REVIEW ARTICLE

B cell-derived cytokines in disease*

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ABSTRACT. B cells regulate immune responses during infectious, inflammatory and autoimmune diseases. Beside their unique and characteristic antibody production, B lymphocytes can modulate physiological and pathological processes by presenting antigens or synthesizing signaling molecules. In human and mouse diseases, immunointervention, targeting B cells, has revealed and highlighted their antibody-independent regulatory contribution. In this review, we focus on B cell-cytokine production, which is commonly disturbed in inflammatory disorders, and describe the B cell cytokine profile in different diseases. Finally, we discuss some key issues for future B cell-targeted therapies.

Key words: B lymphocyte, autoimmunity, inflammation, cancer

The contribution of B cells to immune responses extends far beyond antibody production; it also includes antigen presentation and cytokine secretion [1] (*figure 1*). B cells participate in the pathophysiology of inflammation and autoimmunity, playing both regulatory and pathogenic roles. In this review, we mainly focus on the role of B lymphocyte-derived cytokines in diseases.

B lymphocytes that secrete cytokines can be subdivided in two different subsets: regulatory B cells (Breg), producing IL-10 or TGF-β, and B effector cells (Be), expressing distinct arrays of cytokines depending on their maturation stage and environment. By analogy to helper T cell (Th) polarization, Be cells have been initially classified as producing Th1 cytokines (Be1) and Th2 cytokines (Be2), thus regulating leukocyte migration and inflammatory cell infiltration [2]. Nevertheless, the factors driving B cell development toward Be1 or Be2 and controlling their cytokine production remain largely unknown. Be1 polarization is the default developmental pathway and requires T-bet/IFN-γ/IL-12 signaling [3]. On the other hand, orientation toward a Be2 phenotype depends on IL-4 and Th2 cells. IL-4 signalization is sufficient and essential for the deviation from Be1 to Be2 cells, and constitutes, together with the T-bet/IFN-γ/IL-12 pathway, a negative feedback loop establishing the Be phenotype [3].

Be and Th cells exert a mutual interplay during their respective polarized development through cytokine and survival signal production. Be1 cells promote Th1 differentiation by producing IFN-γ, while IL-4 expression by Be2 cells is required for Th2 differentiation (*figure 1*). Moreover, Be1 cells amplify IFN-γ production by T cells [4]. B cells also synthesize co-stimulatory molecules (B7.1, B7.2, CD40, inducible co-stimulator ligand…) that promote T cell activation [2, 5, 6]. B cell cytokines can also indirectly regulate the T cell response by either modulating dendritic cells activation (IL-6, IL10 and TNF-α) [2], and/or driving phenotypic characteristics and functional properties of macrophages [7, 8].

The ability of B cells to regulate T-cell differentiation suggests that their cytokine production may be involved in autoimmune conditions and in responses against pathogens [2]. In many autoimmune diseases (systemic lupus erythematosus (SLE), multiple sclerosis (MS)…), B cell abnormalities comprise an altered cytokine production pattern rather than quantitative variations [9, 10]. The expression level of a given cytokine may vary according to the pathological condition considered: whereas in MS, B cells exhibit a deficient IL-10 production [10-12], an IL-10 overproduction is detected in B lymphocytes from patients with SLE and Sjögren's syndrome (SS) [10, 13, 14]. Moreover, a large set of data implicates B cell cytokines in the pathophysiology of several chronic inflammatory responses and diseases. Animal models indicate that selective modification of B cell cytokine expression may have deleterious effects on autoimmune disease (MS, experimental autoimmune encephalitis (EAE)…) evolution, thus defining and establishing B cells as relevant targets for therapeutic intervention [11, 12, 15-17]. Whereas animal studies reveal and emphasize the Ab-independent contributions of B cell-derived cytokines [3, 18], comparatively few data have been published about their participation in the regulation of human immune responses [10]. Clinical studies using Rituximab seem to confirm animal studies. B cell depletion is now a well-established therapy that improves human disease evolution (SLE, rheumatoid arthritis (RA), nephritis, transplant rejection) [1]. The mechanism effecting the beneficial effects of B cell depletion is poorly understood and often occurs independently of autoantibody levels.

