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EDITORIAL

The target on B cells in Systemic Sclerosis: a "midsummer dream" to extinguish inflammation and prevent early disease progression to fibrosis

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The review by Melissaropoulos and Daoussis, focusing the attention on B-cell aberrations, provides a comprehensive overview on B-cell depletion as a therapeutic approach in systemic sclerosis (SSc) [1]. Several points deserve attention: *the origin of B-cell activation in SSc*, *the role T and B-cells cross-talk*, *the B-cells differentiation into plasmacells and autoantibodies production*, *and B-cells as therapeutic target.*

In the late 1980s, the polyclonal hyperactivity of B-lymphocytes emerged as a major immunologic feature in SSc [2]. Studies have shown that B-cells were significantly expanded, with increased naïve population and reduced activated memory B-cells [3], while B-regulatory cells were decreased and functionally impaired [4].

Likely, the continuous loss of memory B-cells and plasmablasts/early plasmacells may lead to an increased production of naïve B-cells in the bone marrow to maintain B-cell homeostasis [3, 5]. Although memory B-cell numbers are decreased in SSc patients, remaining cells have an enhanced ability to produce immunoglobulins and autoantibodies [6].

In the tight-skin mouse model, a B-cell hyper-reactive phenotype has been identified, reflecting a dysregulation of the CD19/CD22 "positive/negative" loop [7]. In the bleomycin-induced mouse model, the CD19 deficiency attenuates skin and lung fibrosis and downregulates inflammatory and pro-fibrotic cytokines [8].

In SSc, both the triggers and the origin of B-cell activation and B-cell dysregulation remain elusive.

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Retracing B-cells lifecycle, in the bone marrow lies the first checkpoint of the immune system, which concerns the modification of immature autoimmune B-cells with receptor editing or clonal deletion. The failure of this mechanism of central tolerance can lead to the genesis of autoimmune clones that may trigger systemic autoimmune diseases like SSc. Infectious agents have been widely proposed as triggers of autoimmunity. Parvovirus-B19 bone marrow infection has been identified in SSc, indirectly suggesting a role as a trigger for B-cells clone expansion [9]. Infections could also act as triggers for the activation of immune system, driving B-cells expansion [10]. Antibodies against human cytomegalovirus (CMV) have been shown to induce endothelial cell apoptosis, being a possible link between CMV infection and SSc onset in susceptible individuals [10].

In SSc patients, the association of anti-RNA polymerase-III antibodies (RNAP) with cancer in close temporal relationship with the disease onset [11] suggests that tumorigenesis may be involved in B-cell activation and differentiation towards RNAP-producing B-cells, with a potential pathogenic role in SSc progression (Fig. 1).

Together with endothelial dysfunction, tissue inflammation is an early pathogenic event in SSc, preceding and paralleling the evolution of fibrosis. As for many human diseases, a prompt activation of the innate immunity represents the front line in response to various stimuli. Experimental data support the role of innate immunity in SSc, with cellular metabolism imbalance, inflammasome activation, and interleukin (IL)-1β release as main early events [12]. These are followed by a robust inflammatory cascade, involving downstream pro-inflammatory and pro-fibrotic pathways, promoting SSc progression. The inflammatory outburst is involved in adaptive immune activation and in B-cell activation. In SSc, evidence indicates that also fibrotic tissue is infiltrated by B-cells. Lung biopsies and bronchoalveolar lavage fluids present an increased number of B-cells [13]. In SSc involved skin, mononuclear cells are found [14], underlying the possible role of

