



## Review

## Regulatory B cells in inflammatory diseases and tumor

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## ABSTRACT

As antigen-presenting cells (APC), B cells exert a variety of immune regulatory functions mainly by presenting antigens, triggering immune response, and producing antibodies for immune regulation. Regulatory B cells (Bregs) are special subpopulations of B cells with immune-regulating or immune-suppressing properties and play a role in peripheral tolerance. Bregs suppress immune response through inhibiting the differentiation of dendritic cells (DCs), suppressing the proliferation of helper T1 (TH1) cells and helper T17 (TH17) cells, inducing the differentiation of fork head transcription factor p3 positive regulatory T cells (FoxP3<sup>+</sup> Tregs). Different subsets of Bregs have distinct phenotypes and markers. Different subsets of Bregs participate in immune modulation by different ways. The absence or loss of Bregs exacerbates the severity of many disease such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and graft-versus-host-disease (GVHD). Bregs are also involved in tumor immunosuppressive effect and inhibit the antitumor immune process. In this article, we review the research advances of Bregs in autoimmune diseases, GVHD and tumor.

## 1. Introduction

As antigen-presenting cells (APC), B cells exert a variety of immune regulatory functions mainly by presenting antigens, triggering immune response, and producing antibodies for immune regulation [1–3]. In autoimmune diseases, B cells are involved in the damage of target tissues by releasing autoantibodies and are therefore considered to be pathogenic factors. In addition, activated and memory B cells are also capable of producing different proinflammatory cytokines including tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-12 (IL-12), and interleukin-13 (IL-13), and so on [4]. Regulatory B cells (Bregs) are special subpopulations of B cells with immune-regulating or immune-suppressing properties and play an important role in peripheral tolerance [5,6].

It was first reported that Bregs could regulate immune system in the 1970s [7]. Multiple Bregs have been found, and different subsets of Bregs have different phenotypes and markers [8–10]. Different subsets of Bregs participate in immune modulation in different way. Bregs mediate inflammation and maintain homeostasis mainly via the secretion of suppressive cytokines such as interleukin-10 (IL-10), transforming growth factor- $\beta$  (TGF- $\beta$ ) and interleukin-35 (IL-35) [11–13]. In addition to suppressive cytokines, Bregs also exert regulatory effect by intercellular contact and directly kill effector cells by expressing Fas Ligand (FasL) [14,15]. TLRs/MyD88 signaling pathway is involved in

the activation of Bregs, which is essential for immunoregulatory role of Bregs [15]. Immunoregulatory role of Bregs has been demonstrated in autoimmune disease and graft-versus-host-disease (GVHD) [16,17]. The absence or loss of Bregs exacerbates the severity of disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), graft-versus-host-disease (GVHD) and so on [18–21]. Bregs restrain GVHD response by inhibiting the proliferation of CD4<sup>+</sup> T cells and suppressing the differentiation of TH1 cells [22]. In addition, Bregs are involved in tumor immunosuppressive effect by inhibiting T cells [23]. Tumor cells inhibit the antitumor immune process by inducing Bregs generation [24,25]. In this article, we review the research advances of Bregs in autoimmune diseases, GVHD and tumor.

## 2. Phenotypes and markers of Bregs

Clear phenotypes and characteristic markers of Bregs are not yet definite. IL-10 is a key cytokine in Bregs, which is involved in different diseases. Regulatory functions of Bregs are mainly identified by IL-10 production. Bregs producing IL-10 are also called B10 cells [8,26]. Marginal zone (MZ) B10 cells have been found to produce elevated level of IL-10 upon lipopolysaccharides (LPS) or CpG stimulation [27,28]. In murine cardiac transplantation model, MZ B10 cells are essential for the