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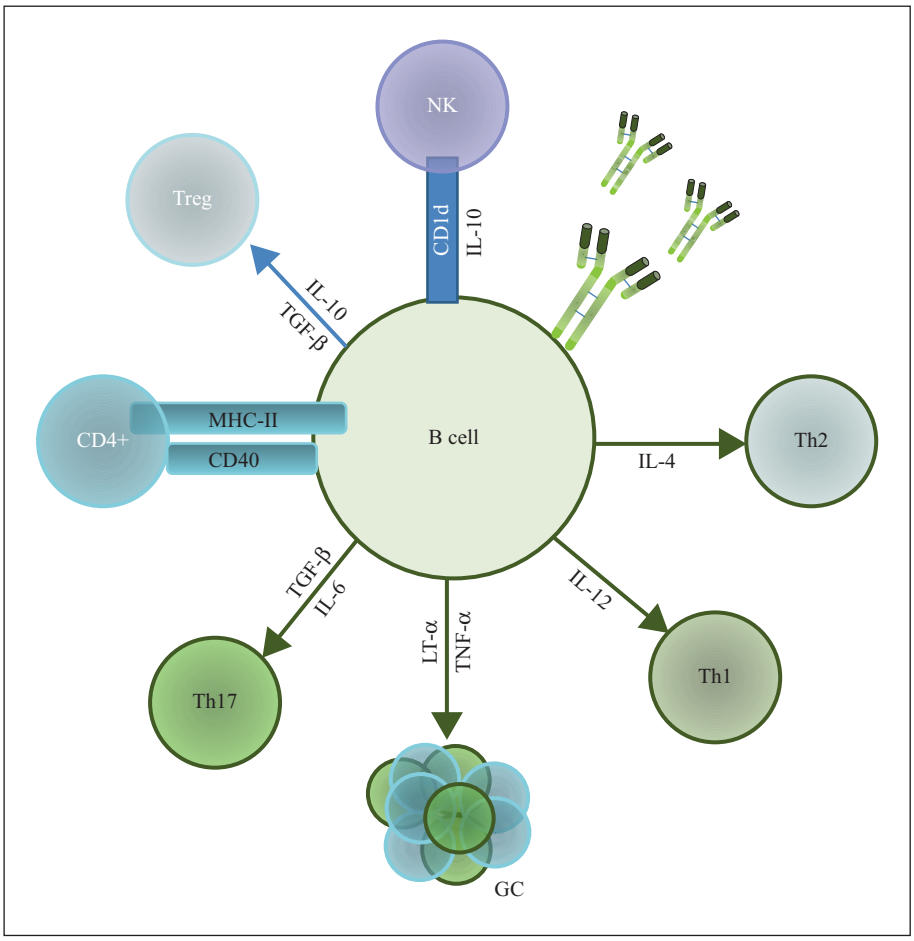

Figure 1
Pleiotropic functions of B cells. An efficient immune response requires T-B cell interaction in germinal centers whose formation depends on LT-α and TNF-α secretion by B cells. B cell-derived cytokines control T cell polarization. The production of IL-12 leads to Th1 differentiation, whereas IL-4 induces Th2 maturation. IL-6 and TGF-β are necessary for Th17 pathway development. On the other hand, B cells may act as antigen-presenting cells and modulate cell activity via cognate interactions through CD40 (CD4+ cells) and CD1d (NK cells). They also produce antibodies and suppressive cytokines (IL-10, TGF-β).

