Immunology Letters xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Pathogenic roles of B lymphocytes in systemic sclerosis

Ayumi Yoshizaki

Department of Dermatology, The University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, 113-8655, Japan

ARTICLE INFO

Keywords:
Systemic sclerosis
Autoimmunity
Fibrosis
B cell
Therapy

ABSTRACT

Systemic sclerosis (SSc) is a collagen disease characterized by autoimmunity and excessive extracellular matrix deposition in the skin and visceral organs. Although the pathogenic relationship between systemic autoimmunity and the clinical manifestations of SSc remains unknown, SSc patients show a variety of abnormal immune activation including the production of disease-specific autoantibodies and cytokine production. Many recent studies have demonstrated that immune cells, including T cells, B cells, and macrophages, have a variety of immunological abnormalities in SSc. So far, several groups and our group reported that B cells play a critical role in systemic autoimmunity and disease expression through various functions, such as cytokine production, lymphoid organogenesis, and induction of other immune cell activation in addition to autoantibody production. Recent studies show that B cells from SSc patients demonstrate an up-regulated CD19 expression, a crucial regulator of B cell activation, which induces chronic hyper-reactivity of memory B cells and SSc-specific autoantibody production and also causes fibrosis of several organs. Furthermore, in SSc-model mice, such as tight-skin mice, bleomycin-induced SSc model mice, and DNA topoisomerase I and complete Freund's adjuvant-induced SSc model mice, have abnormal B cell activation which associates with skin and lung fibrosis. Indeed, B cell depletion therapy using anti-CD20 Ab, Rituximab, is considered to one potential beneficial treatment for patients with SSc. However, there is no direct evidence which can explain how B cells, especially autoantigen-reactive B cells, progress or regulate disease manifestations of SSc. Collectively, B cell abnormalities in SSc is most likely participating in fibrosis and tissue damage of SSc. If the relationship between SSc-specific tissue damage and B cell abnormalities is revealed, these findings lead to novel effective therapy for SSc.

1. Introduction

Systemic sclerosis (SSc) is a collagen disease characterized by excessive extracellular matrix (ECM) deposition in the skin and visceral organs with an autoimmune background [1]. Although the pathogenesis of SSc remains unclear, three major abnormalities, including immune cell activation, collagen accumulation, and vascular damage, are considered as a triad of disease conviction [2–4]. Collagen accumulation crucially causes fibrosis of the several organs, such as skin, lungs, heart, and intestine. Vascular damage mainly consists of Raynaud's phenomenon, digital ulcers/gangrene, scleroderma renal crisis, and pulmonary hypertension. Immune cell activation is characterized by the release of various fibrogenic cytokines and autoantibody production. SSc patients have autoantibodies that bind to various intracellular components, such as DNA topoisomerase I (topo I), centromere, RNA polymerases, U1RNP, U3RNP, Th/To, and histones, though these distinct subsets of autoantibodies do not have a proven pathogenic role [5]. However, the presence of autoantibodies is a central feature of immune activation associated with SSc, because antinuclear antibody (Ab) has been detected in > 90% of patients [5].

Recent studies have shown that B cells have various crucial roles in immune response regulation [6–8] than that had been previously appreciated (Fig. 1). For example, B cells exert the function of antigen presentation, cytokine production, lymphoid organogenesis, and differentiation and/or activation of T cells, dendritic cells, and macrophages. In Consequence, not only autoantibody production but also abnormalities of other B cell function could lead to the induction or development of autoimmune disorders. In fact, SSc patients have polyclonal B cell hyperactivity and hyper-γ-globulinemia in addition to autoantibody production [9]. Thus, B cell abnormalities are likely to be critical for the development and progression of the disease, including SSc-specific tissue fibrosis and vascular damage (Fig. 2). However, it remains unknown how these three major abnormalities can be unified into one hypothesis. In this review, we will focus on the B cell abnormalities that may participate in initiating and/or developing fibroblast modifications that are characteristically observed in SSc.

E-mail address: ayuyoshi@me.com.

https://doi.org/10.1016/j.imlet.2018.01.002
Received 8 September 2017; Received in revised form 4 January 2018; Accepted 4 January 2018

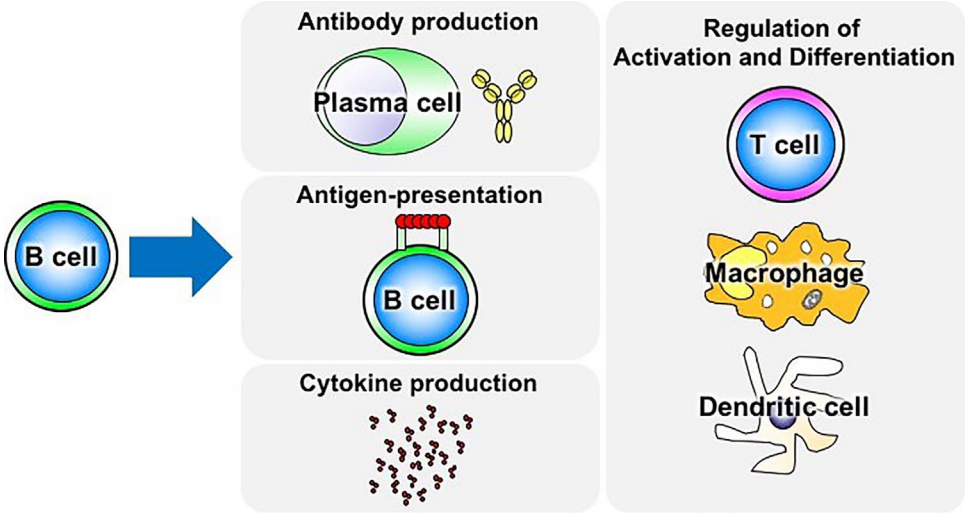

Fig. 1. Multiple roles of B cells in the immune system. B cells regulate the immune system activation and development. B cells are not only involved in autoantibody production but also antigen-presentation, cytokine production and interaction with T cells and other antigen presenting cells, including macrophages and dendritic cells.