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induction of regulatory T follicular helper cells (TFH cells) and tolerance toward allograft [29]. And most of transitional 2-marginal zone precursor (T2-MZP) Bregs express high levels of CD21, CD23, CD24, IgM, CD1d and IL-10 [30,31]. CD138<sup>+</sup> Bregs are also the main source of IL-10 during experimental autoimmune encephalomyelitis (EAE) [13]. In mice, there are various subsets of Bregs possessing immunoregulatory functions. CD19<sup>+</sup> CD5<sup>+</sup> CD1d<sup>high</sup> Bregs inhibit immune system with the capacity to produce IL-10 [32]. CD1d<sup>high</sup>CD23<sup>high</sup> CD21<sup>int</sup> Bregs in mucosa show a protective role depending on IL-10-expressing [27]. CD19<sup>+</sup>CD43<sup>+</sup>CD21<sup>high</sup>CD23<sup>+</sup>CD24<sup>high</sup>IgD<sup>+</sup>IgM<sup>+</sup>AA4<sup>int</sup>CD1d<sup>high</sup> Bregs produce IL-10 and inhibit TH1 response [33,34]. CD19<sup>+</sup>CD1d<sup>+</sup>CD21<sup>+</sup>CD23<sup>+</sup>IgM<sup>+</sup>CD24<sup>+</sup>CD62L<sup>+</sup> Bregs, CD19<sup>+</sup>CD43<sup>+</sup>CD80<sup>+</sup>CD86<sup>+</sup>CD40<sup>+</sup> Bregs and CD19<sup>+</sup>CD43<sup>+</sup>CD5<sup>+</sup> Bregs produce IL-10 and/or TGF- $\beta$ , induce T cells differentiate into Tregs, and inhibit Th1 co-stimulation response via B7 [27,32,35,36]. Discrepant phenotypes of human Bregs also have been described. IL-10 remains the best phenotypic marker for defining human Bregs. CD1d<sup>high</sup> Bregs and CD5<sup>+</sup> IL-10<sup>+</sup> Bregs producing IL-10 are identified in human [37–39]. Upon CD40 stimulation, human CD19<sup>+</sup>CD24<sup>high</sup> CD38<sup>high</sup> Bregs can suppress the differentiation of TH1 cells mainly via producing IL-10 [40]. CD19<sup>+</sup>CD25<sup>high</sup>CD27<sup>high</sup>CD86<sup>high</sup>CD1d<sup>high</sup>IL-10<sup>high</sup>TGF- $\beta$ <sup>high</sup> Bregs suppress the proliferation of CD4<sup>+</sup> T cells [41]. GrB<sup>+</sup> B cells activated by IL-21 reveal a CD19<sup>+</sup>CD38<sup>+</sup>CD1d<sup>+</sup>IgM<sup>+</sup>CD147<sup>+</sup>IL-10<sup>+</sup>CD25<sup>+</sup> expression signature showing regulatory function [42,43]. From these findings, Bregs might not belong to any clearly defined B cell subsets. However, immunoregulatory functions of Bregs are determined through the secretion of IL-10.

