Review

Interleukin 6 in Systemic Sclerosis and Potential Implications for Targeted Therapy

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ABSTRACT. ***Objective***. The purpose of this study was to review the potential importance of interleukin 6 (IL-6) in systemic sclerosis (SSc).

Methods. PubMed and Scopus databases and American College of Rheumatology (from 2009-10) and European League Against Rheumatism abstracts (2009-11) were searched using keywords "scleroderma; SSc; cytokines; interleukins; interleukin 6" and publications were excluded if not pertaining to IL-6 in SSc. Data were extracted from selected articles to construct a cell interaction model of the effects of IL-6 in SSc.

Results. A total of 416 reports were found (PubMed, n = 82; Scopus, n = 331; 3 abstracts); 372 were excluded (irrelevant) leaving 41 publications and 3 abstracts (39 from PubMed, 18 from Scopus; but 16 were repeated from PubMed search), where 40 suggested IL-6 was important in SSc and 4 did not. Effects of IL-6 in SSc were summarized schematically.

Conclusion. Of the 44 publications, 40 suggested that IL-6 may be important in SSc, allowing for a conceptual framework within SSc including effects on macrophages, fibroblasts, plasma cells, monocytes, and extracellular matrix. (First Release April 15 2012; J Rheumatol 2012;39:1120–4; doi:10.3899/jrheum.111423)

Key Indexing Terms:
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Systemic sclerosis (SSc or scleroderma) affects more women than men, with peak onset between age 40 and 55 years[1]. The consequences may be devastating, with increased mortality especially in those with inflammatory markers such as the erythrocyte sedimentation rate (ESR)[2,3,4,5]. To date, altering cytokines such as interferon have not been proven to be of benefit in SSc[6].

Interleukin 6 (IL-6) is a pleiotropic proinflammatory multifunctional cytokine produced by many cells such as lymphocytes, fibroblasts, and monocytes[7]. The functions of IL-6 include T cell activation, initiation of acute-phase reactants (e.g., C-reactive protein), and stimulation of hematopoietic precursor cell growth, causing maturation of B cells into antibody-producing cells and cell differentiation. Many autoimmune diseases have upregulation of IL-6 including SSc, rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis[8,9]. Basic and clinical research suggests that IL-6 has an important role in the pathobiology of SSc. Thus a systematic review of the literature was performed to determine whether mechanisms influenced by IL-6 within SSc could be identified.

Ethics approval was not required for our study as it is a review using previously published data.

MATERIALS AND METHODS

PubMed and Scopus databases were searched by 2 reviewers from the inception until May 2011 for English-language original articles, and meeting abstracts of both the American College of Rheumatology 2009-10 and European League Against Rheumatism (EULAR) 2009-11 were searched. The key words searched were "scleroderma; systemic sclerosis; SSc; cytokines; interleukin; and IL-6." Data were extracted from articles (involving studies of any of "in vivo, in vitro, human, animal models") to construct a cell interaction schematic model of the effects of IL-6 in SSc where each pathway was from 1 or more publications. Negative articles were included in the literature review but not highlighted within the schematic. Data were excluded if they were found to be irrelevant to the objective, i.e., determining the mechanisms of IL-6 in SSc.

RESULTS

Four hundred sixteen publications were found (PubMed, n = 82; Scopus, n = 331; 3 abstracts); 372 were excluded (as irrelevant), leaving 41 publications and 3 abstracts (39 from

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Table 1. Importance of interleukin 6 (IL-6) in serum of patients with systemic sclerosis (SSc).

1.	IL-6 is elevated in serum and skin biopsies from SSc patients[10,11]. Study 11 demonstrated elevated local dermal expression of IL-6 in established, but not early, diffuse SSc but numbers were small.
2.	Serum IL-6 is significantly elevated in patients with early dcSSc[12-18].
3.	Serum IL-6 is related to disease activity of SSc[12-18].
4.	Serum IL-6 is correlated with total skin score and the extent of skin thickening[13,21].
5.	Serum IL-6 is negatively associated with lung function; lower IL-6 levels if better percentage of forced vital capacity predicted[13,15] and digital ulcer healing[19].
6.	Serum IL-6 is related to erythrocyte sedimentation rate, C-reactive protein, and immunoglobulin levels in SSc[13,17,20].
7.	SSc serum may have anti-IL-6 antibodies[22], which can bind to IL-6 receptors with high affinity[23].

dcSSc: diffuse cutaneous SSc.

