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Review Article

Regulatory and effector B cells: Friends or foes?

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ABSTRACT

B cells have moved to the center stage in many autoimmune diseases including autoantibody-mediated diseases and T cell-mediated autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. B cells play an important role for immune response beyond antibody production through mechanisms like antigen presentation and cytokine production. However, not all B cells positively regulate immune responses. Regulatory B cells negatively regulate immune responses by production of anti-inflammatory cytokines such as IL-10, IL-35, and TGF-β. Regulatory B cells have been found to be decreased and/or functionally impaired in various autoimmune diseases. In contrast, B cells also produce pro-inflammatory cytokines, such as IL-6, IFN-γ and GM CSF. These effector B cells contribute to the pathogenesis of autoimmune diseases. Regulatory and effector B cell balance regulates immune response through the release of cytokines. Furthermore, a protocol that selectively depletes effector B cells while sparing regulatory B cells would represent a potent therapy for autoimmune diseases rather than pan-B cell depletion using anti-CD20 mAb.

1. Introduction

B cells have been characterized by their ability to differentiate into plasmocytes (plasmablasts and plasma cells) and produce antibodies (Abs). Abs have a beneficial role in protecting the host against infections. However, if autoreactive B cells develop, autoAbs are produced which have harmful effects and cause damage to the host. In addition, B cells play a critical role in regulating pathogenesis of the autoimmune disease that extends beyond Ab production. Shlomchik et al first revealed the role of B cells beyond Ab production using MRL/*lpr* mice, a systemic lupus erythematosus (SLE) mouse model. Although B cell-deficient MRL/*lpr* mice developed less pronounced disease, nephritis and vasculitis was observed in mIgM.MRL/*lpr* mice that expressed transgenic membrane IgM but did not secrete serum Ig [1,2]. These results suggest that B cells are essential for development of autoimmunity by promoting pathogenic CD4$^+$ T cell activation through their antigen presenting cell (APC) function, T cell-B cell interactions and cytokine production independent of serum autoAbs. Thus, B cells have a disease promoting role and are considered as potential therapeutic targets in a broad range of autoimmune disorders. For example, B-cell depletion by anti-CD20 Ab has shown unpredicted significant effectiveness in treating patients with not only autoantibody-mediated diseases such as idiopathic autoimmune thrombocytopenia, anti-neutrophil cytoplasmic antibody associated vasculitis but also various other T cell-mediated autoimmune disorders like rheumatoid arthritis (RA) and multiple sclerosis (MS). It had been shown that B cell depletion therapy with rituximab, anti-CD20 Ab has a dramatic effect on some patients with SLE. However, phase-III trials of rituximab in patients with SLE did not achieve the primary endpoints [3]. This ineffectiveness may be attributed to depletion of not only effector B (Beff) cells but also regulatory B (Breg) cells. There are two opposing B cell subsets; Beff cells which promote immune responses and Breg cells which inhibit it. Thus, B cell depletion therapies may be a double-edged sword for some patients. Indeed, autoimmune mouse models in experimental autoimmune encephalomyelitis (EAE) [4], murine model of MS, as well as SLE model mouse [5] have indicated that B cell depletion therapy in early phase of the disease exacerbate disease severity while the same in late phase of the disease attenuate disease severity. The therapeutic effects of B cell depletion for the treatment of autoimmunity may therefore depend on the relative contributions and the timing of these opposing B cell activities during the course of disease initiation and pathogenesis. Cytokine production capability is the most beneficial factor to distinguish these

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opposing B cell subsets, Breg cells and Beff cells. Breg cells have protective functions in autoimmune diseases through the provision of anti-inflammatory cytokines such as IL-10, IL-35, and transforming growth factor (TGF)-β. On the contrary Beff cells have disease promoting functions through the provision of pro-inflammatory cytokines such as IL-6, interferon (IFN)-γ and granulocyte macrophage colony-stimulating factor (GM -CSF) in autoimmune diseases. However, these roles are changed in other infectious diseases and tumor immunity. Beff cells have a beneficial effect on the promotion of immune responses against pathogens or tumors. Whereas, Breg cells suppress the excessive inflammatory response via anti-inflammatory cytokines to protect the host. The balance of these opposing B cell subsets is important for the maintenance of immune systems.

