<td>IL-25</td>
<td>[61]</td>
</tr>
<tr>
<td>GATA3</td>
<td>TGF-β</td>
<td>[38]</td>
</tr>
<tr>
<td>Foxp3</td>
<td>TGF-β</td>
<td>[39]</td>
</tr>
<tr>
<td>SOCS3</td>
<td>IFN-β</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Not determined</td>
<td>[66]</td>
</tr>
<tr>
<td>AHR</td>
<td>TCDD</td>
<td>[5]</td>
</tr>
</tbody>
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www.rheumatology.oxfordjournals.org 1367
On the other hand, AHR activation by 6-formylindolo[3,2-b] carbazole (FICZ) interferes with Treg-cell development, boosts Th17-cell differentiation and increases the severity of EAE in mice [51, 52]. These data imply that the reciprocal differentiation of Th17 and Treg cells is controlled by specific transcription factors, or at least in a ligand-dependent fashion.

The differentiation of Th17 cells is also negatively regulated by other transcription factors. These transcription factors include T-box-containing protein expressed in T cells (T-bet) [60], GATA-binding protein 3 (GATA3) [61], E26 transformation specific-1 (Ets-1) [62], STAT5 [63], STAT1 [47], suppressors of cytokine signalling 3 (SOCS3) [64, 65], peroxisome proliferators-activated receptor γ (PPARγ) [66] and Foxp3 [39].

In summary, these data have important implications for how the balance between Th17 and Treg cells is maintained in the presence of pro- and anti-inflammatory cytokines and the activation of positive and negative transcription factors.

**Regulation of Th17- and Treg-cell differentiation by therapeutic agents**

Currently, there are several reported therapeutic agents that may be able to regulate the reciprocal differentiation of Th17 and Treg cells (Table 2). Inhibition of EAE through TCDD-induced AHR activation was associated with a significant increase in T-reg-cell frequencies and decreased Th17-cell frequencies [51]. However, TCDD is very toxic in animal and human studies, and is far from clinical application in the treatment of autoimmune diseases.

The vitamin A metabolite all-trans-retinoic acid (RA) is capable of inhibiting the IL-6-driven induction of Th17 cells and promoting anti-inflammatory Treg-cell differentiation [34]. Recent study showed that RA enhances TGF-β signalling by increasing the expression and phosphorylation of Smad3. RA also inhibits the expression of IL-6Rα, IRF-4 and IL-23R, thus inhibiting Th17 development in vitro [67]. Additional studies confirmed that RA can relieve inflammatory diseases through regulation of the Th17 and Treg cell balance [68, 69]. These data indicate that a common metabolite can regulate the balance between pro- and anti-inflammatory immune responses. Rapamycin, a potent immunosuppressant, can inhibit differentiation of Th17 cells and promote the generation of Foxp3+ Treg cells in vitro [70]. However, corresponding in vivo studies have not been reported.

H471-94, a naturally occurring nucleosomal histone peptide epitope, when injected subcutaneously into lupus-prone mice, markedly increases the lifespan by inducing Treg-cell generation, and suppress inflammatory Th17 cells that infiltrate the kidneys of untreated mice with lupus [25]. However, H471-94 induces tolerogenic phenotype in a substantial fraction of dendritic cells (DCs), but does not directly induce Treg cells or suppress Th17 cells.

These data indicate that there are therapeutic agents that can regulate the balance of Th17 and Treg cells, and have the potential to treat autoimmune diseases.

**Table 2 Therapeutic agents for regulating the balance of Th17 and Treg cells**

<table>
<thead>
<tr>
<th>Therapeutic agents</th>
<th>Known functions</th>
<th>Mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Down-regulation of Th17-cell differentiation and up-regulation of Treg cells in vitro and in vivo</td>
<td>Inhibition of RORγt expression and promotion of Foxp3</td>
<td>[34, 67]</td>
</tr>
<tr>
<td>TCDD</td>
<td>Down-regulation of Th17-cell differentiation and up-regulation of Treg cells in vitro</td>
<td>Activation of AHR</td>
<td>[51]</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Down-regulation of Th17-cell differentiation and up-regulation of Treg cells in vitro</td>
<td>Not determined</td>
<td>[70]</td>
</tr>
<tr>
<td>H471-94</td>
<td>Down-regulation of Th17-cell differentiation and up-regulation of Treg cells in vivo</td>
<td>Induction of DCs to produce increased amounts of TGF-β, which controls the reciprocal development of Th17 and Treg cells.</td>
<td>[25]</td>
</tr>
</tbody>
</table>
such as SLE. However, it is important to explore not only effective, but also safe, therapeutic agents for the treatment of autoimmune diseases caused by an imbalance in Th17 and Treg cells.

Regulating the balance between Th17 and Treg cells for the treatment of SLE

As discussed above, both Th17 and Treg cells are involved in the pathogenesis of SLE as the dynamic balance between these cells is damaged in SLE patients [6, 11, 13, 15, 16, 71]. We hypothesize that restoring the immune balance between Th17 and Treg cells, rather than exclusively focusing on Th17 cells, will yield better results for the treatment of SLE (Fig. 3). This hypothesis is supported by the following experimental findings: (i) in the immune system, feedback regulators initiate and activate immune responses. Exclusive inhibition of Th17 cells may result in the expansion of other effector cells [72]. For example, neutralization of IL-17 aggravates colitis in mice with increased mucosal infiltration of CD4^+ T cells and monocytes [73], and absence of donor Th17 can lead to augmented Th1 differentiation and exacerbated acute graft-vs-host disease [74]. Thus, promoting the regulatory function of Treg cells to control secondary immune responses will benefit the patient by eliminating the inflammation caused by effector cells [75]. (ii) Although Th17 cells play a key role in the pathogenesis of SLE, Th1 and other effector cells also play important roles in the induction of SLE [17, 29, 76–78]. Therefore, antagonism of Th17 cells alone will not be enough to relieve the general activation of effector cells in SLE patients. (iii) Treg cells are powerful regulatory cells that can inhibit the function of Th17, Th1 and other effector cells; inhibit inflammation; and prevent autoimmunity [8, 79–81]. (iv) Previous studies have confirmed the ability of agents such as TCDD, rapamycin and RA to promote the conversion of Th17 to Treg cells [34, 51, 70]. This results in a concomitant decrease in Th17-cell differentiation and a subsequent immune balance between Th17 and Treg cells. Together, these data suggest that it may be possible to identify therapeutic agents that regulate the balance between Th17 and Treg cells for the treatment of SLE.

Conclusions

The potent pro-inflammatory activities of Th17 cells can explain a number of pathological features of SLE, such as the induction of vascular inflammation, recruitment of leucocytes, activation of B cells and autoantibody production [16, 20, 24]. Treg cells in SLE patients are deficient in number and in their ability to control the function of effector T cells. This results in a failure to maintain immunological homeostasis and attenuate autoimmune injuries [10, 11, 71]. Furthermore, there is evidence that Th17 and Treg cells arise in a reciprocal manner, depending on potentially pro- or anti-inflammatory cytokines and activation of specific transcription factors. Therefore, therapeutic agents that can regulate the immune balance between Treg (Yin) and Th17 (Yang) cells by modulating the pro- or anti-inflammatory cytokines and the specific transcription factors, may be promising choices for the treatment of SLE.

Rheumatology key messages

- The imbalance between Th17 and Treg cells contributes to the pathogenesis of SLE.
- Regulating the balance between Treg and Th17 cells may be a promising option for the treatment of SLE.

Acknowledgements

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