Cancer Immunology, Immunotherapy (2025) 74:125
https://doi.org/10.1007/s00262-025-03973-w

REVIEW

Revealing the role of regulatory b cells in cancer: development, function and treatment significance

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Received: 29 November 2024 / Accepted: 7 February 2025 / Published online: 25 February 2025

Abstract

B cells are essential components of the immune response, primarily recognized for their ability to produce antibodies. However, emerging research reveals their important roles in regulating immune responses and influencing tumor development, independent of antibodies. The connection between tumor progression and alterations in the tumor microenvironment is well-established, as immune infiltrating cells can enhance the survival of tumor cells by modifying their surroundings. Despite this, the majority of studies have focused on T cells and macrophages, creating a gap in our understanding of B cells. Regulatory B cells (Bregs) represent a crucial subpopulation that plays a significant role in maintaining immune balance. They may have a substantial impact on tumor immunity by negatively regulating tumor-infiltrating immune cells. This paper reviews the existing literature on Bregs, examining their development, phenotypes, functions, and the mechanisms through which they exert their regulatory effects. Furthermore, we highlight their potential interventional roles and prognostic significance in cancer therapy. By addressing the current gaps in knowledge regarding Bregs within tumors, we hope to inspire further research that could lead to innovative cancer treatments and improved outcomes for patients.

Keywords Breg cells · Breg development · Breg function · Breg subtypes · Cancer prognosis

Introduction

Bregs were initially discovered in the 1970s by Katz SI et al. [1] who discovered that splenocyte B cell depletion significantly reduced the inhibition of delayed-type hypersensitivity in an animal model, thus unmasking the fact that B cells can inhibit inflammation by producing IL-10. Over the next few decades of research, it has been established that Bregs can inhibit inflammation, which is often associated with various pathological processes, such as viral infections, anti-tumor responses, autoimmune disorders, and transplant rejection [2–4]. The emergence of Bregs provides a new direction for further research on the mechanism of pathological processes such as tumorigenesis, infection, inflammation, and autoimmune reactions. In addition to producing anti-inflammatory cytokines, TGF-β, IL-35, and IL-10, for example, also stimulates the development of regulatory T cells (Tregs). Meanwhile, the activation of Bregs intracellular signaling pathway potentially enhance IL-10 and IL-35 expression, and further control the process of peripheral immune tolerance in vivo [5–8]. Therefore, understanding the mechanism and function of Bregs in the pathological process of tumors and other diseases has great guiding and application significance in clinical application [8–12]. Here, this review will explore some concepts about the phenotype and differentiation of Bregs in-depth, focusing on providing the most recent debates over Bregs' function in tumor immunity and their potential intervention role and prognostic significance in cancer treatment.

Development, subgroups, and function of Breg

Growth and development of Bregs

B cells are distinct precursors of plasma cells that undertake specific humoral immunity. These cells grow and mature in the bone marrow, the central immune organ of mammals. In bone marrow, these cells go through several stages of development, such as pro-B cells, pre-B cells,

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immature B cells, and mature B cells [13]. These cells undergo gene recombination and negative selection at the immature stage to express intact BCR (mIgM), therefore developing immunity to self-antigens at the central level, ultimately leading to the formation of mature B cells that can express both mIgM and mIgD. Once matured, these cells move to the peripheral immune organs' B cell region, activate and grow in value in reaction to antigen stimulation, and grow later into memory B cells and plasma cells to complete the immune response [14].

Breg cells are differentiated in response to varied antigen recognition and various stimuli in the whole process of B cell growth and development and mainly come from the B2 cell line of peripheral lymphoid organs. Common lymphoid progenitor cells (CLPs) first differentiate in B2 precursor cells in bone marrow, then mature into progenitor B and pre-B cells, further growing into immature B cells, and then differentiate into transitional cells mature in the spleen after emerging from the bone marrow, and subsequently differentiate into MZ or FO B cells. FO cells undergo complete activation before differentiating into memory B cells and plasma cells, which generate particular antibodies. Most Breg cells are mainly found in mature memory B cells (Fig. 1). These Breg cells are largely antigen-specific and can regulate IFN-γ and TNF- α to affect the activity of $CD4^{+}$T cells. At present, there is evidence that Breg cells have immune functions to regulate the tumor microenvironment, autoimmunity, and infectious diseases, which means that Bregs are linked to the pathogenesis of infectious, neoplastic, and autoimmune illnesses. However, abnormally elevated Breg cells may prevent cells from killing pathogens, which in turn promotes cancer metastasis. It is worth mentioning that recent research has also proven the presence of Breg cells in human peripheral circulation, which revealed the necessity of further comprehensive investigation of the immune response of Breg cells and their role in various diseases [15–26].