2. Regulatory B cells

Negative regulation of immune responses by B cells subset termed "regulatory B cells" have been recognized as an important new component of the immune system in mice and human. Breg cells play an essential role in various immune responses and diseases, from simple contact hypersensitivity (CHS) response to complex systemic autoimmune diseases. IL-10-producing Breg cells are primarily investigated with respect to immune responses and diseases. Recently, role of IL-35 and TGF-β for negative regulation by B cells have been elucidated [6]. 'Breg cells' subset and its functional knowledge relative to the preceding literature focusing on mouse and human Breg cells are described in Fig. 1.

2.1. IL-10 producing regulatory B cell (IL-10$^+$Breg)

IL-10 is an anti-inflammatory cytokine which can negatively regulate pro-inflammatory cytokine production in T cells and APC function in dendritic cells (DCs) and macrophages. IL-10 is produced by various immune cells such as T cells, macrophages, and B cells. IL-10 producing Breg (IL-10$^+$Breg) cells have been gradually recognized as a major subset regulating immune responses due to the critical functions performed by them. Janeway et al. first showed the requirement of B cells for EAE recovery [7]. Further Fillatreau et al. reported that IL-10 from B cells plays an essential role for negative regulation in EAE [8]. Mizoguchi et al. used the term "regulatory B cells" for the first time and demonstrated suppression of mouse colitis by IL-10$^+$Breg cells from the mesenteric lymph nodes by promoting apoptotic cell clearance and predominant expression of the CD1d^{high}B cell phenotype [9]. IL-10$^+$CD1d^{high}Breg cells (including marginal zone B cells and transitional T2-like B cells) have been shown to negatively regulate immune responses in lupus prone mice [10] with CHS [11] and EAE [4] diseases. In contrast, CD5$^+$B1 B cells, which are abundant in the peritoneal cavity are also a source of IL-10 production in mice. Studies have highlighted the role of CD5$^+$Breg cell IL-10 production in the negative regulation of mouse colitis [12] and neonatal infection [13]. We have also investigated the existence of CD5$^+$B1 B cells in the spleen and the critical role of IL-10$^+$CD5$^+$Breg cells in CHS regulation [14] and tumor immunity (manuscript in preparation). Additionally, our group and other groups have identified CD9 as a novel marker for IL-10$^+$Breg cells by transcriptomics [14,15], since CD9 is a marker for CD1d^{high} marginal zone B cells, CD5$^+$ B1 B cells and plasma cells in mice. Recently, CD138^{high}regulatory plasmocytes with a capacity to produce a larger amount of IL-10 during inflammation in EAE [16,17] and *Salmonella* infections [18] have been reported using IL-10 reporter mice. CD138^{high}plasmocytes develop from several B cell subsets including B1 B cells [18]. Thus, CD1d^{high}Breg cells and CD5$^+$Breg cells may differentiate into IL-10$^+$CD138^{high} regulatory plasmocytes depending on adequate stimulation. IL-10$^+$Breg cells can also inhibit T helper 1 (Th1) and Th17 responses and APC function of macrophages and DCs via IL-10 modulation [4,10,19]. Furthermore, IL-10$^+$Breg cells can induce naïve CD4$^+$ T cell differentiation into regulatory T (Treg) cells [14,19].

IL-10$^+$Breg cells have also been identified in humans [20,21]. Regulatory B cells in humans normally represent <1% of the peripheral blood B cells [20]. The reported human IL-10$^+$Breg cells phenotypes are CD24^{high}CD27$^+$ (memory) B cell subset [20,22] or CD24^{high}CD38^{high} (immature) B cells [21]. Human IL-10$^+$Breg cells are also enriched in plasmablasts, defined as CD27^{int}CD38$^+$ [16] or