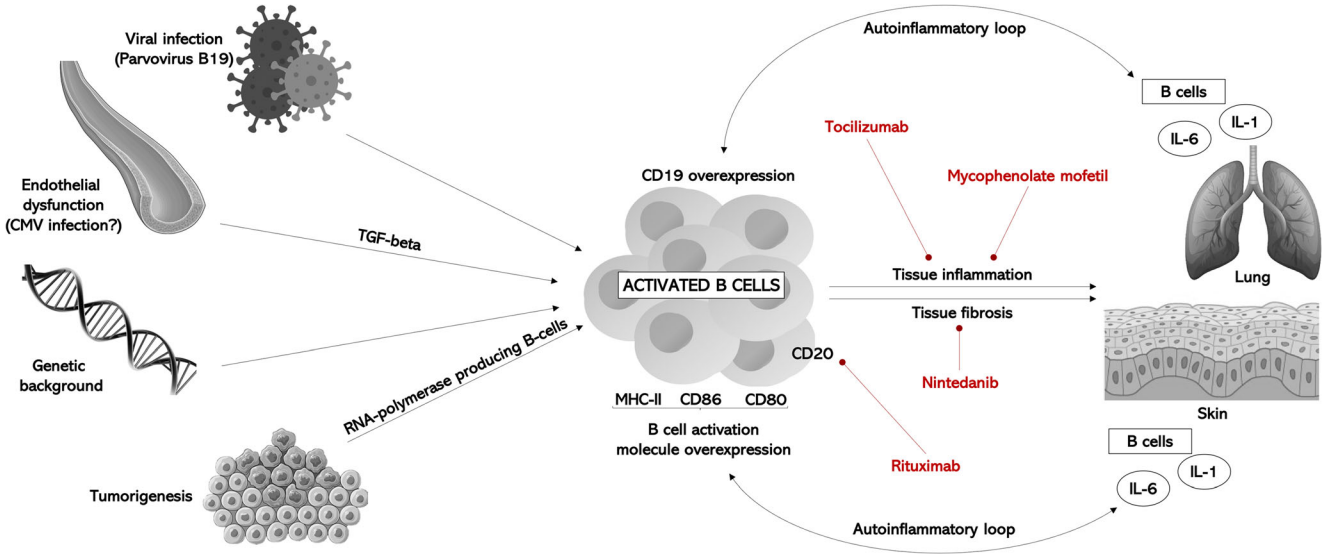

Fig. 1 B cells in systemic sclerosis. B cells are activated and dysregulated in systemic sclerosis (SSc), infiltrate target organs and tissues such as the skin and the lungs, and represent a possible target for therapy. In early SSc, an interplay between endothelial dysfunction, innate immunity, the pro-inflammatory/pro-fibrotic Th2-cytokine milieu, and the adaptive immunity with T-cells and B-cells cross-talking, synergistically lead to B-cell activation and differentiation. Infectious agents and tumorigenesis might further boost these events and, together with genetic background, might promote B-cell activation and, possibly, B-cell clonal expansion in some SSc patients. Activated B cells overexpress CD19, MHC-II, and co-stimulatory molecules, secrete inflammatory cytokines as IL-6, and migrate to the site of inflammation, thus contributing to tissue damage and foraging this detrimental pro-inflammatory/pro-fibrotic loop. Currently available therapeutic strategies could target both inflammatory pathways (with anti-CD20 Rituximab and/or mycophenolate mofetil or anti-IL6 tocilizumab), and pro-fibrotic pathways (with nintedanib), to extinguish inflammation and to prevent early disease progression to fibrosis

inflammatory cell infiltrates, while B-cells infiltration in the skin characterizes SSc patients with early diffuse disease and correlates with skin progression [14]. These results, together with the fact that lung and skin fibrosis is always preceded by an early inflammatory phase, might be the proof that activated B-cells migrate to the site of inflammation and contribute to tissue damage.

The early inflammatory activation is important for plasmacells differentiation and T-cells/B-cells cross-talk. Among the inflammatory pathways, the pleiotropic cytokine IL-6 is a key cytokine in the immune-inflammatory SSc pathogenesis, and is regarded as a B-cell differentiation factor [15, 16]. IL-6 is produced by B-cells and various other cell types, and induces the production of collagen and glycosaminoglycans by dermal fibroblasts, stimulates the proliferation and differentiation of B-cells, and enhances antibodies production [6]. The increased IL-6 levels in SSc skin and serum suggest its role in promoting fibrosis by enhancing inflammation and promoting B-cells activation [6]. Moreover, IL-6 is fundamental in B-cell differentiation to plasmacells and in polyclonal plasmacells abnormalities [17]. The IL-6 rich milieu typical of SSc patients could support both B-cells activation and differentiation [16].

The humoral immunity and B-cell activation are facilitated by a T-helper (Th)-2 environment, characterized by increased production of IL-4, IL-5, IL-6, IL-10, and IL-13. These Th2-cytokines enhance immunoglobulin production by B-cells, and stimulate the synthesis of collagen by human fibroblasts [6, 18]. Therefore, a shift to Th2 cytokines can induce tissue fibrosis, B-cells activation, and antibody production. Activated B-cells express high levels of class-II major histocompatibility complex and co-stimulatory molecules, and are nearly as effective as dendritic cells in their antigen-presenting capacity. Antigen-presenting cells (APC) have a role in Th: B-cells differentiation, and their APC activity promotes the development of Th2-cells [6, 19]. Activated B-cells also produce IL-6 and IL-10, both of which induce Th2-dominant immune responses, foraging this detrimental biologic loop [6].