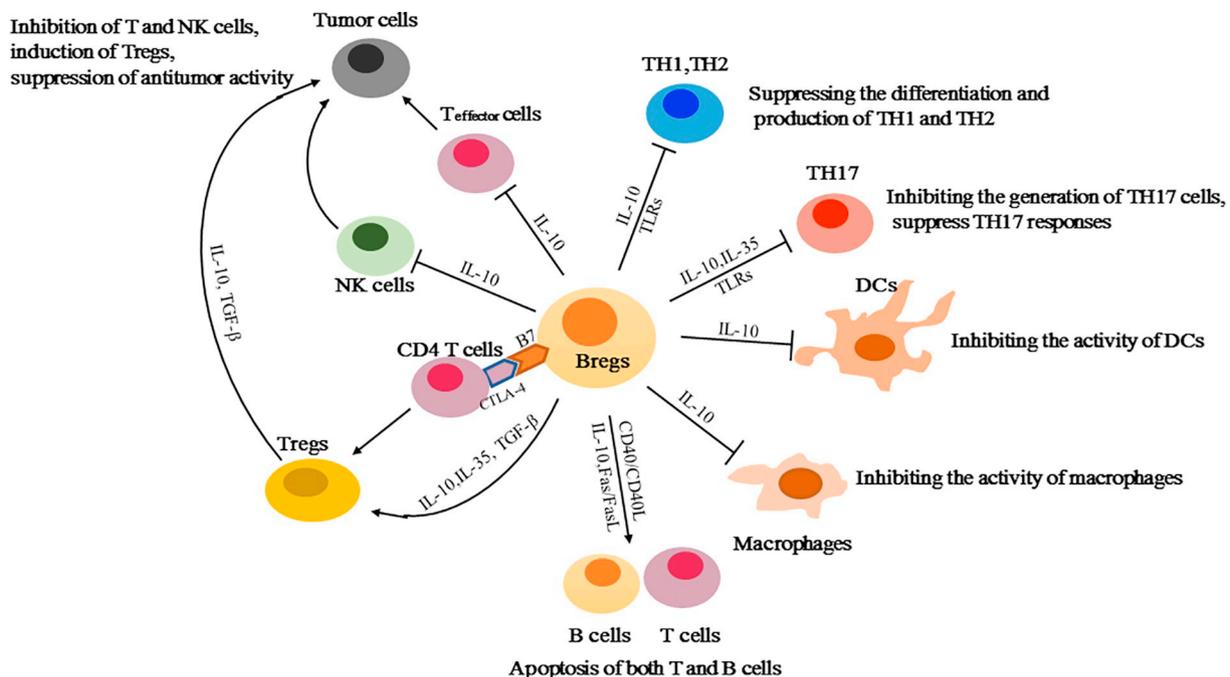
### 3. Immunoregulatory role of Bregs

#### 3.1. Bregs play immunoregulatory role by secreting cytokines

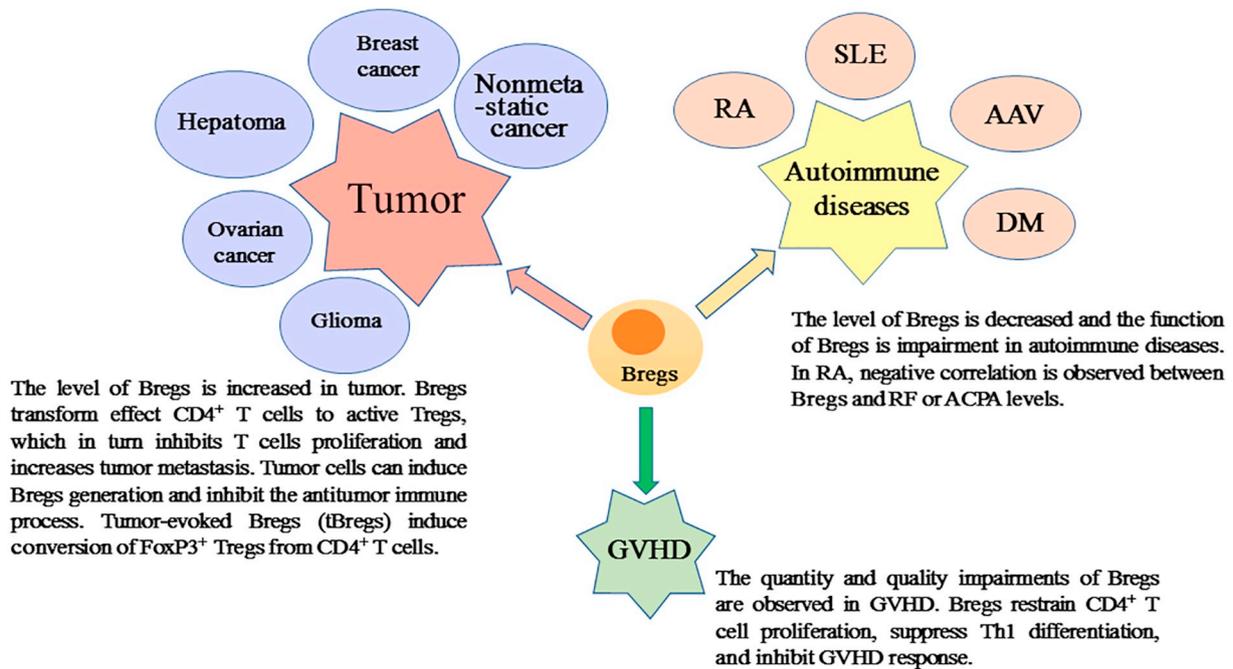
Bregs exert immunoregulatory role mainly through secretion of cytokines (Fig. 1) [44]. The most characteristic populations of Bregs in

