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Review

Systemic sclerosis: New evidence re-enforces the role of B cells

Lazaros I. Sakkas [a,b,*], Dimitrios P. Bogdanos [a,c]

[a] Department of Rheumatology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa 41 110, Greece
[b] Center for Molecular Medicine, Old Dominion University, Norfolk, VA, USA
[c] Division of Transplantation Immunology and Mucosal Biology, Kings College School of Medicine, London SE5 9RS, UK

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ABSTRACT

Systemic sclerosis (SSc) is characterized by widespread fibrosis, microangiopathy (vasospasms and stenosis), and formation of autoantibodies. T cell activation has been shown to contribute to fibrosis and microvasculopathy in SSc. However, recent evidence suggests that B cells are also likely to contribute in the pathogenesis of the disease. B cells are hyperactivated in SSc, as indicated by the overexpression of the stimulatory CD19 receptor and impairment of the inhibitory CD22 receptor. They lead to the production of many autoantibodies, some of which induce collagen production and vasoconstriction. They promote fibroblast collagen production through cell contact. Furthermore, B cells can function as antigen-presenting cells to T cells and induce dendritic cell maturation that promotes profibrotic Th2 response. Lately, interleukin (IL)-10-producing B regulatory cells, which induce generation of T regulatory cells and can ameliorate autoimmune diseases, were found to be reduced in SSc, favoring autoaggression of B cells in this disease. Finally, B cell depletion with rituximab improves or stabilizes skin fibrosis and lung function. These finding suggest that new therapeutic strategies targeting B cell function(s) can be developed for SSc.

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1. Introduction

Systemic sclerosis (SSc) is chronic multisystem disease characterized by widespread fibrosis, autoantibodies, and microangiopathy. Fibrosis involves the skin and internal organs, including lung, gastrointestinal tract, and heart. Microangiopathy is characterized by vasospastic episodes and fibrointimal proliferation causing vascular stenosis that leads to digital ulcers, pulmonary arterial hypertension, and scleroderma renal crisis. The etiopathogenesis of SSc is incompletely understood [1,2]. Environmental factors play a major role [3], since in a twin study the concordance rate of SSc in monozygotic twins is low and equal to that in dizygotic twin [4].

Fibrosis of the skin and internal organs is the hallmark of the disease, and for years the pathogenesis of SSc has been evolved around fibroblasts. However, the evolution of SSc in the skin, an easily accessible organ to study, has shown that there are lymphocytic infiltrates early in the disease process before even histological fibrosis [5]. In the early inflammatory skin stage, there is also apoptosis of endothelial cells. In

* Corresponding author at: Department of Rheumatology, Medical School, University of Thessaly, Biopolis, Larissa 41 110, Greece.
E-mail address: lsakkas@med.uth.gr (L.I. Sakkas).

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fact, endothelial cells were the first cell type to undergo apoptosis in UCD 200/206 chicken, an avian model of scleroderma [6]. Autoantibodies and microangiopathy, as detected by nailfoldcapillaroscopy, may occur years before clinical skin fibrosis and are now included in the new classification criteria for SSc [7–9]. These findings alluded to the possibility that immune cells might activate fibroblasts to produce excess collagen.

T cells and macrophages are the predominant mononuclear cell infiltrates in the skin of SSc [5,10,11]. T cells in SSc skin are activated. They express the early activation antigen CD69 [11], and suction blisters in SSc skin contain elevated levels of soluble IL-2 receptor [12]. T cells in SSc are of TH2 type producing the profibrotic cytokines IL-4 and IL-13 [1]. The finding that T cells in SSc skin lesions exhibit oligoclonal expansion and certain T cell clones persist in skin lesions over time indicates an antigen-driven immune response and further re-enforces the concept of T cell involvement in SSc pathogenesis [1,13].

In recent years, the role of B cells in the pathogenesis of SSc has become increasingly apparent. B cells can promote fibrosis by cytokines, autoantibodies, and cell–cell contact.

2. B cells are hyperactivated in SSc

B cells infiltrates in SSc lesions are variable[14–18], yet there is convincing evidence for the participation of B cells in the pathogenesis of the disease. B cells in SSc are hyperactive, as exemplified by the presence of hyper-γ-globulinemia, autoantibodies, and increased serum free light chains of immunoglobulins [19]. B cells from patients with SSc overexpress the B cell stimulatory receptor CD19 by 54% in patients with early SSc and by 28% in patients with long-standing disease [20]. Overexpression of CD19 in SSc, although to a lesser degree, was also reported earlier [21]. It should be mentioned that small increase (15–29%) in B cell CD19 expression in transgenic mice–induced autoantibody production [21]. B cell activating factor (BAFF), a B cell survival factor, is increased in SSc [22]. In contrast, the function of CD22, an inhibitory B cell molecule, is inhibited by anti-CD22 autoantibodies present in patients with SSc [23]. B cells are also activated in a model of systemic sclerosis, namely, chronic graft-versus-host disease (cGVHD), a condition that develops after allogeneic hematopoietic stem cell transplantation, and shares clinical and serological features with human SSc [24] and in tight-skin (TSK) mice, another model of SSc [25].

