AUTOIMMUNE CONNECTIVE TISSUE DISEASES

IMMUNOLOGICAL ABNORMALITIES IN SYSTEMIC SCLEROSIS

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Systemic sclerosis (SSc) is an autoimmune disease marked by excessive extracellular matrix deposition in the skin and internal organs. Three major abnormalities, including autoimmunity, vasculopathy, and fibrosis, are considered to play important roles in the pathophysiology of SSc. A variety of immunological abnormalities of cytokines, T cells, B cells, and macrophages have been detected in SSc. Among them, IL-6 thought to be a potential target for treating SSc. Serum IL-6 levels are elevated in patients with SSc and associated with the extent of skin fibrosis, and IL-6 plays a critical role in tissue fibrosis and autoimmunity in mouse models of SSc. Furthermore, the administration of anti-IL-6R Ab in mice attenuated skin fibrosis in the scleroderma mouse models. In humans, a phase-III trial of anti-IL-6 receptor antibody tocilizumab demonstrated clinically improvement of the fibrosis in patients with SSc.

B cells also thought to be a potential target for treating SSc, since over 90% of the patients are positive for autoantibodies, which react to various intracellular components. SSc patients have been reported to show distinct abnormalities in blood B lymphocyte compartments, characterized by expanded naive B cells and activated memory B cells. In addition, B cells from SSc patients overexpress CD19, a critical cell-surface signal transduction molecule, by ~20%. B cell activating factor belonging to the tumor necrosis factor family (BAFF) has also been reported to be elevated in patients with SSc and to be correlated with the severity of SSc. Furthermore, B cell depletion therapy with rituximab, a CD20 mAb that depletes human pan-B cells, has shown beneficial effects on skin and lung fibrosis in patients with SSc. However, there are two opposing B cell subsets: regulatory B cells and effector B cells. Interleukin (IL)-10-producing regulatory B cells inhibit the immune system, inflammation, and autoimmunity, while IL-6 producing effector B cells promote it. Our study has shown that the skin and lung fibrosis was attenuated in B cell-specific IL-6-deficient mice, whereas B cell-specific IL-10-deficient mice showed more severe fibrosis. Thus, IL-6 producing effector B cells play a pathogenic role in SSc while IL-10 producing regulatory B cells play a protective role. Therefore, a protocol that selectively depletes effector B cells would represent a potent therapy for SSc. In this paper, I will review the immunological abnormalities in SSc, focusing on IL-6 and B cells.