The Role of T Cells in Systemic Sclerosis

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Systemic sclerosis (SSc) is a chronic disease characterized by microvasculopathy, autoantibodies (autoAbs), and fibrosis. The pathogenesis of the disease is incompletely understood. Microvasculopathy and autoAbs appear very early in the disease process. AutoAbs, such as those directed against DNA topoisomerase I (Topo I), are disease specific and associated with disease manifestations, and indicate activation of the adaptive immune system. B cells are involved in fibrosis in SSc. T cells are also involved in disease pathogenesis. T cells show signs of antigen-induced activation; T cells of TH2 type are increased and produce profibrotic cytokines interleukin (IL)-4, IL-13, and IL-31; CD4+ cytotoxic T lymphocytes are increased in skin lesions, and cause fibrosis and endothelial cell apoptosis; circulating T follicular helper (TFH) cells are increased in SSc produce IL-21 and promote plasmablast antibody production. On the other hand, regulatory T cells are impaired in SSc. These findings provide strong circumstantial evidence for T cell implication in SSc pathogenesis and encourage new T cell-directed therapeutic strategies for the disease.

systemic sclerosis T cells T lymphocytes Tregs TH2 cells treatment

1. Introduction

Systemic sclerosis (SSc) is a complex disease characterized by microvasculopathy with exaggerated response to stimuli and fibrointimal proliferation that leads to tissue ischemia, extensive fibrosis of skin and internal organs, and autoantibodies (autoAbs). The disease is divided according to the extent of clinical skin involvement into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) and can be very difficult to manage leading to morbidity and increased mortality [1].

The pathogenesis of SSc is complex and incompletely understood. There is activation of adaptive and innate immune system and intermingled inflammatory, fibrotic, and vascular processes. Myofibroblasts, which lay down collagen and other extracellular matrix components, can be activated by cells of the immune system and derive from various cell types via trans-differentiation [2][3][4]. AutoAbs, including anti-Topoisomerase I abs (ATA, anti-Scl70), anticentromere abs, and anti-RNA polymerase III (ARP) antibodies, are detected very early, predict subsequent development of SSc, and indicate activation of the adaptive immune system [5]. Many autoAbs exert direct pro-fibrotic effects, and others also activate endothelial cells [6]. Furthermore, B cells with B cell antigen receptor (BCR) recognizing DNA-topoisomerase I with high affinity are increased in SSc, produce interleukin (IL)-6, and promote fibrosis in mice [7].

2. Antigenic Activation of T Cells in Systemic Sclerosis

The early presence of IgG autoAbs in SSc along with the presence of T cell infiltrates in skin before fibrosis and the production of T cell cytokines IL-4 and Il-13 indicate T cell activation very early in the disease process [8]. Next-generation sequencing of peripheral blood T cells in SSc revealed a profile associated with chronic antigenic stimulation [9][10]. Also, transcriptome analysis of peripheral blood T cell subsets in SSc revealed activated CD4+ and mucosal-associated invariant T(MAIT) cells (innate-like cells located at mucosal sites) but also increased expression of inhibitory molecule PD-1 which indicated functionally adapted T cells in response to chronic stimulation [10].

Dendritic cells are the most potent antigen-presenting cells and are likely to function as such in SSc; pDCs' increase in SSc may also function as antigen-presenting cells [11]. In bleomycin-induced scleroderma mice, pDCs were increased in the affected organs, whereas pDC depletion reduced skin and lung fibrosis, as well as T cell and B cell infiltrates, and genes related to immune cell activation, chemotaxis, and fibrosis [12]. Macrophages and B cells have the machinery to process and present antigens to T cells and can function as antigen-presenting cells in SSc [13].

T cell antigen receptor. The conventional T cell antigen receptor (TCR), expressed on the vast majority of peripheral blood T cells, is composed of an α and a β chain. Sequence analysis of the β-chain of TCR of T cells from SSc skin lesions revealed oligoclonal T cell expansion and persistence of particular clones over 12 months [14]. Oligoclonal expansion of T cells in skin lesions from early SSc patients was also found by TCR complementarity-determining region 3 (CDR3) length analysis [15]. Another study reported oligoclonal expansion of peripheral blood CD4+ and CD8+ T cells from SSc that persisted over four years [16]. Also, CD4+CTLs (CD4+CD319+ T cells) strikingly increased in peripheral blood of SSc patients and very active in producing cytokines, were oligoclonal [17].

The inciting antigen driving T cell proliferation is not known. The finding of the same T cells clones in skin lesions from early SSc patients and in co-cultures of SSc fibroblasts with autologous peripheral blood mononuclear cells (PBMCs) suggests that fibroblasts may provide autoantigens for T cell activation [15]. Endothelial cells, sharing B cell autoantigens with fibroblasts, may also provide autoantigens for T cells [18]. The detection of endothelial cell damage before fibrosis in skin biopsies supports this concept. Male offspring T cell clones generated from female SSc patients reacted with maternal HLA antigens and produced IL-4, raising the possibility for the contribution of GVHD mechanisms to the development of SSc [19]. Inorganic substances, such as hypochlorous acid (HOCL), can elicit an adaptive immune response, likely by modifying self-antigens. HOCL-induced mouse model of SSc induced by subcutaneous injection of HOCL, exhibit skin fibrosis with increased skin infiltration of CD4+ CD8+ T cells, macrophages, and B cells [20].