mice and human are B10 cells [45,46]. Most studies have focused on the role of IL-10 which is a critical factor in regulating immune responses and preventing excessive inflammation. IL-10 produced by Bregs has a wide range of inhibitory effects on different types of cells and has been extensively regarded as an immunoregulatory factor in patients with different chronic inflammatory diseases [12]. IL-10 by Bregs inhibits the activity of dendritic cells (DCs) and macrophages, suppresses the production of TH1 and TH2, and induces inflammatory phenotypes on above cells to differentiate into inhibitory or tolerant phenotypes [47]. In healthy individuals, B10 cells exert their immunosuppressive effect by suppressing TH1 and TH17 responses, impairing APC and monocytes functions, influencing inflammatory cytokine production, and transforming effector CD4<sup>+</sup> T cells into FoxP3<sup>+</sup>CD4<sup>+</sup> Tregs [40,48–50]. In mice, B10 cells inhibit CD4<sup>+</sup> T cell to secrete IFN- $\gamma$  and TNF- $\alpha$  in vivo and in vitro [6]. However, after IL-10<sup>-/-</sup> mice are infected with parasites, B cells can still inhibit allergic and autoimmune inflammatory reactions, suggesting that IL-10 is not necessary for Bregs to play regulatory role [51].

It was later proved that Bregs play an immunoregulatory role by secreting TGF- $\beta$  and IL-35 (Fig. 1). TGF- $\beta$  produced by Bregs is involved in many processes including tissue remodeling and immune regulation [52–54]. Most somatic cells express TGF- $\beta$  receptors and can respond to TGF- $\beta$  signaling. Inhibition of proliferation is a major feature of TGF- $\beta$ , which is the main way for Bregs to play immunoregulatory role. What's more, in the context of immune tolerance, Bregs producing TGF- $\beta$  can convert naive CD4<sup>+</sup> T cells to Tregs [12,55]. IL-35 has also been linked to immunoregulatory role of Bregs [13]. IL-35, a heterodimeric IL-12 family member, is a critical immunoregulatory cytokine and plays an important role in regulating autoimmune [13,56,57]. IL-35 enhances immune tolerance by inducing the proliferation of Tregs and inhibiting the response of TH17 [12]. In addition, IL-35 can further transform B cells into Bregs producing IL-35, thus forming a positive feedback loop [58].



**Fig. 1.** Regulatory role of Regulatory B cells (Bregs) in immune cells and tumor cells. Bregs exert immunoregulatory role mainly through secretion of IL-10. Bregs suppress the differentiation and production of helper T1(TH1) and helper T2(TH2) cells, inhibit the generation and response of helper T17(TH17) cells mainly depend on TLRs and IL-10, inhibit the activity of dendritic cells (DCs) and macrophages by secreting IL-10, lead T and B cells to apoptosis through intercellular contact. Bregs transform CD4<sup>+</sup> T cells into FoxP3<sup>+</sup> Tregs by secreting IL-10, IL-35 and TGF- $\beta$ . Also, Bregs can transform CD4<sup>+</sup> T cells into FoxP3<sup>+</sup> Tregs by intercellular contact through B7(CD86)/CTLA-4. Bregs inhibit the differentiation and production of T and NK cells and induce the produce of Tregs by secreting IL-10, thereby inhibiting antitumor activity.



**Fig. 2.** Regulatory B cells (Bregs) in diseases. The level of Bregs is decreased and the function of Bregs is impairment in autoimmune diseases, such as SLE, RA, AAV, DM and so on. For example, in RA, Bregs exert lower ability to inhibit  $IFN-\gamma$  production of  $CD4^+$  Th1 cells. And negative correlation is observed in RA between Bregs and rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) levels. In graft-versus-host-disease (GVHD), the quantity and quality impairments of Bregs are observed. Bregs restrain  $CD4^+$  T cell proliferation, suppress Th1 differentiation, and inhibit GVHD response. In tumor, the level of Bregs is increased. Bregs transform effect  $CD4^+$  T cells to active Tregs, which in turn inhibits T cells proliferation and increases tumor metastasis. Tumor cells can induce Bregs generation and inhibit the antitumor immune process. Tumor-evoked Bregs (tBregs) induce conversion of  $FoxP3^+$  Tregs from  $CD4^+$  T cells.