The observations that deregulation of B lymphocyte cytokine expression contributes to pathological situations reflect their role in normal immune responses. In humans, cytokine production by B cells is context-and subset-dependent [10]. Duddy *et al.* found that IL-10 derives mainly from naive B cells, whereas most inflammatory cytokines such as TNF-α and lymphotoxins (LT) are expressed by memory B cells [10]. The transcription of cytokine-encoding genes in normal B cells is tightly controlled and requires cellular activation [2]. We still have not identified the selective regulators of the pro- and anti-inflammatory pathways. However, individual signals modulating distinct B cell cytokine responses during *in vivo* disease induction have been described [10]. The production of IL-10 by B cells is intensely amplified following TLR engagement. Innate signals are essential for optimal regulatory activity [19-21]. TLR ligands and anti-CD40 also cooperate to stimulate IL-6 secretion by B cells [19, 22], although the precise mechanism linking IL-6 production to TLR activation remains unknown [19, 21], Isolated human B cells activated via their BCR alone are unable to produce LT, TNF-α or IL-10 [10]. Nevertheless, anti-CD40 stimulated B cells secrete low levels of LT. Interestingly, B cells from normal individuals, activated via BCR stimulation and CD40 engagement, produce high levels of LT and low levels of IL-10 [10].

It is worth mentioning that tissular B lymphocytes produce chemokines essential for lymphangiogenesis, induce T cell activation and control local immune responses through expression of different sets of cytokines.

Herein, we review some of the significant alterations in cytokine production by B cell subsets in pathology, and their contribution to systemic and tissue inflammation.

CHRONIC INTESTINAL INFLAMMATION

B cells were originally identified as responsible for intestinal inflammation [23, 24]. However, the $CD1d^{+}$ B lymphocytes that home to the gut-associated lymphoid tissue produce IL-10, and therefore repress intestinal inflammation (*figure 2*). In this process, IL-10 acts by downregulating the IL-1-related signalization pathways and STAT3-dependent inflammation rather than by regulating T cell functions. Interestingly, Misoguchi *et al.* showed that the TCRα KO mouse strain develops spontaneous intestinal inflammation in mesenteric lymph nodes, associated with an accumulation of protective B cells [25]. Moreover, observations from B cell-deficient mice (IgHμ-TCRα double KO), reveal a protective role for B cells, requiring an initial CD1d engagement followed by a spontaneous and sustained production of IL-10, and

