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Survey

New insights into CD4$^+$ T cell abnormalities in systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is an autoimmune connective tissue disease that is characterized by vasculopathy and excessive deposition of extracellular matrix, which causes fibrosis of the skin and internal organs and eventually leads to multiorgan dysfunction. Studies have shown that CD4$^+$ T cell activation is a key factor in the pathogenesis of scleroderma because activated T cells can release various cytokines, resulting in inflammation, microvascular damage and fibrosis. T helper cell 17 (Th17) and regulatory T (Treg) cell activities are a hallmark SSc, as Th17-type cytokines can induce both inflammation and fibrosis. More recently, several studies have reported new T cell subsets, including Th9 and Th22 cells, along with their respective cytokines in the peripheral blood, serum and skin lesions of individuals with SSc. Herein, we review recent data on various CD4$^+$ T helper cell subsets in SSc, and discuss potential roles of these cells in promoting inflammation and fibrosis.

Contents

1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterized by inflammation and vascular abnormalities of the skin and internal organs, which lead to progressive fibrosis. The incidence of SSc is approximately 20 cases per million individuals per year and its prevalence is more than 250 patients per million individuals in the USA [1]. SSc mainly affects middle-aged women, in whom the average age of onset is 45 years old; however, it can also affect men, children, and the elderly [2]. Clinically, SSc is a heterogeneous disease, and its overall progression can vary from relatively benign to rapid changes, resulting in an extremely shortened life expectancy of patients. Based on the extent of skin involvement, autoantibody titers, and the pattern of organ involvement, SSc can be divided into the following two major

Abbreviations: ACA, anti-centromere antibodies; ACR, American College of Rheumatology; ANA, anti-nuclear antibodies; ARA, anti-RNA polymerase III antibodies; CCL-20, chemokine (C–C motif) ligand 20; CXCR-4, chemokine (C-X-C motif) receptor 4; dcSSc, diffuse cutaneous subset; DVSMCs, dermal vascular smooth muscle cells; ET-1, endothelin-1; EULAR, European League Against Rheumatism; ICAM-1, intercellular adhesion molecule 1; ICOS, inducible costimulator; IL-17, interleukin-17; lcSSc, limited cutaneous subset; NKT, natural killer T cell; PD-1, programmed death-1; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, sjögren syndrome; SSc, systemic sclerosis; Tfh, T follicular helper cells; TGF-β, transforming growth factor-β; Th17, T helper cell 17; TNF, tumor necrosis factor; Treg, regulatory T cell; TSK-1, tight skin-1; VCAM-1, vascular adhesion molecule 1.

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clinical subgroups: the limited cutaneous subset (lcSSc) and the diffuse cutaneous subset (dcSSc). Because of the heterogeneity of clinical symptoms and signs, the American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR) recently developed a new classification criteria [3,4], which will improve sensitivity and lead to earlier diagnoses. No curative treatment yet exists for SSc, and current therapies are tailored to treat its clinical manifestations and SSc-related pathologies. Currently, there are limited therapeutic options for patients with SSc, so advances in understanding the pathogenesis of this disease will be critical to the development of novel treatments. In the past two decades, one important advance has been the characterization of aberrant $CD4^+$ Tcell activation in SSc. In this review, we analyze the role of T cells and their associated cytokines in SSc based on experimental and clinical data.

2. An autoimmune abnormality: linking vascular dysregulation to fibrosis

Vascular dysregulation is an important feature of SSc, which occurs at the earliest stage and exists throughout the course of the disease. In the early stages of scleroderma, endothelial cells are activated and adhesion molecules expressed on endothelial cells promote the perivascular infiltration of inflammatory cells, which ultimately leads to endothelial dysfunction and apoptosis [5]. Activated endothelial cells can also release endothelin-1 (ET-1), a potent vasoconstrictor that promotes leukocyte adhesion, vascular smooth muscle cell proliferation, and fibroblast activation [6]. Abnormal vascular reactivity associated with structural fibrosis of blood vessels can result in severe tissue hypoxia, reduced capillary blood flow, intimal hyperplasia, and outer membrane fibrosis.Ultimately, these responses can result in corresponding clinical manifestations, such as Raynaud's phenomenon, digital ulcers, pulmonary hypertension, and hypertensive renal crisis [7,8].

Fibrosis, another clinical hallmark of SSc [9], results from increased extracellular matrix (mainly types I and III collagen) synthesis and reduced degradation, which results from the dysfunction of fibroblasts, smooth muscle cells and stromal cells. The normal connective tissue is gradually replaced by abundant extracellular matrix, leading to affected organ dysfunction and causing pathological changes. In SSc, fibroblast or vascular smooth muscle cells can be converted into myofibroblasts or synthetic vascular smooth muscle cells, which can produce collagen, transforming growth factor-β (TGF-β), CTGF, IL-6, ET-1, or monocyte chemoattractant protein-1, which can promote cell proliferation and reduce apoptosis.