3. T Cell Subsets and Function in Systemic Sclerosis

It has been found that skin changes with T cell infiltrates and endothelial cell apoptosis are very early events in the SSc process. T cells and macrophages were detected in the skin of SSc patients before histological evidence of fibrosis [21].

T cells are the predominant cell type in the inflammatory infiltrates of skin lesions in SSc [9][22] reaching 72 cells (mean number/7.36 mm^2) compared to 26 macrophages and to 5 B cells [22]. Next-generation RNA sequencing in skin biopsies from early dcSSc patients (disease duration 1.3 years) showed adaptive immune cell signatures to be associated with shorter disease duration [23]. T cells infiltrating skin lesions in SSc express the early activation antigen CD69 [24], a C-type lectin, and a marker of tissue-resident memory T cells which play a vital role in immune response and surveillance [25][26].

There is a complex interaction of T cells with B cells, macrophages, dendritic cells, fibroblasts, and endothelial cells which result in apoptosis or activation of endothelial cells and fibroblasts, and activation of B cells and macrophages with the production of autoAbs, profibrotic, inflammatory, and vasoconstrictive mediators, such as IL-4, IL-13, TGFβ, IL-6, CC chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein 1), endothelin, platelet-derived growth factor (PDGF) leading to fibrosis and microvasculopathy [8]. Animal models of SSc also support the role of T cells in the pathogenesis of fibrosis [27].

TH2 cells. T cells in peripheral blood in SSc are predominantly TH2 cells producing profibrotic cytokines IL-4 and IL-13 and TH2 cells are also detected in affected tissues [8][9][28][29]. In untreated early dcSSc skin among CD4+ T cells TH2 cells are detected along with TH17 cells, T follicular helper (TFH) cells, and regulatory T cells (Tregs) [9]. CD4+CCR7- memory T cells produced IL-13, IL-4, and TNFα, particularly in dcSSc [30]. Furthermore, CD8+ T cells overproducing IL-13 [29], and CD4+CD8+ double positive T cells overproducing IL-4, were detected in SSc skin lesions [31][32].

Apart from direct effect on fibroblasts, IL-4 stimulates macrophages to profibrotic alternatively activated phenotype (M2), which is mediated by IL-4 receptor (IL-4R), since blockade of IL-4Rα decreased alternatively activated (M2) macrophages and attenuated profibrotic changes in mice [33]. IL-4 signaling also stimulated proliferation of fibro/adipogenic progenitors in vitro [34]. IL-4 induces the development of granulocyte macrophage-colony stimulating factor (GM-CSF) producing CD30+B cells which are increased in SSc and promote differentiation of monocytes to profibrotic M2 macrophages [35]. Of note, GM-CSF induced trans-differentiation of monocytes to myofibroblasts [36].

IL-4 derived from innate immune cells and the type of antigen can drive TH2 polarization in SSc [28]. Dendritic cells play a major role in T cell responses as they present antigens to T cells. Plasmacytoid dendritic cells (pDCs) appear to promote TH2 immune response and fibrosis. pDCs correlated with CD4+ T cells, IL-4-producing T cells, and IL-3 levels in the bronchoalveolar lavage (BAL) from SSc patients [12], whereas IL-3-stimulated pDCs induced TH2 differentiation [37]. CXCL4, a chemokine secreted by pDCs, induced endothelial cell activation and promoted TH2 cytokines in vitro [38].

IL-33, a member of IL-1 superfamily, widely expressed and released during cell damage [39], induces TH2 differentiation and is elevated in peripheral blood [40][41][42], affected skin and internal organs in SSc patients [43]. IL-33 enhanced IL-4-induced IL-31 production [44]. In mice, IL-33 induced IL-13-dependent cutaneous fibrosis [45][46]. IL-33 promoted extracellular matrix deposition and M2 macrophage polarization in diabetic mice [47].

Cytotoxic T lymphocytes. A recent study found that in the skin of untreated early dcSSc patients, the major component of inflammatory infiltrates was CD4+ cytotoxic ($CD57^{high}CD4+$) cells (CD4CTLs) and CD8+ T cells [9]. These CD4+CTLs apparently cause apoptosis of endothelial cells in SSc, as many apoptotic endothelial cells with granzyme B visible in their cytosol and in close proximity to CD4+CTLs expressed HLA-class II molecules in early dcSSc skin lesions [9]. Circulating $CD28^{low}CD57^{high}CD4+$ CTLs from early dcSSc patients were effector cells expressing genes related to metabolic activity, fibrosis, and cytotoxicity (granzyme B and perforin) and were associated with the number of myofibroblasts in paired skin samples [9].