### 3.2. Bregs play immunoregulatory role by intercellular contact

Bregs inhibit immune response by intercellular contact through B7(CD86)/CTLA-4, CD40/CD40L, Fas/FasL and so on (Fig. 1). Human Bregs decrease the proliferation of  $CD4^+$  T cells and enhance the expressions of FoxP3 and cytotoxic T lymphocyte associated antigen-4 (CTLA-4) in Tregs by intercellular contact [41]. When Bregs and  $CD4^+$  T cells are co-cultured mixedly, the expressions of FoxP3 and CTLA-4 on  $CD4^+$  T cells are increased. Compared to mixed co-culture, the expressions of FoxP3 and CTLA-4 on  $CD4^+$  T cells are decreased in separated culture [40]. CD28 and CTLA-4 are two ligands of B7 molecule and are expressed on Tregs. Therefore, combination of B7 on Bregs and CTLA-4 on Tregs is involved in the activation and mobilization of Tregs [59].

Bregs contact with effector T cells through CD40/CD40L, which leads T cell to death and reduces T cell response to autoantigen [32]. Chimeric mice lacking  $CD40^+$  B cells develops more severe disease than wild-type in EAE model, which suggests that CD40 on B cells is required for immunoregulatory role of Bregs [10,60].

$CD5^+$  Bregs in spleen are FasL positive and mediate T cell to apoptosis by intercellular contact [61].  $CD5^+$  Bregs uptake and present autoantigens to T cells through Fas/FasL, which would lead to the selective elimination of autoreactive T cells and alleviation of autoimmune disease [62]. Thus, in addition to secreting inhibitory cytokines, intercellular contact also plays an important role in immunoregulatory role of Bregs.

### 3.3. Bregs play immunoregulatory role through TLRs/MyD88 signaling pathway

Toll-like receptors (TLRs), one of the most important groups of pattern recognition receptors (PRR), provide the first line of defense against invading pathogens [63]. To date, many murine and human TLRs have been described, each responsible for identifying different

stimuli and inducing/inhibiting inflammation [64–66]. TLRs signals trigger regulatory functions of Bregs, which inhibits the differentiation of Th1 and Th17 and induces inflammatory T cell transform into self-limited [15]. TLR-9 activated lupus Bregs modulate inflammatory responses of T cells by producing IL-10 [67]. Eliminating TLR-9 gene in Bregs aggravates the SLE symptoms of lupus prone mice. And TLR-9 gene polymorphism leads to the low expression of TLR-9 in Bregs, which increases the tendency of developing SLE [68]. Mammalian TLRs signal restrain autoimmune diseases through the adapter protein MyD88 [69]. Bregs suppress the differentiation of Th1 and Th17 critically depend on TLRs and MyD88 [70]. Bregs lacking of MyD88 enhance the responses of Th1 and Th17 cells [70]. From these findings, TLRs/MyD88 signaling pathway might be involved in the activation of Bregs, which is essential for immunoregulatory role of Bregs (Fig. 1).

## 4. Regulatory roles of Bregs in diseases

### 4.1. Regulatory roles of Bregs in autoimmune diseases

#### 4.1.1. Bregs in RA

B lymphocytes and humoral immunity play a key role in RA, especially with anti-citrullinated protein/peptide antibodies (ACPA) and rheumatoid factor (RF) production [71] (Fig. 2). Several laboratories reported that Bregs are quantitatively and functionally altered in patients with active RA. The percentage and absolute number of Bregs are significantly reduced in RA patients [72]. Functional impairment of Bregs from RA patients is correlated with the reduction of Bregs [73]. Bregs in RA patients exert lower ability to inhibit  $IFN-\gamma$  production of  $CD4^+$  Th1 cells [19]. In addition, Bregs are also lower in RA patients with RF positive. And negative correlation is observed between Bregs and RF or ACPA levels (Fig. 2) [49]. IL-21 can significantly increase the number and immunoregulatory role of Bregs in RA patients [74,75]. Therefore, the percentage decrease and functional impairment of Bregs might contribute to the pathogenesis of RA.

