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Recent Advances on Pathogenesis and Therapies in Systemic Sclerosis

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Abstract Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by extensive fibrotic changes in various organs, including skin and lung. Although the etiology of SSc remains unknown, three major abnormalities, abnormal humoral immunity, microvasculature, and fibroblast dysfunctions are considered to play important roles. Significant progress has been made in understanding the pathogenesis on SSc, and has been also providing clues to the treatment for this disease. This review summarizes recent advances on the pathogenesis and new therapeutic strategy for SSc.

Keywords Scleroderma · Autoimmune diseases · Therapy · Pathogenesis · B cell · Fibroblast · Pulmonary hypertension · Cytokine · Chemokine

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by excessive extracellular matrix deposition in the skin and visceral organs. SSc is a rare disease and affects about 0.01% of the population, predominantly women. The disease can occur at any age, but it is most common among middle-aged women. Patients with juvenile onset SSc more frequently have an overlap syndrome with myositis, with serum anti-PM-Scl and anti-U1RNP antibody (Ab), fatal cardiac disease, and improved survival compared with adult onset SSc cases [1]. There are some risk factors for developing SSc, including genetic backgrounds and environmental factors. The geographic distribution of SSc is worldwide with a notably low prevalence in Caucasians and high prevalence in Africans. A high prevalence of SSc in a homogenous population of Choctaw American natives is reported [2, 3]. Racial variation in clinical and immunological manifestations was reported that blacks developed disease onset at an earlier age than whites and were more likely to have diffuse disease, digital ulcers, impaired lung function, and anti-U1RNP, and anti-Ro antibodies. On the other hand, Caucasians were more likely to have anti-centromere antibodies [4].

One of the prominent features of SSc is a clinically heterogeneity. SSc is classified into two clinical subsets, diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), defined by the extent of skin sclerosis. dcSSc patients have severe internal organ manifestations, including lung fibrosis and scleroderma renal crisis. By contrast, lcSSc patients have a low frequency of internal organ manifestation, except for late prevalence of pulmonary hypertension. This classification is useful for the evaluation of clinical manifestation, prediction of prognosis, and choice of treatments in each patient. Although the pathogenesis of SSc remains unknown, three distinctive abnormalities, including collagen excessive accumulation, vascular injury, and immune activation are considered to play important roles in the development of the disease [5]. As these three abnormalities are not likely to occur independently, it appears important to clarify how these abnormalities affect each other in the pathogenesis. This

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review focuses on recent scientific endeavors exploring the pathogenesis and treatments for SSc.

Pathogenesis

Abnormal Immune Activation

Autoantibodies

Anti-nuclear antibodies (ANA), observed in various autoimmune disorders, are a well-known evidence suggestive of abnormal lymphocyte activation. More than 90% of patients with SSc are supposed to have ANA, which are usually present before the onset of the disease. High prevalence of autoantibodies including ANA indicates the existence of immunological abnormality in SSc patients. Three major anti-nuclear antibodies exclusively detected in SSc patients have been recognized: anti-topoisomerase I (anti-topo I) antibodies, anti-RNA polymerase Abs, and anti-centromere antibodies (ACA). Anti-U1-RNP antibodies are also often positive, although disease specificity is relatively low. In addition, anti-U3RNP and anti-Th/To antibodies are also found in SSc patients. It is interesting to note that the specificities of autoantibodies are closely associated with the disease subsets of SSc: for example, anti-topo I and anti-RNA polymerase antibodies are associated with dcSSc, whereas ACA is linked to lcSSc. ACA is relatively specific for lcSSc but is occasionally positive in patients with other rheumatic disorders, including primary biliary cirrhosis [6]. Gelber et al. have reported a distinct recognition of antibodies to centromere proteins (CENPs) among rheumatic disorders [7]. Whereas patients with primary Sjogren's syndrome predominantly recognize CENP-C alone, dual recognition of CENP-B and CENP-C is common in SSc. Thus, the determination of autoantibodies in SSc patients is helpful in assessing the prognosis, monitoring, and treatment.