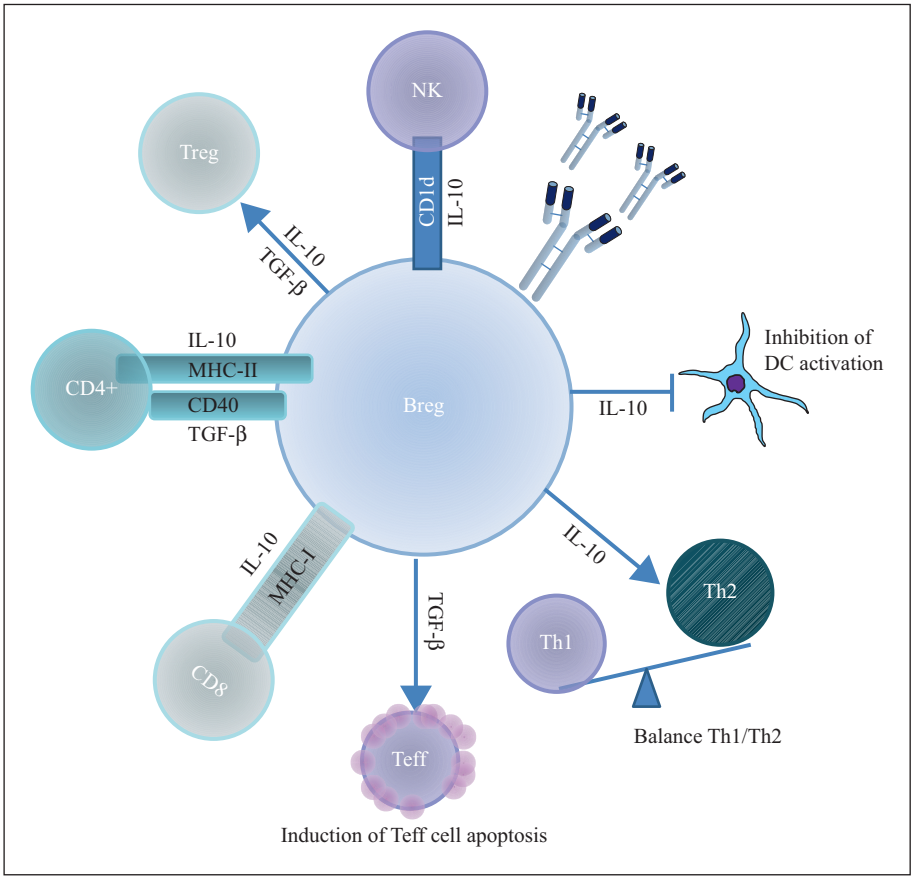

Figure 2
Diverse Breg functions. In addition to antibody production, Breg inhibit the function of other immune cells (CD4+ or CD8+ T cells, NK, DC), mainly via cytokine secretion (IL-10 or TGF-β). Interaction between co-stimulatory molecules is required for optimal Breg-mediated suppression.

an association with disease improvement [25]. IL-10 also induces the development of IL-12-producing B cells that regulate the Th2 intestinal response (*figure 3*) [26]. The same mechanism is also implicated in the inhibition of colitis at early stages of infection [25]. Finally, IL-12 deficiency induces the development of a much more severe colitis [26].

Interestingly, IL-8 overproduction by human B cells is a relevant marker of chronic mucosal inflammatory disease. Indeed, B cells of Crohn's disease (CD) and ulcerative colitis (UC) patients produce increased levels of IL-8 in response to TLR2 stimulation [27].

However, the functional role of B cell-mediated regulation in human intestinal inflammation [28] is unknown.

PERIODONTAL DISEASE (PD)

The majority of cells in periodontal lesions are B lymphocytes that exacerbate disease severity [29-31], at least partially, by overproduction of the deleterious cytokine IL-6 (*figure 3*) [32, 33]. Furthermore, these cells sustain a high production level of IL-1β, another pro-inflammatory cytokine that aggravates PD lesions [27, 34]. Surprisingly, B cells also secrete the receptor activator of nuclear factor kappa-B ligand (RANKL) that promotes osteoclastogenesis and bone destruction (*figure 3*) [35]. RANKL-expressing B cells are sufficient to promote bone resorption [36]. In addition, TLR2/4 stimulation amplifies the constitutive production of IL-8 and TNF-α by gingival B cells [27, 37]. B cell-derived IL-8 production slightly exceeds the physiological concentrations, facilitates neutrophil accumulation and increases PD lesion size. TLR2 activation of Breg from PD patients up-regulate IL-10 secretion. In contrast, B cell TLR4 engagement antagonizes TLR2 effects [27, 37].

DIABETES MELLITUS

B cells participate in Tcell-mediated inflammation in metabolic disorders. They promote the development of glucose intolerance and obesity-associated insulin resistance in diet-induced, obese mice. In this model, B cells infiltrate and accumulate in visceral adipose tissue. Moreover, B cell depletion reduces disease and ameliorates metabolic parameters [38]. However, the mechanism involving Breg and Be in diabetes remains to be elucidated [27].