#### 4.1.2. Bregs in SLE

SLE is an autoimmune disease that involves multiple systems [76]. The pathogenic mechanisms of SLE are unclear. However, the immune balance between regulatory B cells and effector B cells is damaged, which contribute to autoimmune injuries in SLE [9,77–79]. The critical role for Bregs in the pathogenesis of SLE has long been investigated in mice and humans. MZ Bregs downregulate the production of pro-inflammatory cytokine induced by TLR-9 receptor in lupus, which is IL-10-dependent [80]. Transferring splenic CD1d<sup>high</sup>CD5<sup>+</sup> Bregs from wild-type NZB/W mice (a murine lupus model) into CD19<sup>-/-</sup> NZB/W mice (lacking CD1d<sup>high</sup>CD5<sup>+</sup> Bregs) can significantly prolong CD19<sup>-/-</sup> NZB/W mice survival [81]. The function of CD19<sup>+</sup>CD24<sup>high</sup>CD38<sup>high</sup> Bregs isolated from peripheral blood of SLE patients is impaired, and the type of Bregs produce less IL-10 and lack of regulatory capacity [40] (Fig. 2). The level of CD1d<sup>+</sup> Bregs is decreased in SLE, which is associated with the over-expression of CD86 on B cells [82] (Fig. 2). However, contradictory result is that the percentage of peripheral blood CD19<sup>+</sup>CD5<sup>+</sup>CD1d<sup>high</sup> Bregs is significantly increased in active SLE patients and positively correlated with disease activity [18]. In general, Bregs mainly play immunoregulatory role in SLE. The upregulation of Bregs in active SLE patients might reflect a regulatory feedback mechanism to restore cellular tolerance and ameliorate harmful autoimmune responses.

#### 4.1.3. Bregs in antibody-associated vasculitis (AAV)

Rituximab has been shown to be effective in treating AAV, suggesting that B cells play an important role in the pathophysiology of AAV [83] (Fig. 2). Compared with healthy people, levels of CD5<sup>+</sup> Bregs and B10 cells are lower in active AAV patients [84,85]. In contrast, the level of CD5<sup>+</sup> Bregs in remission patients is similar to healthy people [86]. Patients with AAV have an increased frequency of the IL-10-1082AA genotype that is associated with decreased IL-10 production [87]. Nevertheless, Todd et al. found that CD19<sup>+</sup>CD24<sup>hi</sup>CD38<sup>hi</sup> Bregs are more decreased in remission patients than that during active disease [88]. Considering the decreased level of Bregs, it may be possible to treat AAV by inducing the production of Bregs. And the reduction of Bregs in remission patient might be owing to the depletion of total B cells.

#### 4.1.4. Bregs in dermatomyositis (DM)

DM is a systemic autoimmune disorder that is characterized by the inflammation of muscles and skin. It may also affect joints, esophagus, lungs, and heart [89]. Immunological dysfunctions have been described in patients with DM, including expanded autoinvasive T cells and B cells in skin lesions, increased autoantibody production, and aberrant cytokine production [90,91]. Considering the key role of Bregs in immunoregulatory, it is reasonable to speculate that Bregs may play a pivotal role in the pathomechanism of DM. Wenli et al. found the presence of CD19<sup>+</sup>CD24<sup>high</sup>CD38<sup>high</sup> Bregs in the peripheral blood of patients with DM. And the level of Bregs is remarkably decreased in DM patients compared to healthy people [92] (Fig. 2). These findings suggest that Bregs are damaged in patients with DM and that the occurrence and development of DM might be related to the decline level of Bregs.