Whereas the functions and roles of these ANAs remain unknown, intriguing functional autoantibodies have been reported in SSc recently. IgG from SSc patients has been known to show reactivity with human fibroblasts. Stimulatory antibodies to the platelet-derived growth factor (PDGF) receptor are found in patients with SSc [8]. PDGF stimulates the production of reactive oxygen species (ROS). These autoantibodies bind PDGF receptor on fibroblasts and stimulate fibroblasts, and thus may have a causal role in the pathogenesis of the disease [8]. Autoantibody to lipoprotein lipase (LPL), a key enzyme that hydrolyzes triglycerides, suggests a role of autoimmunity for elevated serum triglyceride levels and atherosclerosis in patients with systemic lupus erythematosus (SLE). The vascular damage in SSc consists mainly of microvascular changes, although recently macrovascular changes with dyslipidemia have been recognized. High prevalence of IgG or IgM anti-LPL antibodies has been detected in SSc patients [9]. The presence of IgG anti-LPL antibody is associated with elevated serum triglyceride levels, greater extent of skin fibrosis, and more frequent presence of lung fibrosis, heart involvement, and anti-topoisomerase I antibodies.

SSc patients also exhibit autoantibodies to a variety of extracellular matrix (ECM) regulation proteins, such as fibrillin 1, matrix metalloproteinases (MMPs), and heat-shock protein 47 [10–13]. Autoantibodies to MMP-1 is detected both in ~50% of SSc patients [12, 14]. MMPs are zinc-dependent endopeptidases that can digest extracellular matrix components. Fibrosis is caused by an abnormal accumulation of extracellular matrix components, which is regulated by both synthesis and degradation. Anti-MMP-1 antibody is unique because it can possibly act as a pathogenic autoantibody inducing fibrosis in SSc as it can inhibit MMP enzymatic activity and reduce the turnover of ECM [12]. In addition, a recent report has demonstrated that anti-topo I antibodies bound specifically to fibroblast surfaces and subsequently stimulated adhesion and activation of monocytes [15].

Cytokines and Chemokines

The abnormality of cytokines and chemokines, reflecting a deviated immune response, has been shown in SSc patients. Recently, interesting findings on the mechanism of cytokine-related skin fibrosis have been reported. Ferreira et al. have demonstrated that mice without monocyte chemoattractant protein-1 (MCP-1) do not develop skin fibrosis induced by bleomycin, suggesting that MCP-1 influences collagen fiber formation in vivo [16]. Indeed, serum MCP-1 levels are higher at the early stage of SSc [17]. Furthermore, serum endothelin-1 levels correlate with MCP-1 levels in SSc patients [18]. Expression of CCL2/CCR2 is upregulated in early dcSSc on cell types known to be activated in the disease, including myofibroblasts, pericytes, lymphocytes, macrophages, and endothelial cells. They suggest potential autocrine regulation of key profibrotic properties via a CCL2/CCR2 loop in early-stage dcSSc [19]. Kodera et al. have reported that serum concentration of pulmonary and activation-regulated chemokine (PARC) was elevated in SSc patients with pulmonary fibrosis and that monitoring PARC levels more sensitively reflected the PF activity than did serum KL-6 or SP-D levels in SSc [20]. Serum levels of monocyte chemotactic protein-3/CCL7 are also positively correlated with extent of skin sclerosis and severity of pulmonary fibrosis [21].

In SSc, serum levels of the Th2 cytokines interleukin 6 (IL-6) and IL-10 are higher at the early stage. Then, levels

of all Th2 cytokines generally decrease as skin sclerosis regresses. Conversely, serum levels of IL-12, a Th1-inducing cytokine, are initially lower but increase at later time points. A shift from Th2 to Th1 response correlates with improvement in skin fibrosis in SSc, and IL-12 level is a serologically useful marker for disease activity and prognosis [17].