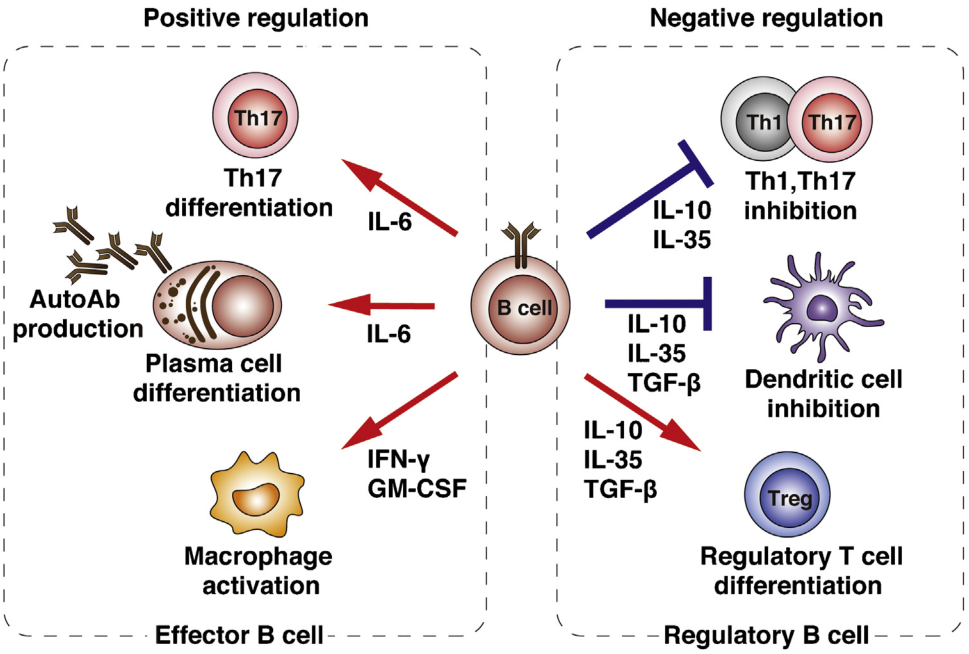

Fig. 1. Regulatory and effector B cell function. Effector B cells positive regulate immune responses through provision of IL-6, IFN-γ, and GM CSF, while regulatory B cells negatively regulate immune responses through provision of IL-10, IL-35, and TGF-β.

$CD27^{high}CD38^{high}$ [22] similar to mice Breg cells. IL-10$^+$Breg cells inhibit TNF-α and IFN-γ production by T cells [20,23] and regulate monocyte function in humans [20]. Moreover, the suppressive capacity of IL-10$^+$Breg cells were reported decreased or absent in patients with various autoimmune diseases [21,24]. Thus, IL-10$^+$Breg cells suppress immune responses and have been recognized as a new component of prime importance to the immune system in mice and humans.

2.2. IL-35 producing regulatory B cells (IL-35$^+$breg)

IL-35 is a member of the IL-12 cytokine family composed of Ebi3 and IL-12p35 heterodimers. It was earlier thought that IL-35 production is restricted to Treg cells. However, IL-35 production by B cells and its contribution to the immune regulatory capacity in mice has been demonstrated [17,25]. In addition, IL-35 from B cells suppresses EAE and experimental autoimmune uveitis and enhances susceptibility to *Salmonella* infection inhibiting anti-*Salmonella* immunity [17,25]. $CD138^{high}$ plasma cells are a major source of IL-35 during *Salmonella* infection and EAE in mice [17]. IL-10 is also produced by $CD138^{high}$ plasma cells, however, individual B cells either produce IL-10 or IL-35, but not both [17]. Thus, IL-10 and IL-35 cytokines are produced by different plasma cell subsets, suggesting that IL-10 and IL-35 producing “regulatory plasma cell” can operate parallelly. Mechanistically, IL-35$^+$Breg cells negatively regulate APC functions of macrophages, inflammatory T cells and B cells [17], while IL-35$^+$Breg cells expand Treg cells [25]. Moreover, IL-35 induces $CD5^+B220^{low}$ IL-10$^+$Breg cells and IL-35$^+$Breg cells [25]. In humans, IL-35$^+$Breg cells have found to be elevated in patients with advanced gastric cancer [26]. Taken together, IL-35$^+$Breg cells play a critical regulatory role in autoimmune diseases and various other immune responses.

2.3. TGF-β producing regulatory B cell (TGF-β$^+$Breg)

TGF-β is a multifunctional cytokine, which play an important role not only in immune regulation but also during tissue fibrosis. Most importantly, TGF-β can induce naïve CD4$^+$ T cells to differentiate into Treg cells and induce immature DCs to tolerogenic DCs. Although Treg cells are a major source of TGF-β, B cells have also been shown to produce TGF-β. Adoptive transfer of B cells from hilar lymph nodes could suppress allergic airway inflammation in mice. This negative regulation of B cell was TGF-β dependent but not IL-10 [27]. Furthermore, TGF-β$^+$Breg cells expressed CD5 and induced naïve CD4$^+$T cells to differentiate into functionally suppressive Treg cells in vitro [27]. TGF-β$^+$CD5$^+$Breg cells also suppressed food allergy-induced intestinal inflammation in mice [28]. It is also reported that TGF-β$^+$Breg cells induce Treg cells and promote immune transplantation tolerance in mouse transplantation model [29]. In human, TGF-β$^+$Breg cells have been shown to convert the interacting T cells into IL-10$^+$ and TGF-β$^+$Treg cells in collaboration with indoleamine 2,3-dioxygenase [30]. Thus, TGF-β$^+$Breg cells have an ability to induce naïve CD4 T cells differentiation into Treg cells in mice and human.

