Systemic lupus erythematosus (SLE) is a T cell-dependent disorder of generalized autoimmunity characterized by B cell hyperactivity with numerous autoantibodies. Studies in both experimental animal models of lupus and patients with SLE have revealed a number of cytokine pathways that are important in the disease process. An imbalance between pro- and antiinflammatory cytokines might be responsible for the pathogenesis and development of SLE. For example, serum levels of interferon-α (IFN-α), tumor necrosis factor-α (TNF-α), IFN-γ, interleukin 1 (IL-1), IL-6, IL-18, and B cell activating factor are increased in patients with SLE in comparison with healthy individuals and have been shown to correlate with disease activity. Anticytokine and anti-cytokine receptor therapy have shown a significant decrease in disease activity in SLE and other autoimmune diseases, further suggesting that enhanced proinflammatory cytokines are associated with disease development. Conversely, a decreased ability of T cells to produce immunosuppressive cytokines such as transforming growth factor-β (TGF-β) has been reported. In contrast, IL-10 is another immunosuppressive cytokine whose level is actually elevated in active SLE. Although IL-10 can suppress T helper cell and dendritic cell responses, it has a strong stimulatory effect on B cells. This feature of IL-10 makes it deleterious in SLE development.

Despite the previous study documenting a decreased ability of SLE T cells to produce TGF-β, questions concerning the value of serum TGF-β in SLE pathogenesis and development remain unresolved. Many cells such as lymphocytes, monocytes, and natural killer (NK) cells can produce TGF-β and its biological half-life in serum is very short due to quick degradation to its inactive form. In fact, early studies revealed no significant differences of levels of bioactive TGF-β in serum between healthy control subjects and patients with inactive and active SLE. However, in their study in this issue of The Journal, Becker-Merok, et al provide new evidence that lower serum TGF-β levels may be the most consistent cytokine abnormality in SLE. They found that a lower TGF-β level correlates with disease activity, a reduction in CD4+, CD8+ and NK cell numbers, and severe organ damage in active SLE. The authors also demonstrated that decreased TGF-β level seems to be an intrinsic defect, since corticosteroid treatment did not interfere with its production in patients with active SLE. Their study provides not only a biomarker for the disease activity, but also a therapeutic target for patients with SLE.

The pivotal effects of TGF-β in immune regulation were revealed by the studies of mice with genetic deletion of this cytokine. These mice develop a rapidly progressive multiorgan inflammatory syndrome and die by 3 to 4 weeks of age. Transgenic mice with a dominant-negative TGF-βRII under a T cell-specific promoter, where TGF-β signaling was specifically blocked in T cells, exhibited a spontaneous T cell differentiation pathology and autoimmune disease. These studies indicate that a lack of TGF-β or lack of response to TGF-β by T cells is attributed to autoimmune and inflammatory diseases.

Although serum TGF-β levels reflect the total production from many cellular sources, Becker-Merok, et al have demonstrated that decreased TGF-β production correlated with decreased CD4+, CD8+, and NK cell frequency, implicating the reduction of these cell subsets as responsible for the decreased level of this cytokine. Recent studies have also revealed that CD4+CD25+Foxp3+ regulatory/suppressor (Treg) cells may be another important source for the TGF-β expression and/or production. It has been reported that the frequencies of circulating CD4+CD25high Treg cells were positively correlated with the levels of serum TGF-β in SLE patients (r = 0.433, p < 0.005). Ample evidence has demonstrated that Treg cells suppress autoimmunity through their production of TGF-β and via T cell response to TGF-β. Our recent observation revealed that TCR-stimulated CD4+CD25+ cells isolated from BWF1 lupus mice expressed less membrane-bound TGF-β and secreted less active TGF-β (Zhou XH and Zheng SG, unpublished observation), raising a possibility that decreased TGF-β expres-

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sion by Treg cells possibly accounts for the dysfunction of these cells in SLE and other autoimmune diseases.

Another area where TGF-β may be important in SLE concerns the T cell response to TGF-β. It has been reported that isolated T cell populations from SLE patients showed no TGF-β1 mRNA expression and at least one member of the TGF-β1 pathway was also missing (TGF-βRI, Smad2 and Smad3) in more than half of the patients. Another group also reported that the expression levels of TGF-β1 mRNA and mRNA for TGF-βRII and RIII were significantly lower in patients. Lack of TGF-βRII in T cells that lead to autoimmunity also emphasizes the importance of T cell response to TGF-β in the development of autoimmune responses.