PubMed, 18 from Scopus; but 16 were repeated from the PubMed search), where 40 suggested IL-6 was important in SSc and 4 did not. Table 1 summarizes findings for IL-6 in serum of patients with SSc with various disease manifestations. Mechanisms of fibroblast cell-cytokine interactions in SSc and IL-6 are illustrated in Figure 1.

SSc skin fibroblasts produce high levels of IL-6[24] and activation of the IL-6 gene[25]. Expression of IL-6 gene is correlated with collagen production[26]. IL-1, platelet-derived growth factor (PDGF), and tumor necrosis factor-α (TNF-α) induce fibroblasts to produce IL-6[27,28,29,30]. SSc fibroblasts produce IL-1 that feeds back to fibroblasts to produce IL-6, PDGF, and procollagen type I[31,32]. T cells, B cells, mast cells, basophils, and eosinophils stimulate fibroblasts through CD154/CD40 interaction[33], resulting in production of IL-6, IL-8, intercellular adhesion molecule 1,

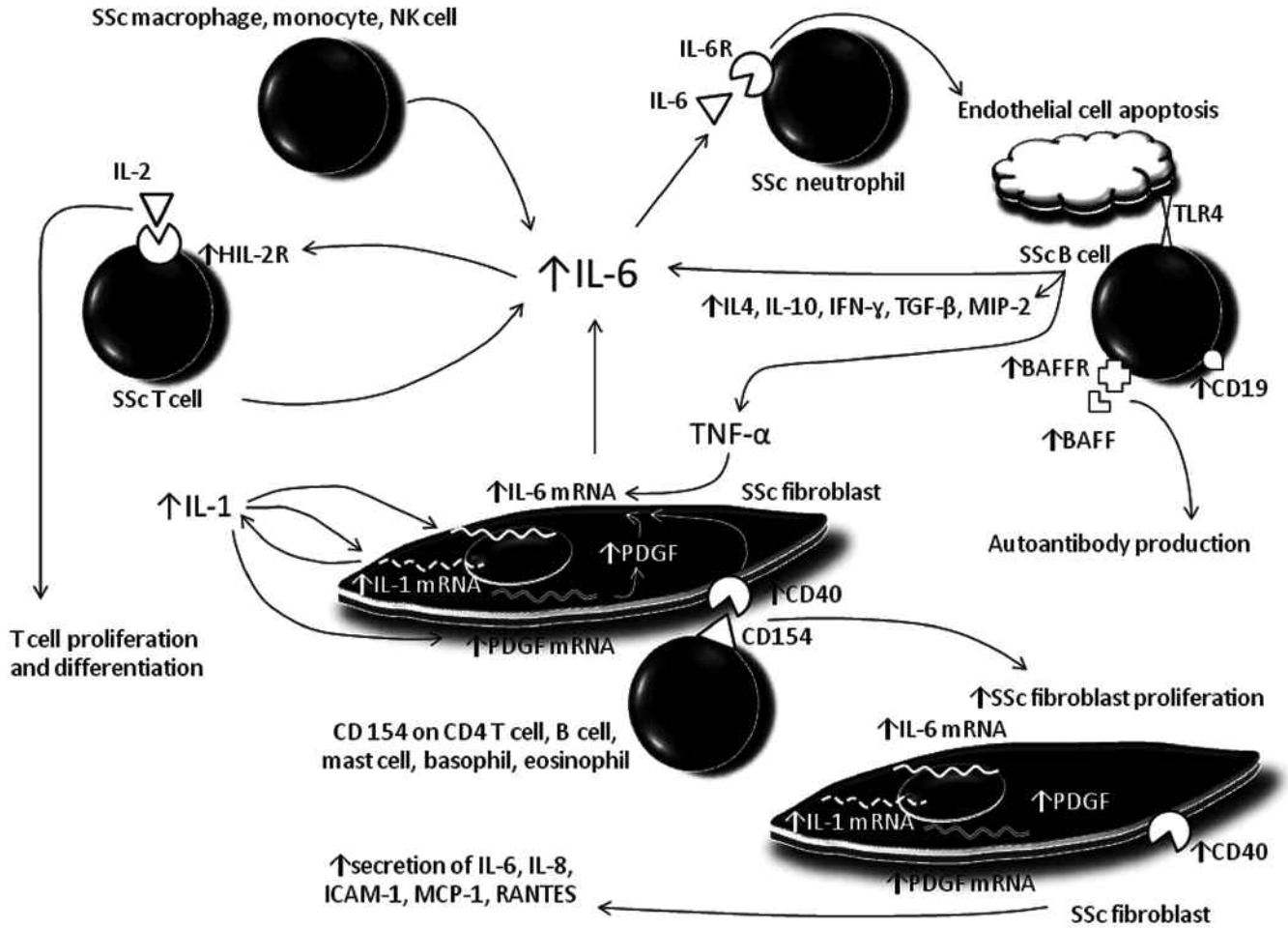

Figure 1. Fibroblast cell-cytokine interactions in systemic sclerosis (SSc) and interleukin 6 (IL-6). BAFF: B cell-activating factor; BAFFR: B cell-activating factor receptor; ICAM-1: intercellular adhesion molecule 1; IFN-γ: interferon-γ; HIL-2R: high affinity IL-2 receptor; MIP-2: macrophage inflammatory protein 2; MCP-1: monocyte chemoattractant protein 1; PDGF: platelet-derived growth factor; RANTES: regulated upon activation normal T cell expressed and presumably secreted; TLR4: Toll-like receptor 4; TGF-ß1: transforming growth factor-ß1; TNF-α: tumor necrosis factor-α; mRNA: messenger RNA.