Lymphocytes

The infiltration of mononuclear cells into the skin and other organs is one of the typical pathological findings at early stage in SSc patients. This inflammatory cell infiltration precedes the development of fibrosis, suggesting an integral role for the presence of these cells in the fibrotic events observed in the lesion. Furthermore, understanding the interplay between T and B cells, and the processes that promote the fibrotic cytokine pattern seen in SSc patients is important for the development of effective therapies to treat this disease.

a) T cells

T cells infiltrate organs undergoing fibrotic changes and may participate in dysregulated production of collagen by fibroblasts finally lead to abnormal excessive collagen deposition. The skin in early-stage SSc patients contained T cells that preferentially produce high levels of Th2 cytokine IL-4. Th2 cells are less potent than Th1 cells in inhibiting collagen production by normal fibroblasts via cell-to-cell interaction, and SSc fibroblasts are resistant to inhibition [22]. Despite their production of IL-4, Th2 cells reduce type I collagen synthesis by dermal fibroblasts because of the dominant effect of TNF alpha [22].

b) B cells

Initial studies of the pathogenesis in autoimmune diseases have been focused on the role of T cells. Numerous studies on the role of B cells have shown that B cells are more than just the precursors of antibody-secreting cells [23]. More essential functions of B cells in regulating immune responses have recently been reported. B cells have various kinds of functions including antigen presentation, production of various kind of cytokines, lymphoid organogenesis, differentiation of T effector cells, and influence of antigen-presenting dendritic cell (DC) function [23]. Abnormal B cell functions contribute to the induction and development of autoimmunity in systemic autoimmune diseases.

Recently, Matsushita et al have reported that BAFF, a potent B cell survival factor, are elevated in SSc patients and that BAFF levels are correlated positively with the extent of skin fibrosis [24]. Decreasing BAFF levels were accompanied by regression of skin sclerosis, whereas increasing levels of BAFF were associated with the new onset or worsening of organ involvement [24]. These results suggest that BAFF and its signaling in B cells contribute to B cell abnormalities and disease development in patients with SSc. Recently, Novobrantseva et al. have reported that B cells have an impact on fibrosis of the liver in an antibody- and T cell-independent manner [25], which suggests that B cells may also have some role for fibrosis in SSc patients.

Cell surface molecules on B cells are reported to be involved in the development of SSc. CD19 is a 95,000 Mr glycoprotein of Ig superfamily which is expressed by early pre-B cells from the time of immunoglobulin heavy chain rearrangement until plasma cell differentiation [26]. CD19-transgenic mice produce autoantibodies, including anti-topoisomerase I antibodies. Indeed, overexpression of CD19 is detected on B cells from SSc patients [27]. Studies of tight-skin (TSK) mice deficient in CD19 expression demonstrated that CD19 deficiency significantly decreased skin fibrosis in TSK mice [28]. Furthermore, CD19 polymorphisms are associated with genetic susceptibility to SSc [29].

c) DCs

DCs are central to the integration of innate and adaptive immunity and play a key role in regulating immune responses, especially in priming naive T cells. Recently, DCs have been suggested to be involved in SLE development by activating autoreactive T-helper lymphocytes by presenting self-antigens from apoptotic cells. DC activation by nucleic acid-containing IgG complexes has been implicated in SLE pathogenesis [30]. In case of SSc, recent study reported that topo I is recruited to nucleoplasmic proteosomes in response to xenobiotics for processing and antigen presentation in DCs from anti-topo I positive SSc patients [31]. Recruitment of topo I suggests a role for altered antigen processing in SSc.

Abnormality of Fibroblast Function

Specimens of the skin from SSc patients reveal excessive dermal accumulation of collagen fiber produced by fibroblasts. Excessive collagen deposition in the skin and viscera lead to organ dysfunction, and is responsible for the morbidity and mortality. Transforming growth factor (TGF)-beta is a key mediator of tissue fibrosis as a consequence of ECM accumulation in pathological states in SSc [32]. TGF-beta regulates diverse biological activities including cell growth, cell death or apoptosis, cell differentiation, and ECM synthesis. TGF-beta is known to induce the expression of ECM proteins in mesenchymal cells and to stimulate the production of protease inhibitors that prevent enzymatic breakdown of the ECM.