#### 4.2. Bregs in GVHD

Regulatory roles of Bregs have been shown in GVHD (Fig. 2). Bregs restrain the proliferation of CD4<sup>+</sup> T cells, suppress the differentiation of TH1 cells, and inhibit GVHD response [22]. The quantity and quality impairments of Bregs are observed in human chronic GVHD [93–95]. After allogeneic stem cells transplantation, CD24<sup>hi</sup>CD27<sup>+</sup> Bregs are decreased in patients with chronic GVHD and are less likely to produce IL-10 than those from healthy donors and patients without chronic GVHD [94–96]. Eliminating IL-10 gene specifically in B cells, mice develop serious acute GVHD, which confirming an IL-10-dependent

suppression role of Bregs in GVHD [97]. What's more, STAT3 and extracellular regulated protein kinase (ERK) signals are detected in chronic GVHD patients, which is responsible for the decreased of Bregs in chronic GVHD [98]. Mesenchymal stem cells (MSCs) treatment can improve the symptoms of chronic GVHD patients by increasing the level of CD5<sup>+</sup> B cells and IL-10 [99]. In addition, immunoregulatory role of Bregs is used to suppress acute GVHD without effecting graft-versus-leukemia (GVL) activity [100]. Based on above results from the mouse model and clinical study, Bregs might be able to inhibit chronic and acute GVHD, which provides a new target for the prevention and treatment of GVHD.

#### 4.3. Bregs in tumor

In B-cell-deficient mice, enhanced antitumor immunity is associated with an increased activity of T and NK cells, which indicates that Bregs are involved in tumor [101] (Fig. 2). What's more, the antitumor effect of T cells is suppressed by IL-10 production of B10 cells [23]. Bregs transform effect CD4<sup>+</sup> T cells to active Tregs through secreting TGF- $\beta$ , which in turn inhibits the proliferation of T cells and increases tumor metastasis [102,103]. GrB<sup>+</sup> Bregs exist in the microenvironment of different types of tumor and contribute to the escape of tumors from an efficient antitumor immune response [43]. In human hepatoma, PD-1<sup>hi</sup> Bregs suppress tumor-specific T-cells immunity and promote tumor growth via producing IL-10 [104]. In ovarian cancer, Bregs significantly suppress IFN- $\gamma$  production of CD8<sup>+</sup> T cells, which is mediated by IL-10 and low CD80/CD86 expression [105]. Also, tumor cells convert normal B cells into Bregs, which suggests that tumor cells can induce Bregs generation and inhibit the antitumor immune process [25,102]. Nonmetastatic cancer cells express and utilize metabolites of the 5-lipoxygenase (5-LO) pathway to induce generation of Bregs [106]. Glioma cells-released placenta growth factors (PIGFs) can induce Bregs to suppress CD8<sup>+</sup> T cell activities [107]. In the mouse 4 T1 model of breast cancer, tumor-evoked Bregs (tBregs) induce TGF- $\beta$ -dependent conversion of FoxP3<sup>+</sup> Tregs from CD4<sup>+</sup> T cells, directly suppress the proliferation of T and NK cells and inhibit the secretion of Th1 cytokines [24,108]. What's more, PD-1<sup>-</sup>PD-L1<sup>+</sup>CD19<sup>+</sup> Bregs exert great inhibitory effect on T-cells immunity, which is dramatically up-regulated in the peripheral blood of breast cancer patients [109]. In gastric cancer and tongue squamous cell carcinoma, tBregs induce conversion of FoxP3<sup>+</sup> Tregs from CD4<sup>+</sup> T cells in a TGF- $\beta$ -dependent manner [110,111]. All the results suggest that Bregs play a critical role in regulating immune response to murine and human tumors and may also participate in carcinogenesis. Above results throw out a good understanding of Bregs-targeted therapies (Fig. 2).

### 5. Conclusion

Bregs play important roles in autoimmune diseases, inflammatory diseases and tumors. Functions of Bregs in these diseases are well described. In decades years, the subpopulations of Bregs that performed significant immunoregulatory role have been described. Even though more and more literatures focus on the function of Bregs, the clear phenotypes and characteristic markers of Bregs are still not definite. There are still some problems of Bregs to be solved. Whether different subsets of Bregs participate in immune regulation in different ways have not been illustrated. And further studies are needed to research on diseases treatment through targeting Bregs.

#### Conflict of interest

The authors have declared no conflicts of interest.

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