monocyte chemoattractant protein 1, and RANTES (regulated upon activation normal T-cell expressed and presumably secreted)[34,35,36]. Peripheral blood mononuclear cells (PBMC) are another source of IL-6[15,37,38,39]. PBMC also produce oncostatin M and soluble IL-6 receptor (sIL-6R), which modify IL-6 transsignaling[40]. Elevation of sIL-6R is correlated with decreased forced vital capacity (FVC) and DLCO[40]. Soluble gp130 (a blocker of IL-6/sIL-6R that interacts with membrane gp130) is not elevated in SSc serum, thus allowing activation of cells through the IL-6 complex and membrane gp130[40]. SSc T cells and natural killer cells overproduce IL-6[15,41]. Through IL-6 stimulation, SSc T cells will overexpress IL-2 using high-affinity IL-2R[42]. Overexpression of CD19 caused SSc B cells to lose peripheral tolerance. Reduction of CD19 can decrease skin and lung fibrosis and lower IL-6, with subsequent suppression of serum levels of IL-4, IL-6, IL-10, interferon-γ (IFN-γ), TNF-α, transforming growth factor ß1, and macrophage inflammatory protein 2 (MIP-2) and decreased production of autoantibodies[43,44,45,46]. B cell-activating factor (BAFF) produced by macrophages is overexpressed in SSc skin and BAFF receptor is increased in B cells from patients with SSc. In serum from patients with diffuse cutaneous SSc (dcSSc), increased BAFF levels are correlated with IL-6 levels, skin fibrosis, decreased FVC, arthritis, myositis, high ESR, and immunoglobulin production. Decreased BAFF levels correlate with regression of skin fibrosis, whereas increased levels are associated with new onset of organ involvement[47]. Increased levels of IL-6 in SSc serum interact with IL-6R expressed by neutrophils, which caused endothelial cell apoptosis and breakdown of extracellular matrix[46,48]. Hyaluronan (a product of extracellular matrix breakdown) stimulates B cells through Toll-like receptor 4 (TLR-4) to produce IL-4, IL-6, IL-10, IFN-γ, TNF-α, TGF-ß1, and MIP-2[46].