In addition to vasculopathy and fibrosis, autoimmune abnormalities are another hallmark of SSc that can play crucial roles in the development of these aforementioned histopathological abnormalities [10]. Recently, it has become more accepted that the pathogenesis of SSc might be described by the autoimmune abnormality theory, which can link vasculopathy and fibrosis (see Graphical abstract). Innate and adaptive immune abnormalities can be observed in SSc, and immune cells may trigger the complex molecular and biochemical changes that occur in vasculopathy and fibrosis; however, the details of the underlying mechanism remain to be elucidated. Multiple studies have provided direct evidence that immunity is involved in the pathogenesis of SSc. Histological examinations of the skin of patients with SSc during the early edematous inflammatory phase have revealed the presence of mononuclear cell infiltrates that contain γdT cells with a perivascular distribution,which precedes the development of microangiopathy and fibrosis [11–15]. Notably, fibroblasts with increased expression of type I and III procollagen mRNA can frequently be detected in areas adjacent to the infiltrating mononuclear cells, suggesting that inflammatory cells, particularly T cells, are responsible for the altered functional fibroblast phenotype [16]. T cell infiltration is more obvious in the edema stage than in the hardening stage. $CD4^+$ T cell infiltration is significantly increased in skin lesions and peripheral blood of patients with SSc, and most of the T cell clones in skin lesions can express the CD4 co-receptor. Recently, it has been reported that $CD4^+CD8^+$ double-positive T cells exist in skin lesions of patients with scleroderma [17]. A TCR analysis of T cells infiltrating in skin lesions of SSc patients reveal oligoclonal T cell characteristics, suggesting that T cell proliferation and clonal expansion in response to unknown specific antigens may occur [18]. Activated T cells can activate adjacent fibroblasts via direct cell–cell contact or via paracrine cytokine and chemokine production. Furthermore, autoreactive T cells may interact with B cells to promote the production of characteristic autoantibodies. Antinuclear antibodies (ANAs) are present in approximately 95% of SSc patients and typically show speckled or nucleolar patterns in stains of cells, such as for anti-topoisomerase-I antibodies, anti-centromere antibodies (ACA) and anti-RNA polymerase III antibodies (ARA). The identification of different types of ANA is important for the diagnosis, classification and prognosis of SSc, but no definite evidence that such antibodies can promote tissue fibrosis has been reported [19]. Thus, T cell abnormalities may contribute to the initiation and/or promotion of pathological process, leading to vasculopathy or fibrosis in patients with SSc. However, the causative events that may trigger an altered immune reaction remain unknown.

2.1. The Treg/Th17 dichotomy in SSc

Although the classic paradigm of Th1/Th2 polarization in the pathogenesis of SSc has long been appreciated, and recent evidence indicates that Th1/Th2-type cytokines often act in collaboration with cytokines that are elaborated by newly discovered $CD4^+$T cell subsets. Evidence for functional and numerical changes of regulatory T (Treg) cells in SSc has been obtained in several studies, but the role of Treg cells in scleroderma is controversial. Some studies have shown that the number of $CD4^+CD25^+FoxP3^+$Treg cells in skin lesions and peripheral blood of patients with SSc increase significantly [20], especially in patients in the active stage or who are seriously ill [21]. Other studies have shown that, compared with healthy subjects, the number of Treg cells in patients with SSc are reduced and show an abnormal function [22–26]. Klein et al. [27] have shown that the absolute number of Treg cells in the peripheral blood was similar in SSc patients and healthy controls. Radstake et al. [28] found an increased overall number of Treg cells in SSc patients, but these cells had a diminished functional capacity to suppress effector $CD4^+$ T cells, which was dependent upon an unidentified serum factor. Some studies have indicated that Treg cells can be transformed into Th17 cells in the presence of IL-1β, IL-2, IL-23 or TGF-β [29]. Thus, conditions may exist that both favor fewer Treg cells and more Th17 cells in SSc patients [25]. Therefore, understanding the role of Treg cells in SSc will require further study.

More recently, the importance of Th17 cells and interleukin (IL)-17 in the pathology of human diseases have become apparent. Th17 cells are a novel subset of $CD4^+$ T helper cells that primarily secrete IL-17A, IL–17 F and/or IL-22, and act as anti-bacterial and anti-fungal agents [30,31]. Th17 cells and their associated signature cytokines play pivotal roles in the pathogenesis of many autoimmune-mediated inflammatory diseases, including experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, and collagen-induced arthritis [32]. Previous studies have shown that