3. Effector B cells

Beff cells promote immune responses through provision of various pro-inflammatory cytokines such as IL-2, IL-4, IL-6, IL-12, IL-17, IFN-γ, TNF-α, and GM CSF [6,31,32]. Especially, IL-6, IFN-γ or GM CSF producing Beff cells have emerging importance for immune responses. This section focuses on the Beff cell subset and what is known about its function from preceding literature describing mouse and human Beff cells (Fig. 1).

3.1. IL-6 producing effector B cells (IL-6$^+$beff)

IL-6 is a multifunctional cytokine produced by various cell types such as B cells, T cells, monocytes, natural killer cells and fibroblasts. B cells are the major source of IL-6, which can induce T follicular helper (Tfh) and Th17 cells differentiation from naïve CD4$^+$ T cells, and plasma cell differentiation from B cells. Additionally, IL-6 also play an important role for various autoimmune diseases such as MS and systemic sclerosis (SSc). It is reported that B cells specific IL-6 deficient mice show diminished EAE severity with decreased Th17 responses [33]. IL-6$^+$Beff cells are able to induce T cell proliferation as well as Th17 polarization in EAE mice [33]. In addition, IL-6 deficiency in B cells attenuates skin fibrosis in the bleomycin-induced scleroderma model, while IL-10 deficiency in B cells augments skin fibrosis [34]. IL-6$^+$Beff cells can also promote collagen secretion by fibroblasts through interaction with B cells and fibroblasts. Importantly, B cell activating factor belonging to the TNF family (BAFF) has shown to increase IL-6$^+$Beff cells but suppress IL-10$^+$Breg cells. Furthermore, BAFF antagonist attenuated skin and lung fibrosis in scleroderma model with reduction of IL-6$^+$Beff cells but not IL-10$^+$Breg cells [34]. In humans, B cells have been demonstrated to secrete high levels of IL-6 in MS patients [16] and SSc patients [35]. Thus, IL-6$^+$Beff cells have a disease promoting role in autoimmune diseases, such as MS and SSc.

3.2. IFN-γ producing effector B cell (IFN-γ$^+$beff)

IFN-γ is a type II IFN which play important roles in the innate immune response against intracellular infections and in the regulation of adaptive immune responses. IFN-γ, which is thought to be mainly produced by natural killer cells and CD4$^+$ T cells can strengthen innate immunity via induction of antimicrobial factors or degradative pathways in other immune cells such as macrophages. Lund et al. have reported that B cells can produce IFN-γ [31]. Recently, it was also reported that $CD11a^{high}Fc\gamma RIII^{high}$B cells can suppress *Listeria* infection via IFN-γ regulation. In addition, IFN-γ$^+$Beff cells are capable to induce macrophage activation and promote tumor immunity against B16F10 melanoma and allograft rejection via IFN-γ [36]. IFN-γ$^+$Beff cells also exacerbate proteoglycan-induced arthritis with reduction of Treg cells and enhancement of Th cell responses [37]. For phenotype analysis, it was reported that IFN-γ$^+$Beff cells express TIM-4, while IL-10$^+$Bregs express TIM-1 in mice [38]. In human, IFN-γ mRNA from B cells was detected in patients with RA [39]. Taken together, IFN-γ$^+$Beff cells have a major role not only in innate immunity but also in autoimmunity.

3.3. GM-CSF producing effector B cells (GM-CSF$^+$beff)

GM-CSF is a strong activator for myeloid cells such as granulocytes, monocytes/macrophages, and eosinophils. GM-CSF is produced by various cell types including T cells, macrophages, and B cells. Innate B cells, termed as “innate response activator (IRA)” B cells, have demonstrated a protective role against infection via GM-CSF in mice [40]. In humans, B cells from patients with MS produce more GM-CSF compared with healthy individuals [32]. GM-CSF$^+$Beff cells were found to be increased in SSc patients [41]. For phenotype analysis, GM-CSF$^+$Beff cells belonged to the memory B cell subset and co-expressed high levels of TNF-α and IL-6 [32]. Furthermore, GM-CSF$^+$Beff cells efficiently activated macrophages, developing to MS exacerbation. Taken together, GM-CSF$^+$Beff cells play an important role in autoimmunity due to macrophages activation.