Circulating T follicular helper cells. T follicular helper (TFH) cells provide critical help for B cell differentiation and antibody production in germinal centers of secondary lymphoid organs [48][49]. They express inducible T cell costimulator (ICOS), programmed cell death protein 1 (PD)1, transcription factor BCL6, and produce IL-21 [48]. Circulating TFH cells (CD4+CXCR5+PD1+), increased in SSc and particularly in dcSSc, were activated and exhibited increased capacity to stimulate plasmablast secretion of IgG and IgM, partly mediated through IL-21R and JAK1/2 [50]. SSc patients with high TFH cells and plasmablasts more frequently progressed to late nailfold capillaroscopy pattern which correlated with internal organ involvement [51].

TH17 cells. The role of Th17 cells in the pathogenesis of human SSc is unclear. IL-17A showed pro-fibrotic effects in animal models of SSc [52]. TH17 cells and IL-17A promoted skin and lung fibrosis [53], whereas IL-23, a survival and proliferation factor for TH17 cells, induced skin fibrosis in bleomycin-induced SSc mice [54], and IL-21, predominantly produced by TH17 cells and natural killer (NK) cells, inhibited the production of the anti-fibrotic T cell IFNγ [55]. The effect of IL-17 on fibrosis is less clear in human SSc [52]. Serum IL-17B, IL-17E, and IL-17F were elevated in SSc [56][57] and serum IL-21 levels were also elevated, particularly in dcSSc [58][59].

Angiogenic T cells. Circulating angiogenic T (cTang) cells, which are CD3+ T cells characterized by the expression of platelet endothelial cell adhesion molecule-1 (CD31) and the receptor for the chemokine stromal cell-derived factor-1 (CXCR4, CD184) and involved in capillary formation, were increased in SSc particularly in SSc-associated PAH [60].

Tregs. Tregs are functionally impaired in SSc as they fail to produce inhibitory cytokines TGFβ1 and IL-10 and to suppress effector T cells [61][62]. This functional impairment is related to soluble factors, as plasma from early dcSSc patients completely abrogated the suppressive capacity of Tregs from healthy individuals [63]. Tregs ameliorated bleomycin-induced lung fibrosis, and similar effect was achieved by adoptive transfer of Tregs [64]. However, Tregs in affected SSc skin can produce profibrotic IL-4 and IL-13 cytokines [65] and this is likely due to the action IL-33, since IL-33 induced differentiation of Tregs into TH2-like cells producing IL-13 but not IL-4 [65].

T follicular regulatory cells. T follicular regulatory (TFR) cells, a subset of Tregs located within B cell follicles, co-express Treg and TFH markers and restrict TFH function [66]. IL-21 inhibits TFR differentiation [67].

4. Therapeutic Implications

Immunosuppression is the standard of treatment of SSc today [68]. Steroids were positively associated with production of the antifibrotic IFNγ and negatively associated with production of profibrotic IL-4 and IL-13 by peripheral blood CD8+ T cells [69], but they are used with caution in SSc because high doses of steroids are associated with scleroderma renal crisis. Currently, autologous hematopoietic stem cell transplantation (AHSCT), the most effective treatment for severe SSc [70][71], is used to eliminate the autoimmune repertoire of SSc and replace it with a new immune system. Indeed, this concept is supported by the finding, at 1-year post AHSCT where the clinical improvement was related to renewal of the immune system with higher TCR diversity and newly generated Tregs and Bregs [72], as was also shown in multiple sclerosis [73]. Mycophenolate mofetil is an effective medication for skin tightness in SSc and is the standard-of-care for SSc-ILD stabilizing lung function [74]. Rituximab, a monoclonal antibody against CD20, expressed on B cells but also on a subset of T cells [75], improved skin and stabilized lung fibrosis in small observational studies in SSc [76], and the improvement of skin fibrosis was associated with decrease of CD4+ T cells in peripheral blood and skin [76][77].

Tocilizumab an anti-IL-6 receptor (IL-6R) moAb, which inhibits B cell differentiation, TH17 polarization, M2 macrophage polarization, and myofibroblast activation, reduced skin score and stabilized lung function in SSc patients [78][79].

JAK inhibitors may offer an attractive therapeutic choice. The JAK/STAT kinase pathways, present in T cells but also in fibroblasts and macrophages, are important downstream mediators of profibrotic responses, including IL-4, IL-13, and IL-6, and also type I interferons.

Re-enforcing Tregs could be another therapeutic strategy for SSc. Low-dose IL-2 restored the Tregs/TH17 effector cell balance [80] and decreased TFH cells associated with marked reduction in disease activity in SLE patients [81].

An innovative therapeutic strategy could be the use of T cells with chimeric antigen receptor T cells (CAR-T cells) [82][83]. In CAR-T cells TCR is composed of the antigen-binding domain of heavy and light variable chains of a monoclonal antibody and, therefore, it recognizes its target in a non-HLA-restricted manner. CAR-T cells are successfully used in hematological malignancies. The use of CAR-T cells targeting pathogenic B cells, i.e., B cells recognizing DNA topoisomerase I with high affinity, targeting fibroblast activation protein, CAR natural killer cells that target PD-1 to eliminate TFH cells [84] or use of CAR-Tregs might be attractive strategies.

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