3. B cells can produce profibrotic cytokines

Activated B cells can produce profibrotic cytokines IL-6, and TGFβ. IL-6 can induce fibroblast collagen production [26] through the bone morphogenetic protein (BMP) antagonist gremlin and the canonical TGFβ signaling [27]. Serum IL-6 was elevated in SSc patients [28–30], and skin IL-6 expression was also increased [30]. TGFb, increased in scleroderma, is a powerful profibrotic cytokine [31].

4. Autoantibodies promote fibrosis/inflammation in SSc

The hyperactivity of B cells in SSc is exemplified by the presence of a plethora of autoantibodies. Some of autoantibodies found in patients with SSc promote fibrosis and/or pro-inflammatory response. These autoantibodies, and their specific action, are shown in Table 1. Anti-topoisomerase I [32] and anti-centromere antibodies are disease-specific antibodies associated with diffuse cutaneous (dcSSc) and limited cutaneous disease (lcSSc), respectively. More interestingly, anti-Topoisomerase I and anti-centromere antibodies were associated more closely with clinical manifestations than cutaneous SSc subsets were [33]. Anti-topoisomerase I antibodies recognize their target that is released from apoptotic endothelial cells and binds to fibroblast membrane [32]. Anti-fibroblast antibodies induce fibroblast production of chemokines CCL2 (monocyte chemoattractant protein-1) and CXCL8 (interleukin-8) [34]. Anti-RNA polymerase III antibodies are associated with dcSSc [35] and anti-Th/To antibodies are associated with lcSSc and scleroderma renal crisis in some studies [36]. Autoantibodies against platelet-derived growth factor receptor (PDGFR) stimulated activation and collagen production in normal human fibroblasts [37]. Stimulatory anti-PDGFR autoantibodies inducing collagen production were also found cGVHD [38]. Anti-matrix metalloproteinase(MMP)-1 antibodies and anti-MMP-3 antibodies, found in SSc, are functional and inhibit MMP-1 and MMP-3 collagenase activity, respectively, thus reducing extracellular matrix breakdown and promoting accumulation of extracellular matrix [39,40]. Anti-endothelial cell antibodies cause endothelial cell apoptosis [41] and/or endothelial cell activation. Also, anti-ICAM-1 antibodies, frequently detected in SSc patients, cause increased endothelial cell production of reactive oxygen species (ROS) and expression of VCAM-1 [42]. Anti-endothelin-1 type A receptor (ETAR) autoantibodies and anti-angiotensin II type 1 receptor (AT1R) autoantibodies, detected in most SSc patients, are agonist antibodies and cause fibrosis and vasoconstriction [43–45]. They activate vascular endothelial cell production of TGFβ (a powerful profibrotic cytokine), IL-8, and vascular cell adhesion molecule-1 (VCAM-1) [43,46]. SSc-IgG with anti-ETAR and anti-AT1R antibodies, but not normal IgG, when injected to mice, caused obliterative vasculopathy [45]. Anti-ETAR autoantibodies are strong predictors of digital ulcers in patients with SSc [47]. Anti-AT1R autoantibodies are associated with hypertensive entities, such as pre-eclampsia, and severe kidney transplant rejection with malignant hypertension [44]. Furthermore, pregnant mice develop pre-eclampsia when injected with affinity-purified anti-AT1R autoantibodies from women with pre-eclampsia [48]. It should be noted that angiotensin II increased fibroblast production of TGFβ and collagen via its type 1 receptor [49]. Anti-fibrillin antibodies activate fibroblast collagen production [50]. Another autoantibody found in SSc targets CD22, a major inhibitory B cell receptor. Anti-CD22 autoantibodies inhibit CD22 signals and are associated with enhanced skin fibrosis, as detected by the Rodnan skin score [23] (Fig. 1 and Table 1).

The targets of autoantibodies in SSc, apart from contributing to disease pathogenesis, may also serve as mimicry targets of immune response to foreign agents. For instance, anti-topoisomerase I monoclonal antibodies recognize a pentapeptide of topoisomerase I from SSc patients that shares homology with human CMV-derived UL70 protein [51]. Also, many SSc patients have antibodies against human CMV-derived UL94 protein that shares homology with NAG-2 (tetraspan novel antigen-2), expressed on endothelial cell surface. Furthermore,

Table 1
Autoantibody targets in patients with SSc.

Autoantibody target	Comments	Ref
Topoisomerase I	Associated with dcSSc	[32]
Centromere	Associated with lcSSc	[33]
RNA polymerase III	Associated with dcSSc	[35]
Th/To	Associated with scleroderma renal crisis	[36]
Platelet-derived growth factor receptor (PDGFR)	Stimulatory, inducing fibroblast activation and collagen production	[37]
Endothelial cell	Induce endothelial cell activation and/or apoptosis	[41]
ICAM-1	Activate endothelial cells	[42]
Endothelin type A receptor (ETAR)	Stimulatory, strong predictors of digital ulcers	[47]
Angiotensin II type 1 receptor (AT1R)	Stimulatory, associated with pre-eclampsia and malignant hypertension	[44,48]
hCMV-derived UL94	Mimicry targets, cross-reactive with endothelial cells	[52]
CD22	Inhibit the inhibitory CD22 signals	[23]
Matrix metalloproteinase I	Inhibit collagenolyticactivity, thus increased intracellular matrix	[39]
Fibrillin	Increase fibroblast collagen production	[50]

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