To date, there are some case reports of use of an anti-IL-6 antibody (tocilizumab 8 mg/kg once a month) for 6 months to treat dcSSc. Two patients with dcSSc had improved skin scores during treatment with tocilizumab[49]. Another study reported 5 cases of dcSSc with active polyarthritis and insufficient response to conventional disease-modifying antirheumatic drugs. Tocilizumab treatment was found to decrease the swollen and tender joint counts (measured by the Disease Activity Score-28), where 3 of 5 patients achieved a EULAR good response. However, the skin score, quality of life, and lung function did not change[50]. In another report, IL-6 decreased in patients with SSc treated with rituximab (a chimeric monoclonal antibody to CD20, 1 g given and repeated 14 days later) in 9 patients with dcSSc. After 6 months patients presented a median decrease of skin score of 43% (range 21%–64%) and in all patients levels of IL-6 were still suppressed at 6 months[51]. Levels of IL-6 may be abnormally high in pulmonary arterial hypertension (PAH) or other vascular abnormalities; but data on IL-6 and SSc-associated PAH were not found in the literature review, with the exception of a recent report of a scleroderma cohort that described a polymorphism in the gene for TLR-2 that was associated with increased levels of IL-6 and PAH[52].

Not all of the literature supported that IL-6 is important in SSc. Three negative studies were found. One study showed increased *in situ* localization of IL-6 in skin biopsies from atrophic epidermal diseases, including localized scleroderma, SSc, and other diseases, but no elevation of IL-6 in serum from patients with SSc (the study had positive data on skin biopsy but negative in SSc serum)[53]. A different study also did not find elevations of IL-6 in serum of subjects with SSc compared to controls[54]. Another report did not find significant differences in IL-6 polymorphisms in subjects with SSc compared to controls[55].

DISCUSSION

Potential explanation of pathophysiology in SSc related to IL-6. Aberrations of genes[56], changes of the immune system, and environmental triggers cause abnormal immune responses. Increased levels of serum IL-6 secreted from many cells interact with IL-6R, enhancing activation of endothelial cells, expression of adhesion molecules, and apoptosis, which seem to occur early in the pathogenesis of SSc. Various nuclear antigens induce and activate antigen-presenting cells to secrete many cytokines and chemokines, including IL-6, recruiting more changes. T cells are activated, differentiated, and proliferate, and this is partly influenced by IL-6. Activated T cells stimulate SSc fibroblasts, which are overexpressed in CD40 through interactions of CD40/CD154, resulting in proliferation and upregulation of inflammatory cytokines/chemokines, including IL-6. PBMC are another source of IL-6 overproduction in SSc. BAFF is oversecreted from SSc monocytes, macrophages, and other cell types. CD19 B cells in SSc are increased, with more BAFF receptors, which results in loss of peripheral tolerance and immune reaction to self-extracellular matrix breakdown products, which are stimulated through interactions of TLR-4 and oversecretion of IL-6.

IL-6, which is overexpressed especially in early SSc, stimulates SSc fibroblasts to differentiate and proliferate, causing collagen overproduction and fibrosis. IL-6 secreted from many sources has paracrine and autocrine effects on many cell types. This generates a cycle of chronic inflammation and fibrosis in SSc. IL-6 levels in SSc are related to disease activity (global assessments, skin scores, tendon friction rubs, some lung measures).

In addition, IL-6 and TGF-ß facilitate the development of a T helper 17 (TH17) cell subpopulation[57]. Circulating levels of IL-17-inducing cytokines, i.e., IL-6, IL-23, and IL-1, were increased in some patients with SSc[58]. High levels of IL-17 have been reported especially in early SSc[59,60], and diminished over time[60]. These observations

suggest that IL-17 is involved to some extent in SSc pathogenesis and support the importance of IL-6 in SSc.

Our study has limitations. Data were combined from reports of *in vitro* and *in vivo* studies and both human and animal models of SSc. Many had small sample sizes and some of the negative studies may have used samples from patients who did not have high disease activity. The clinical reports that used medications to downregulate IL-6 are few and have very small numbers of cases.

IL-6 has a role in the pathobiology of SSc. Most, but not all, studies support that IL-6 is increased in SSc in animal models, in skin and blood of patients, and especially in early dcSSc with findings within the skin and changes in the lungs. These multiple observations suggest that IL-6 may be a cytokine to target in treatment of SSc.

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