Diversity of Bregs subpopulations

Researchers successfully identified Foxp3, a phenotypic marker that recognizes regulatory T cells. This discovery enlightens us that we may also have made important progress in identifying the phenotype of Bregs. Different

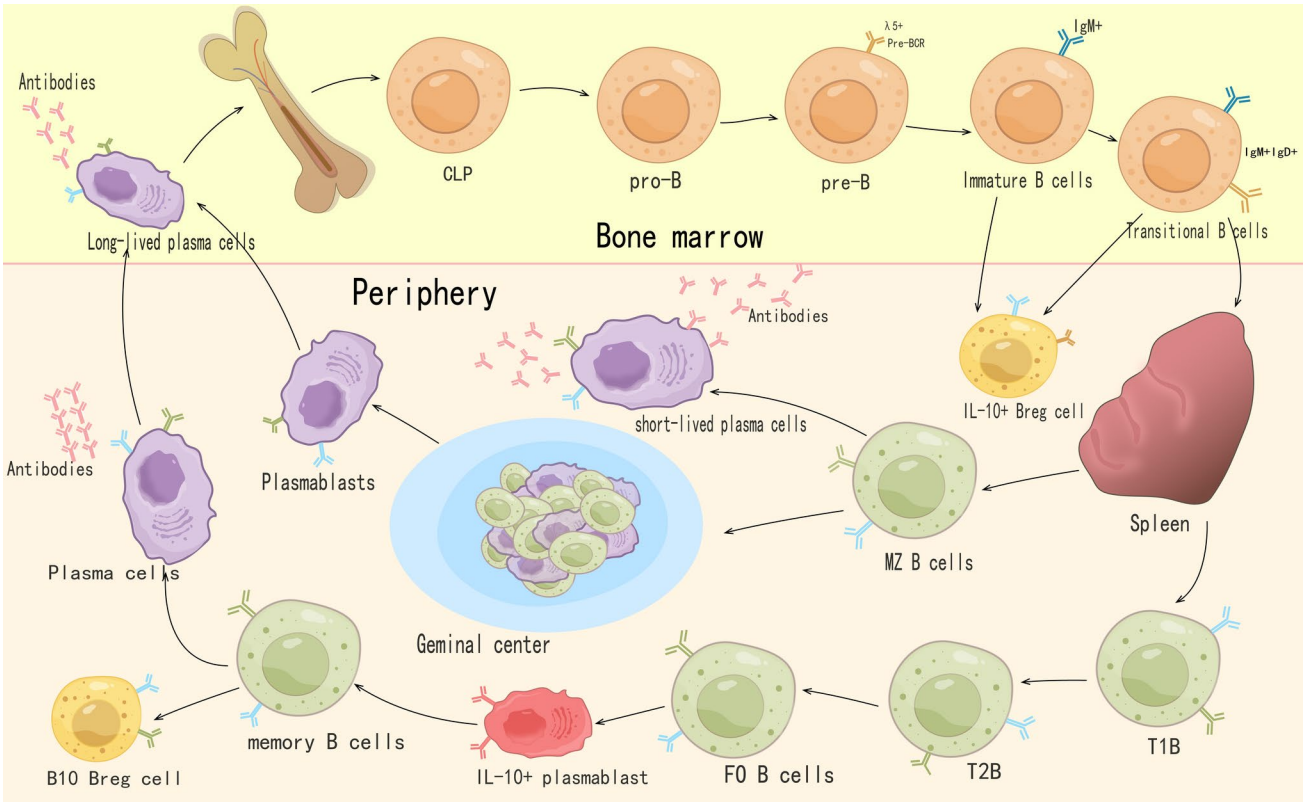

Fig. 1 Growth and development of Bregs. Common lymphoid progenitor (CLP) cells develop into immature cells in bone marrow, and then enter in the circulation, through transitional B cells, separate marginal zone (MZ) B cells and follicular (FO) B cells, and finally become mature B cells. Immature B cells could develop into Bregs with the stimulation of TLR ligands, while mature B cells can also be turned into Bregs by adequate stimulation

phenotypes of Bregs have different immunomodulatory roles in various tumors.

Currently, researchers have begun to explore the phenotypes of Bregs using techniques such as transcriptome analysis and multiparametric flow cytometry (Table 1). However, there is still a need to unearth new insights into a definitive phenotypic marker capable of identifying Bregs. Thus, there is still new and yet-to-be-explored territory for the definition and classification of Bregs, and explorations and discoveries in this direction are expected to lead to more progress and contributions to clinical work [27].