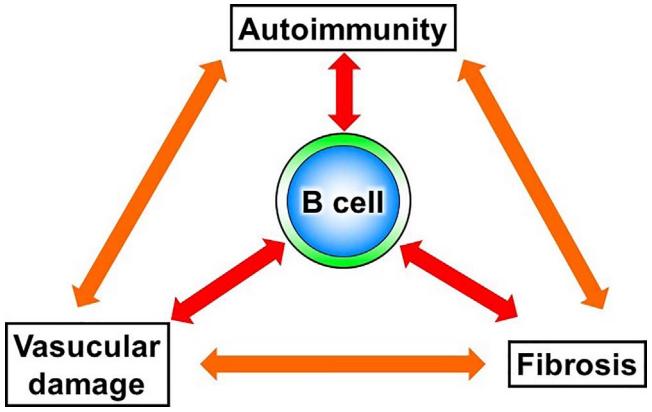

Fig. 2. B cells play crucial roles in three major abnormalities of SSc. SSc is characterized by autoimmunity, tissue fibrosis, and vascular damage. Although the pathogenic relationship among these three major abnormalities are still unclear, it is proven that B cells play central roles in these abnormalities.

2. B cell function and abnormalities in SSc patients

2.1. B cell abnormal activation

B cells respond to a lot of stimulation, which regulates the negative selection in the bone marrow, the generation of humoral immune responses in the peripheral lymphoid organs, and the establishment and maintenance of tolerance and memory. The outcome of these B cell responses is determined by signaling thresholds via B cell antigen receptor (BCR) complex signaling during B cell responses to self and foreign antigens [10]. In SSc patients, autoantibodies are present in > 90% of patients and selectively correlated with disease-specific clinical manifestations. These facts potentially indicate that autoantigen-reactive B cells activate in SSc patients. In addition, hyper-γ-globulinemia and polyclonal B cell activation are also found in SSc patients [11,12]. The circulating memory B cells were shown to exhibit a chronical activation, clonal expansion, and antibody production [13]. Furthermore, elevated levels of B cell activating factor, which is an important mediator in B cell survival, have been detected in the plasma of SSc patients [14]. Recent studies using DNA microarrays have also revealed up-regulation of gene expression related to B cell activation [9]. These observations suggest the presence of intrinsic or extrinsic B cell hyper activation in SSc. These chronic B cell activations are likely to be critical for the development and progression of the disease. In addition, a defective negative selection and/or excessive positive costimulation could predispose to SSc autoimmunity by prolonged survival of circulating autoantigen-reactive B cells.

2.2. Regulatory B cells

Chronic B cell activation is likely to be critical for the development and progression of the disease. By contrast, specific B cell subsets can also negatively regulate immune reaction and have been termed regulatory B cells [15–18]. Regulatory B cells have been identified as the cells which have the ability to express the inhibitory cytokine of interleukin (IL)-10 [16,17,19,20]. Previous studies have shown that IL-10-producing regulatory B cells dramatically inhibit the induction of antigen-specific inflammatory reactions and autoimmunity, though they only represent 1–2% of total B cells [21,22]. Although rare, regulatory B cells are potent negative regulators of antigen-specific inflammation and T-cell-dependent autoimmune diseases [20–22]. Recent our study using a mouse model for multiple sclerosis have revealed that regulatory B cell maturation into functional IL-10-secreting effector cells which inhibit in vivo autoimmune disease requires IL-21 and CD40 dependent cognate interactions with T cells (Fig. 3). Furthermore, both CD40 and IL-21 receptor signals drive regulatory B cell expansion by four-million-fold and induce IL-10 production that can inhibit disease symptoms when transferred into mice with established autoimmune disease [15]. In SSc patients, some studies have revealed that the frequency of blood regulatory B cells significantly decreased than in healthy controls [23] [Mavropoulos A&R 2016, 68; 494–504]. They have indicated that regulatory B cell levels also negatively correlated with the titer of anti-topo I Ab and anticentromere Ab in SSc patients [23]. Furthermore, it is also revealed that memory regulatory B cells especially decreased in SSc patients [Mavropoulos A&R 2016, 68; 494–504]. Taken together, B cells may regulate multiple components of the immune system and development of SSc and other autoimmune diseases through varied combinations of their multipurpose cellular and humoral functions [21,24–26].

2.3. Response regulators of B cells

Recent studies have demonstrated that many response regulator molecules control B cell responses using mice lacking or overexpressing certain molecules [10,27,28]. CD19, CD21, and CD45 have been identified as a group of positive response regulators, which augment signals through the BCR complex, while CD22, CD72, and FcγRIIB have been grouped as negative response regulators that diminish BCR signals [10,27–31]. CD19 transgenic mice which have over expression of CD19 lose tolerance and generate autoantibodies spontaneously [32,33], whereas CD22 deficient mice have chronically activated B cells with