Fibroblasts from SSc patients exhibit numerous phenotypic differences. Previous reports indicated the signifi-

cance of the autocrine TGF-beta loop in the pathogenesis of SSc. There is a report of a disturbed negative regulation of TGF-beta signaling in SSc that the impaired Smad7-Smurf (principal molecules in the negative regulation of TGF-beta signaling)-mediated inhibitory effect on TGF-beta signaling might contribute to maintaining the autocrine TGF-beta loop in scleroderma fibroblasts [33]. TNF-alpha has anti-fibrotic activity. TNF-alpha triggers downregulation of TGF-beta receptor II, leading to desensitization of human dermal fibroblasts toward TGF-beta. These results indicate that TNF-alpha impairs the response of the cells to TGF-beta by regulating the turnover of TbetaRII [34]. In addition, Jinnin et al. indicated that novel lymphokine IL-13 produced by activated Type 2 helper cells play a role in the regulation of ECM [35].

Vascular Abnormality

During last few years, there were some interesting reports concerning functional changes of endothelial cells which lead to disturbances in tension of vessels smooth muscles. Reduced nitric oxide (NO) levels have been proposed to play a role in the pathogenesis of vascular disease in SSc. In SSc, derangement of the peripheral nervous system is linked to vascular tone dysfunction. NO produced by neuronal nitric oxide synthase (nNOS, NOS-I) might play a dynamic role in the control of vascular tone. Total cutaneous innervation and nNOS innervation slowly disappear in the skin of SSc patients [36]. Expression of nNOS depends on the severity of tissue damage in SSc, and increased synthesis of NO also contributes to this process [36]. Although previous studies have reported that circulating concentrations of most angiogenic factors were significantly higher in patients with SSc, there are no clear explanation for these elevation. Recently, Kuwana et al. provided a new insight into the pathogenesis of this disorder in terms of dysregulated vasculogenesis showing the abnormality of the low proportion of circulating endothelial precursors (CEP) (identified as circulating cells positive for CD34, CD133, and the type 2 receptor for vascular endothelial growth factor), which are involved in vasculogenesis in the formation and repair of blood vessels and differentiated into endothelial cells [37].

Treatments

Numerous progress in the understanding of the pathogenesis with identification of key molecules have permitted the introduction of novel treatments that improve the management of some aspects of the disease. ACE inhibitors have been revealed to be effective in resolving renal crisis [38]. Cyclophosphamide is useful for the treatment of fibrosing alveolitis. Prostaglandins, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors permit to improve the treatment of the vascular complications of SSc.

Skin

Skin Sclerosis

Intravenous immunoglobulin (IVIG) is a potent immunomodulating agent whose efficacy has been demonstrated in various immune-mediated disorders [39, 40]. There is a report of three SSc patients whose TSS improved after IVIG therapy [41]. Our study also presented a case of marked improvement of skin sclerosis in SSc patients and demonstrated restoration of expression of TGF-beta receptors by IVIG therapy, which is upregulated in scleroderma fibroblasts [42]. Although additional studies are needed, IVIG therapy for SSc may be a promising choice for treating skin sclerosis in SSc patients.

TGF-beta is also a potential therapeutic target of fibrosis in SSc. Topical application of P144, a peptide inhibitor of TGF-beta effectively inhibit fibrosis in different animal models [43]. Nonetheless, a trial using anti-TGF-beta antibody for SSc patients has been reported to fail to prove an efficacy.

B cells have been recently recognized as therapeutic targets for systemic autoimmune disorders. B cell depletion by chimeric anti-CD20 mAbs, which is a safe therapeutic option for B cell lymphoma, has been shown to be effective for rheumatoid arthritis and SLE. These evidences suggest that, in addition to autoantibody production, other roles of B cells, for example antigen-presentation or cytokine secretion, are also important in disease pathogenesis. B cell depletion therapy using anti-CD20 mAb may be effective also for SSc, as anti-CD20 therapy decrease skin thickening of the TSK mouse by approximately 40% (Hasegawa et al., in press). Furthermore, based on the CD19 importance in SSc, immunotherapy using CD19 monoclonal antibodies might be effective in patients with SSc [44].