B cells from patients with type 2 diabetes (T2D) constitutively produce IL-8 and IL-6 (*figure 3*), but the latter is always secreted in physiological quantities, making any contribution to this disease unlikely [32]. Moreover, B cells from PD or T2D patients produce lower levels of IFN-γ [27, 32], TNF-α and IL-10 [32], independently of TLR stimulation. Conversely, B cells from T2D patients, overproduce IL-8 in response to TLR2, TLR4, and TLR9 stimulation [27, 32] while they fail to upregulate IL-1β [32]. These observations support the notion that increased IL-8 production by B lymphocytes in response to TLR

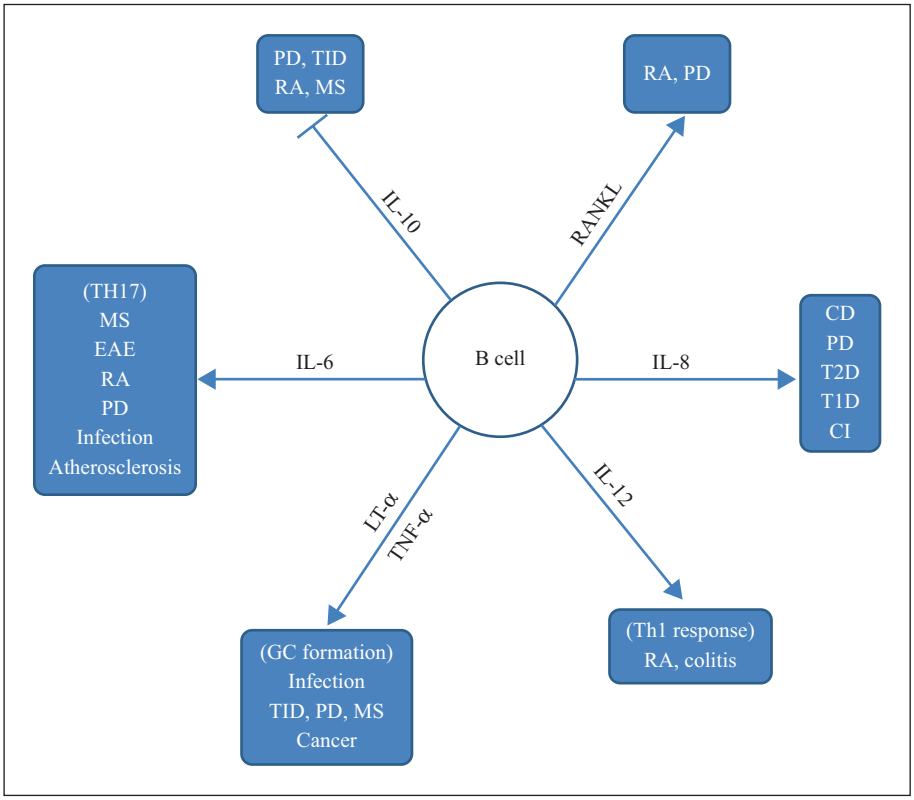

Figure 3

B cell cytokine-driven mechanisms of diseases. B cell-derived cytokines contribute to immune diseases by participating in lymphoid neogenesis (LT-α, TNF-α), regulating T-cell polarization (IL-6, IL-12) and promoting inflammation and tissue damage (IL-8, RANKL). B cells may also secrete immunosuppressive cytokines (IL-10).

engagement is a suitable marker and a common characteristic of inflammatory diseases.

Interestingly, B cells isolated from T1D behave similarly to those from T2D patients and secrete the same range of cytokines (IL-8, IL-6, TNF-α) in similar quantities [32]. They support the intra-islet homing and survival of cytotoxic T lymphocytes, thus promoting diabetes development [39].

MULTIPLE SCLEROSIS

In addition to their regulatory capacity [19, 40, 41], B cells amplify the inflammatory response in EAE and MS [40, 42]. Relapsing-remitting MS (RR-MS) patients display aberrant B cell activation [43]. B cells from MS patients produce increased levels of TNF-α and LT in response to TLR9 engagement or in the presence of IFN-γ [44]. In addition, B cells are the major source of the pro-inflammatory cytokine IL-6 in mice and humans (*figure 3*). B cell depletion improved disease and normalized IL-6 levels. Moreover, mice with B cell-specific IL-6 deficiency exhibit less severe lesions [17]. B cell targeting may also be associated with a reduced Th17 response in mice, raising the possibility that B-cell-secreted IL-6 controls disease evolution via diverse pathways regulating T-cells differentiation and polarization [17, 45].