In early SSc, an interplay between innate immunity, the pro-inflammatory/pro-fibrotic cytokine milieu (leading to tissue inflammation), and the adaptive immunity with T-cells and B-cells cross-talking, synergistically lead to B-cell activation and differentiation, and also to B-cell subsets dysregulation. In this context, infectious agents and tumorigenesis might further boost these events, promoting B-cell activation and, possibly, B-cell clonal expansion in some SSc patients. We know that the interaction between SSc, cancer, and infections stands as a fascinating hypothesis but it is clear that it needs to be further explored.

In the last decade, B-cells emerged as a possible therapeutic target in SSc. Rituximab (RTX), a chimeric monoclonal antibody against CD20 surface antigen, has been used to treat SSc skin and lung involvement [20–28]. Most studies have reported a favorable effect of RTX on skin disease with clinically significant reduction of the skin score, and a stabilization of pulmonary function. This has been recently corroborated by the

data obtained by the EUSTAR registry [28, 29]. The same results have been also obtained with RTX biosimilars [30], and are supported by two meta-analyses [31, 32].

However, most studies are open-label, lack a control group, and are characterized by clinical heterogeneity of the included patients, the background treatment, and the follow-up. Only 3 randomized studies have assessed the use of RTX compared to standard treatment [33–35]. A recent head-to-head open-label, non-inferiority, randomized trial of RTX compared to monthly pulses of cyclophosphamide (CYC) has shown that RTX is a safe and effective alternative to CYC in the primary therapy of SSc skin and lung manifestations [35, 36]. A large-scale study comparing RTX versus CYC in connective tissue disease-ILD (RECITALNCT01862926) is ongoing, and results are awaited. The 2-year follow-up of the 8 patients of the randomized trial with RTX continuing treatment revealed a sustained improvement of the skin score and lung function [25]. A non-randomized prospective multicenter trial involving 51 patients on RTX compared with patients on standard immunosuppressive treatment showed a significant effect of RTX on stabilization of pulmonary function and skin improvement over a 7-year follow-up, revealing a possible need for continuous treatment in RTX responders [26]. Repeated RTX course were reported even in the studies from our group [27, 30]. A continuous intensified RTX treatment protocol (500mg within 2 weeks every 3 months) has been proposed [37].

It has been shown that skin B-cells infiltration is present in early diffuse skin disease and correlates with skin progression [14]. This evidence provides a biologic rationale to support the use of RTX in the early stages of the disease to promptly dampen the progression to fibrosis, but it is undeniable that RTX efficacy should be thoroughly investigated in randomized trials.

The recent FDA-approval of tocilizumab and nintedanib for the treatment of SSc-ILD [38, 39] could further limit RTX to a rescue therapy for lung involvement. The SENSCIS trial has shown that a combination treatment with an anti-inflammatory drug (mycophenolate mofetil-MMF) and an anti-proliferative drug (nintedanib) represents an effective and acceptably safe treatment for SSc-ILD [39]. In the future, a possible combination of RTX/nintedanib might represent an alternative therapeutic approach in early SSc patients. Given the biologic role of B-cells in SSc, at crossroad between inflammation and fibrosis, the possibility to combine RTX/MMF and nintedanib might looks hazardous today, but in the future, it might represent a fascinating opportunity, which should be carefully investigated. In fact, data from the EUSTAR registry and other studies show that the combination RTX/MMF could be effective on lung fibrosis [29, 40]. Thus, the combination of a double anti-inflammation/immunosuppression with an anti-proliferative drug could become a real therapeutic challenge.

Taken together, the bulk of data suggests that B-cells have a role in SSc, particularly in the early phase of the disease, and frequently parallel to the evolution of fibrosis. Therefore, a therapeutic strategy targeting B-cells is highly warranted in early diffuse patients at risk of progressive skin and lung involvement.

The answer to the multitude of questions raised in this editorial should come from thorough experimental studies and large randomized trials, bearing in mind SSc heterogeneity and its capricious course.

Like in a "midsummer dream," we may believe, together with Melissaropoulos and Daoussis [1], that B-cells are a perfect target to block the progressive chain of biological events that make scleroderma *the most terrible of all human illness* [William Osler,1892]. The future will teach us if this vision will have an opportunity to be translated in a validated clinical reality.

Declarations

Disclosures None.

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