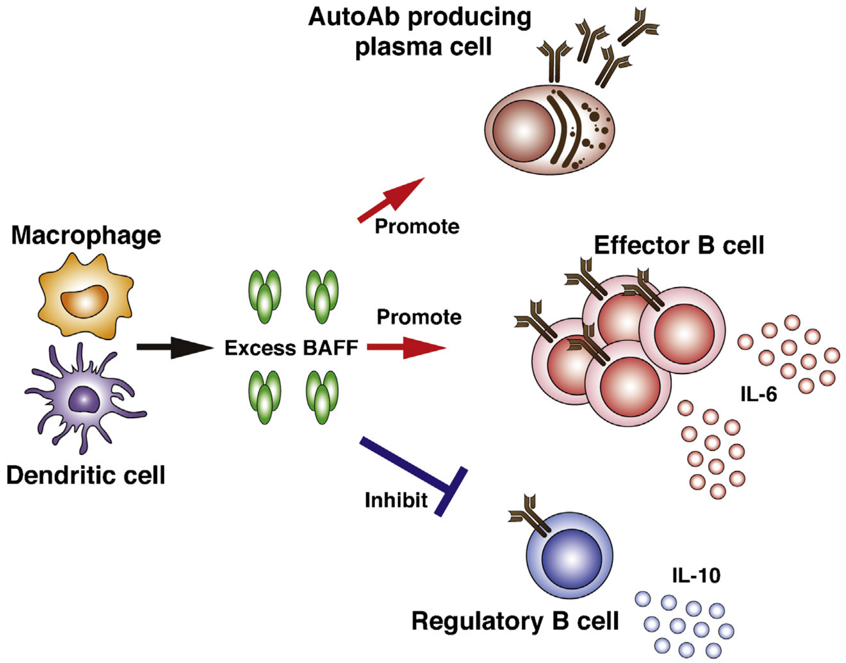

Fig. 2. BAFF role on regulatory and effector B cell balance. Excess BAFF, which produced by macrophage and dendritic cell, induces differentiation of autoAb producing plasma cells and effector B cells, while excess BAFF inhibits regulatory B cells.

4. Regulatory and effector B cells in SLE and SSc

4.1. Systemic lupus erythematosus (SLE)

SLE is a complex autoimmune disease characterized by autoantibodies production and involve various organs including kidney, joints and skin. B cells play critical roles in the pathogenesis of SLE through extend beyond autoAb production. Although, pan-B cell depletion was thought to be effective in patients with SLE, however, phase-III trials of pan-B cell depletion failed to achieve primary endpoints [3]. This ineffectiveness may be due to depletion of not only Beff cells but also Breg cells. Pan-B cell depletion with anti-CD20 Ab started in 4-week-old NZB/W F_1 mice, a spontaneous SLE mouse model, accelerated disease onset with parallel depletion of Breg cells. However, pan-B cell depletion in 12–28 week-old NZB/W F_1 mice significantly inhibited spontaneous disease with parallel depletion of Beff cells [5]. Therefore, there are two distinct B cell populations which have opposing roles both protective and pathogenic during lupus progression. Timing is important for clinical use of this therapy in SLE, since pan-B-cell depletion therapies may cause harmful effects in some patients. In addition, the potential therapeutic roles of Breg cells in SLE have also been highlighted by transferring splenic IL-10^+Breg cells from wild-type NZB/W F_1 mice into CD$19^{-/-}$NZB/W F_1 recipients, which lack IL-10^+Breg cells which significantly prolonged their survival [42]. By contrast, it was reported that IL-6^+Beff cells promoted systemic inflammation in SLE model mouse via germinal center formation, which induced autoAb production [43]. Moreover, B cell-specific IL-6-deficiency protected against immune complex glomerulonephritis in SLE model mouse [43]. Collectively, SLE mouse models suggest that both Breg cells and Beff cells have a definitive role in SLE pathogenesis. In humans, the frequency of IL-10^+Breg cells in patients with SLE is reported significantly high than healthy controls [20]. However, IL-10-competent CD24^{high}CD38^{high} (immature) Breg cells isolated from the peripheral blood of SLE patients were diminished upon further CD40 stimulation, produced less IL-10 and lost the suppressive capacity of their healthy counterparts [21]. CD24^{high}CD38^{high} Breg cells from healthy control, but not SLE patients, suppressed plasmacytoid DCs derived IFN-α production via IL-10 [44]. Thus, IL-10^+Breg cells are functionally impaired in patients with SLE.