Conversely, B cells in human MS exhibit a decreased production of IL-10 [10], a situation also encountered in other inflammatory diseases such colitis and arthritis [11, 15, 25]. Mice, with general or selective B cell deficiency in IL-10, developed severe EAE lesions that did not heal, and could not be cured of the disease [15]. However, EAE regulation by B cells is independent of CD1d expression because $CD1d^{-/-}$ mice develop severe colitis rather than intensified EAE [15]. Breg cell maturation into functional IL-10-secreting effector cells during EAE requires stimulation via the BCR, CD40-dependent cognate interactions with T cells secreting IL-21, and TLR engagement [15, 27, 46]

RHEUMATOID ARTHRITIS

Resident B cells in affected joints amplify inflammation and promote RA [47, 48]. Recent studies have proved that B cells are actual therapeutic targets in RA [48]. Human synovial B cells, similarly to other resident immune cells (macrophages, T cells and neutrophils), express a wide range of cytokines (IL-1α, IL-15, TNF-α, TGF-β), but at higher levels than the corresponding circulating cells [47]. Human B cells also secrete LT-β, which may contribute to synovial tertiary lymphoid tissue formation (*figure 3*) [49]. Moreover, they are probably a major local source of IL-12, a key regulator of Th polarization [47] and IL-6 that has been implicated in tissue and systemic inflammation. IL-6-deficient mice show resistance to collagen-induced arthritis [48]. While RANKL-producing B cells constitute a minor population in the blood of RA patients, human synovial B cells are potent producers of RANKL (40% of B cells are RANKL+) (*figure 3*) [47]. In contrast, Breg have been detected in peripheral blood, but not in the synovium of RA patients [10, 47].

ATHEROSCLEROSIS

B cells are present in low numbers in atherosclerotic intimal plaques, but are prevalent in tunica adventitia at the vicinity of arterial wall lesions [50, 51]. B lymphocytes may exert contradictory influences during atherogenesis. Indeed, B cells were initially considered to be protective. Spleen B cell transfer into atherosclerosis-prone Apoe$^{-/-}$ mouse induces a significant reduction in atherosclerotic lesions [52]. In addition, B cell ablation in Ldlr$^{-/-}$ mice aggravates lesions, thus supporting the atheroprotective hypothesis [53]. These effects are probably due to natural antibodies produced by innate-like B1 lymphocytes. In contrast, two recent studies suggest an atherogenic effect for conventional B2 cells [54, 55]. Anti-CD20-mediated systemic depletion of B cells diminishes atherosclerosis in both Apoe$^{-/-}$ and Ldlr$^{-/-}$ mice. This depletion is associated with reduced T lymphocyte activation, decreased IFN-γ secretion and deviation towards the Th17 pathway [55]. Moreover, injection of splenic B2 lymphocytes results in disease aggravation associated with B2 cell infiltration of arterial lesions [54]. Nevertheless, a recent study demonstrated that B cells present in adventitia carry protective immunity, reducing the atherosclerosis burden independently of circulating B cell numbers [56]. Taken together, these results suggest that B2 cells contribute to disease independently of their Ab production. The context (experimental setting, nature of the diet and age at examination), may explain the contradictory effects of resident B cell cytokines in determining the pro-atherogenic or atheroprotective outcome [54, 56]. We have recently shown that human arterial B cells in advanced lesions have a proinflammatory cytokine profile, expressing notably IL-6, TNF-α and GM-CSF. In contrast, Breg (IL-10, TGF-β) were not present in the arterial walls of atherosclerotic patients [Hamze *et al.*, submitted].