Skin Ulcers

Digital ulcers (DU) occur in up to 50% of patients with limited or diffused SSc. These lesions are extremely painful and lead to substantial functional disability. The pathogenesis of DU differs depending on their location. DU located at distal aspects of digits are thought to be related to tissue ischemia from several processes, including vasospasm secondary to Raynaud's phenomenon, intimal fibroblast proliferation, and thrombosis of digital arteries. DU located over bony prominences, such as the phalangeal joints and elbows, are thought to be caused by repetitive microtrauma and difficulty healing because of atrophic, avascular tissue overlying the

joints. Treatment with sildenafil was effective for severe refractory fingertip ulcerations of SSc [45]. Treatment with the endothelin receptor antagonist bosentan may also be effective in preventing new digital ulcers and improving hand function in patients with SSc [46–48]. Endothelial cell FGF receptors are directly stimulated by bFGF (basic fibroblast growth factor). bFGF promotes the regeneration of capillary-rich granulation tissue. Topical application of recombinant human bFGF successfully treats therapy-resistant ulcers in SSc [49]. A pilot study has shown the efficacy of subcutaneous treprostinil for the treatment of digital ulcers, although the high rate of injection site reactions may limit the utility of this therapy [50].

Lung

Recent studies highlight the contribution of microvascular disorder, autoimmunity, and fibroblast differentiation/activation to the pathogenesis of SSc–interstitial lung disease, particularly in the early phase of disease. It appears as if the balance between various profibrotic/proinflammatory and anti-fibrotic/anti-inflammatory mediators may be central to interstitial lung disease pathogenesis, which presents potential opportunities for therapeutic intervention. The clinical approach to staging of disease activity remains controversial. High resolution computed tomography scans [51], bronchoalveolar lavage [52] and various serum markers (e.g., surfactant protein D and KL-6) [53, 54] each may provide useful information about the degree of activity of the SSc–interstitial lung disease.

A large scale double-blind, randomized, placebo-controlled trial to determine the effects of oral cyclophosphamide on lung function and health-related symptoms in patients with evidence of active alveolitis and scleroderma-related interstitial lung disease was recently reported [55]. One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life [55]. Furthermore, the preliminary data suggest that in patients with dcSSc and recent, clinically apparent alveolitis, early treatment with mycophenolate mofetil and small doses of corticosteroids may represent an effective, well-tolerated, and safe alternative therapy [56].

Heart

Heart disease is a frequent and often severe feature of SSc. Cardiomyopathy with ventricular diastolic dysfunction and arrhythmias is the most important form, as it is associated with a very poor prognosis. Ultrasound cardiography (UCG) is an available method for detecting the cardiac lesion in patients with SSc. Recently, there is a report that magnetic resonance imaging is useful for the detection of myocardial fibrosis in SSc [57].

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is found in approximately 10–15% of patients with SSc. PAH is a major prognostic factor for survival in SSc, independent of interstitial lung disease [58]. Recent investigations brought new information considering the pathogenesis of PAH and allowed new therapeutic approaches to be introduced. Early diagnosis of PAH is a key issue in clinical practice. Chang et al. have reported that the three risk factors for progression of PAH are older age, limited skin disease, and elevated pulmonary artery pressures at the time of initial evaluation [59]. Screening based on dyspnea, Doppler echocardiographic evaluation of velocity of tricuspid regurgitation, and right heart catheterization enables early detection of PAH at a mild stage [60]. Conventional therapy with vasodilators and anticoagulants is effective for only a few cases. Bosentan is clinically beneficial in SSc patients with PAH including patients with restrictive lung disease, although pulmonary hemodynamics and pulmonary function test results often remain stable during treatment [61].

Conclusions

Recent understanding of the pathogenesis of SSc provides many clues for therapy and allows new therapy to be tailored according to the most active events at every stage. Further studies are needed to reveal the mechanisms of developing SSc.

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