BAFF overexpressing mice appear to demonstrate an autoimmune phenotype similar to that of patients with SLE. Furthermore, serum levels of BAFF, which was produced by macrophage and DCs, are significantly elevated in SLE patients. Recently, we have also reported that BAFF increases IL-6^+Beff cells but attenuates IL-10^+Breg cells in mice (Fig. 2), while BAFF inhibition attenuates IL-6^+Beff cells but not IL-10^+Breg cells [34]. Although phase III trials of pan-B cell depletion therapy in SLE failed [3], phase III trials of partial-B cell depletion with BAFF inhibition demonstrated its efficacy in patients with SLE [45]. Our study has shed light on the most likely reason for the superior effects of partial-B cell depletion with BAFF inhibition compared to pan-B cell depletion with anti-CD20 Ab, given that BAFF inhibition therapy may selectively deplete Beff cells while sparing Breg cells in humans.

4.2. Systemic sclerosis (SSc)

SSc is an autoimmune disease characterized by skin and lung fibrosis. Over 90% of patients with SSc are positive for autoAbs. In SSc, IL-10^+Breg cells have an inhibitory function on pathogenesis. We reported that donor-derived IL-10^+Breg cells are important for the suppression of SSc in the sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) model [46]. The absence of IL-10^+Breg cells induced severe Scl-cGVHD. In humans, it was reported that IL-10^+Breg cells are decreased in patients with SSc and decreased IL-10^+Breg cell levels are associated with interstitial lung disease [24]. In a follow-up study, IL-10^+Breg cell levels in patients with SSc were found to be significantly increased after treatment accompanied by decreased disease activity compared with those before treatment [24]. Thus, IL-10^+Breg cell levels were inversely correlated with disease activity of SSc. These results suggest that the decrease in IL-10^+Breg cell frequencies contributes to the development of SSc.

IL-6 plays a critical role in tissue fibrosis and autoimmunity in mouse models of SSc. The administration of anti-IL-6 receptor Ab in mice attenuated skin fibrosis in mouse model of scleroderma [47]. Further, a phase-II trial of tocilizumab, anti-IL-6 receptor Ab, demonstrated clinically significant improvement of skin fibrosis in patients with SSc [48]. IL-6 from B cells play an important role in the SSc pathogenesis. We have shown that the skin and lung fibrosis of scleroderma mouse model was attenuated in B cell-specific IL-6-deficient mice [34]. In humans, B cells from SSc patients exhibited an enhanced ability to produce IL-6 [35,49]. Collectively, these results suggest both Breg cells and Beff cells have a definitive role in SSc pathogenesis; IL-6$^+$Beffs cells play a pathogenic role in SSc, while Bregs cells play a protective role. Therefore, a protocol that selectively deplete Beff cells while sparing Breg cells would represent a potent therapy for SSc, rather than pan-B cell depletion with anti-CD20 mAb. We have also shown that BAFF inhibition is a potential therapeutic strategy for SSc via alteration of regulatory and effector B cell balance [34] since BAFF increases IL-6$^+$Beff cells but attenuates IL-10$^+$Breg cells (Fig. 2). Consistent with that, serum BAFF levels were increased in patients with SSc and was associated with the severity of skin sclerosis [35]. and a small pilot study of BAFF inhibition with belimumab demonstrated improvements in skin sclerosis of SSc patients, though no statistical significance [50]. Taken together, regulatory and effector B cell balance is closely associated with pathogenesis of SSc and modifying this B cell balance, skewing the cytokine balance towards IL-10 production, is a potential therapeutic strategy for SSc, as well as autoimmune diseases.

5. Conclusion

A number of recent studies in human and mouse models have revealed critical roles for Bregs and Beff cells in autoimmune diseases. B cells both positively and negatively regulate the pathogenesis of autoimmune diseases via cytokine production. In addition, Bregs and Beff cells have critical roles in allergic diseases as well as in tumor immunity and other infectious diseases. However, identifying the definitive markers and specific transcription factors of Bregs and Beff cells is necessary for the development of new B cell-targeted therapeutic strategies. Nevertheless, it should now be accepted that Bregs and Beff cells are critically important components of the immune system.

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Conflicts of interest

The authors have no conflict of interest to declare.

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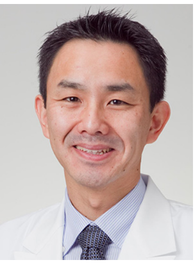

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