TGF-β controls the autoimmune response through either direct or indirect mechanisms. First, TGF-β can directly suppress Th1 and Th2 cell responses, dendritic cell (DC) maturation, as well as B cell activation. TGF-β is also able to induce immunogenic DC to become tolerogenic DC and these DC have developed immune regulation function. It has been reported that B cells have a normal response to TGF-β in SLE. Additionally, TGF-β signaling is required for CD4+CD25+ Treg cells to sustain Foxp3 expression and Treg cell function and thereby indirectly controls the appearance and development of autoimmunity.

TGF-β plays crucial roles in the induction and differentiation of induced CD4+CD25+Foxp3+ and CD8+Foxp3+ regulatory T cells. Blockade of the TGF-β/TGF-βRI or RII pathway signals completely abolished the development of induced Treg cells. Other TGF-β superfamily members such as bone morphogenetic proteins seem to be unable to substitute TGF-β for the development of these cells. TGF-β-induced Treg and natural Treg cells may comprise a Treg cell network or have a synergistic role in the control of autoimmune diseases. The stimulatory and inhibitory role of TGF-β has been summarized as in Figure 1.

There are several factors that may explain the production of lower levels of TGF-β in the serum of SLE patients. The first is lower levels of IL-2 in SLE patients: in human and mouse SLE, IL-2 production is significantly decreased. Although IL-2 was first described as a T cell growth factor, evidence has accumulated that immunologic tolerance crucially depends upon this cytokine. Lack of IL-2 signal in IL-2- and IL-2R-deficient mice results in extensive lymphadenopathy and systemic autoimmunity due to the decreased capacity in the generation and maintenance of Treg cells. IL-2 plays an essential role in the development of induced Foxp3+ regulatory T cells and can induce natural mouse and human CD4+CD25+ as well as TGF-β-induced CD4+CD25+ Treg cells to produce and express mature TGF-β on the cell surface.

A second factor relates to IL-10. As reported by Llorente, et al, there was, on average, a 33-fold increase in IL-10 over healthy control peripheral blood mononuclear cells, and most of the IL-10 was made by monocytes and B lymphocytes. IL-10 is an immunoregulatory cytokine that plays a crucial role in inflammatory and immune reactions. It has potent antiinflammatory and immunosuppressive effects on

![Figure 1. Inhibitory and stimulatory effects of transforming growth factor-β (TGF-β). TGF-β inhibits T helper cell responses, dendritic cell function, and B cell activation and function, but stimulates and induces CD4+CD25+Foxp3+ regulatory T cells.](https://www.jrheum.org)
myeloid cell functions and cellular-based autoimmune diseases. IL-10 also can induce T cell anergy and development of Tr1 regulatory T cells. However, IL-10 may have a deleterious effect on humoral-based autoimmune diseases such as SLE, since excessive IL-10 promotes B cell differentiation and autoantibody production and eventually contributes to SLE development. IL-10 may also suppress the ability of T cells, monocytes, and NK cells to produce TGF-β, thus promoting development of SLE.

Although TGF-β is considered a beneficial cytokine for the control of SLE activity, recent studies have revealed that this cytokine, together with IL-6 or IL-21, promotes the differentiation of Th17 cells and suppresses the transcription factor forkhead box P3, leading to a reduction in regulatory T cells. Increased IL-6 is one of the characteristics of active SLE, and excessive Th17 cell frequency has been found to be associated with lupus nephritis in mouse models and in patients with SLE. However, Kang, et al also reported tolerance induction with a low-dose histone-derived peptide was associated with decreased IL-6 production and increased TGF-β production that paralleled a reduction in the fraction of IL-17-producing T cells and a reciprocal increase in regulatory T cells\(^\text{15}\), suggesting that increased TGF-β actually suppressed Th17 cell production in kidney in lupus disease.

In summary, whereas a large number of different cytokines are produced during immune activation and although it is difficult to determine the precise role of a single cytokine in human autoimmune diseases, the studies such as those of Becker-Merok and coworkers suggest that quantitative TGF-β levels in serum might be a valuable tool for determining the activity and severity of SLE. Accordingly, approaches that can upregulate TGF-β production will likely be potential targets to treat SLE and other autoimmune diseases.

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**REFERENCES**