INFECTION

Cytokine-producing B cells also regulate immune responses to pathogens. While many cells, notably dendritic cells, can secrete IL-6, its secretion by B cells is sufficient and essential for germinal center formation and follicular Th differentiation during antiviral responses (*figure 3*) [57]. B cell cytokine production patterns depend on the pathogen and infection type. B cells produce Th1 cytokines (IL-2, IL-12, IFN-γ, IL-6 and TNF-α) during *T.gondii* infection, whereas *H.polygyrus* infection induces a Th2 secretion pattern (IL-4). B cells may participate in either the initiation or the maintenance of polarized immune responses [58]. Breg reduce pathogen clearance and suppress anti-viral responses by inducing a deviation from a defensive Th1 towards a tolerant Th2 response (*figure 2*). An expansion of IL-10-producing B cells was detected in C57BL/6 mice during infection (*Leishmania major, Schistomamansoni, Brugia, Pahang, Chalymdophilaabortus*). Moreover, IL-10-producing B cell deficiency improves the CD8+ T cell response [12]. However, Breg provide a safe clearance of pathogens, diminishing inflammation and excessive immune responses [12].

Peripheral B cells isolated from HIV-infected patients produce increased levels of IL-6 and TNF-α, which are responsible for virus inductive capacity [59]. These cytokines are also secreted by normal B cells in response to *Staphylococcus aureus* Cowan strain 1 (SAC), but their functional relevance is not yet known [60].

CANCER

B cells may have aggravating or protective effects depending on the cancer type. Negative effects were observed in several murine models and accordingly, B cell-deficient mice exhibited reduced tumor volume (EL4 thymoma and MC38 colon carcinoma), associated with increased tumor-infiltrating T cell counts and amplified Th1 and CTL responses [61]. Moreover, tumor-infiltrating B lymphocytes, in particular B2 cells, promote tumor progression in prostate cancer via LT production (*figure 3*) [62]. Conversely, B cell depletion using anti-CD20 enhances tumor metastasis (leukemia, B16 melanoma) by altering T-cell functions, suggesting that B cells are necessary for optimal T cell-mediated tumor suppression [63, 64]. They can also destroy tumor cells through granzyme B (a serine protease secreted in response to IL-21) or tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) secretion following TLR engagement [65]. These contradictory results can be linked to the B cell activation status, with resting B cells repressing and activated B cells promoting T cell responses. B cells isolated from cancer patients are mainly activated, suggesting that they stimulate anti-tumor immunity [65].

PERSPECTIVES

Recent investigations have revealed a growing interest in B cells as an important source of cytokines, either quantitatively or functionally. Systemic inflammation is often associated with an accumulation of activated B cells at lesion sites such as the synovium or the salivary glands of patients with RA and SS respectively. Although the role of B cells in disease states has been widely addressed, the specific contribution of their cytokine production (systemic and local) remains to be confirmed. Further characterization of the B cell cytokine profile would identify mechanisms underlying the beneficial or adverse effects of B cell depletion in autoimmune disorders.

The chronology of immune cell recruitment differs from one disease to another and plays an important role in their evolution. Early responding B cells may regulate cellular infiltration and local response, such as those homing to inflamed adipose tissue responding to a high fat diet in mice [66], or in breast tumors [65]. Conversely, delayed B cell infiltration is observed in murine EAE lesions [17] and in human atherosclerotic adventitia [67, 68]. Characterizing resident B cell subsets and exploring their infiltration kinetics may establish local B cells as new therapeutic targets.

Another important goal is to decipher (characterize) the signalization cascades involved in human B cell activation, combined with the identification of cytokine expression regulators. In addition, new approaches targeting different factors, such as blockade of BLyS (B lymphocyte stimulator), B cell-activating factor receptor (BAFF R) or other B cell surface markers (CD22) deserve to be tested as an alternative to global B cell depletion that affects the diverse

B cell populations (Be and Breg). These studies may help to identify efficient treatments that could modulate B cell activation and allow selective targeting of B cell subsets.

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