Meanwhile, studies have shown that Breg cells in different organs have different functions, and they are able to produce different cytokines for secretion. Most Bregs are able to secrete Il-10, but there are still some Bregs that secrete other types of cytokines. Therefore, based on the cytokine production status, we are able to categorize and study different Breg subpopulations. So far, several common subgroups of human Bregs have been identified, and progress in this area will help us to understand the biological functions and clinical applications of Bregs more comprehensively [15, 23, 28].

Many studies in mouse models and humans have found various subgroups of Breg cells. However, these subsets differ in their traits and in their expression of inhibitory substances. Table 1 summarizes the distinct Breg types seen in mouse models and human beings. It should be noted that we have yet to obtain unanimity on the definition and grouping of Breg cells. This study categorizes Breg cells into two types. One type secretes the inhibitory cytokine IL-10, known to be made by Breg cells. The other type does not secrete it. In mouse models, innate immunity is defined by CD5 expression. It is the main source of IL-10. B cells and B-1a cells produce low-affinity natural IgM antibodies, too. In 2008, Yanaba et al. [29] found the B10 cells, derived

Table 1 Different Bregs subtypes and functions

Subtype	Mouse phenotype	Human phenotype	Mediating cytokines	Functions
Tim-1$^+$B cells	Tim-1$^+$CD19$^+$	Tim-1$^+$CD19$^+$	IL-10, TGF-β	Enhance IL-10 secretion on Treg cells, regulate Th1 as well as and Th17 cells with inflammation [37]
B10 cells	CD19$^+$CD5$^+$CD1dhi	CD24^{hi}CD27$^+$	IL-10	Reduce Th17 along with effector CD4$^+$T cells during inflammation; control monocytes' production of TNF-α [29]
T2-MZP cells	CD19$^+$CD21^{hi}CD23^{hi} CD24^{hi}		IL-10	Decrease Th1 cells, CD8$^+$T cells, and effector CD4$^+$ cells; activate Treg cells [30]
Br1 cells		CD19$^+$CD25^{hi}CD71^{hi}CD73$^-$	IL-10, IgG4	Suppress the growth of CD4$^+$ T cells, activate Treg cells, and encourage the generation of IgG4 [33]
GrB$^+$B cell		CD19$^+$CD38$^+$CD1d$^+$IgM $^+$CD147$^+$	Granzyme B	T cell receptor degradation, and restricts T cell growth [34]
MZ cells	CD19$^+$CD21^{hi}CD23$^-$		IL-10	Regulate CD8$^+$T cell [38]
Plasmablasts	CD138$^+$CD44^{hi}	CD19$^+$CD24^{hi}CD27^{int} CD38$^+$	IL-10	Inhibit DC functions to produce autoreactive T cells, restrict effector CD4$^+$T cells and DCs [31]
CD73$^+$ B cells	CD23$^{\pm}$CD73$^+$	CD19$^+$ CD39$^+$ CD73$^+$	Adenosine	Promotes adenosine production and mediates immunosuppression [39]
PD-L1^{hi} B cells	CD3$^-$CD19$^+$ PD-L1^{hi}	CD19$^+$ PD-L1^{hi}	PD-L1, IL-10	Reduction of T cell activation and limitation of Tfh cell differentiation [40]
CD9$^+$ B cells	CD19$^+$ CD9$^+$	CD19$^+$ CD9$^+$	IL-10	T cell apoptosis induced [35]
CD5$^+$ B cells	CD19$^+$ CD5$^+$	CD19$^+$ CD5$^+$CD1d^{hi}	Granzyme B, IL-10	Suppress IL-22 production, regulation of th17 and th2 differentiation [41]
Immature transitional B cells		CD19$^+$CD24^{hi}CD38^{hi}	IL-10	Suppress Th1 and Th17 cell differentiation [32]
Plasma cells	CD44^{hi} CD19$^+$CD138$^+$	IgA$^+$PD-L1$^+$IL-10$^+$CD138$^+$	IL-10	Suppress anti-tumor immunity, suppress CD4$^+$T cells and macrophages [36]

from mouse spleen, are $CD5^{+}CD1d^{hi}$ B cells. They block the immune response of Th17 and $CD4^{+}$ T cells. They also regulate TNF-α release by monocytes. B10 cells that produce IL-10 in humans are in circulating $CD24^{hi}$ $CD27^{+}$ B cells. These cells can secrete IL-10 and suppress monocyte TNF-α production. Blair et al. [30] subsequently discovered that mouse T2-MZP-B cells had potent immunosuppressive properties and high expression levels of CD21, IgM, and CD23. They played a significant role in immunological regulation. On the one hand, they reduced the numbers of Th1, $CD8^{+}$T cells, and effector $CD4^{+}$T cells; on the other hand, they stimulated the proliferation of Treg cells. $CD138^{+}$ plasmablasts have the ability to generate IL-10, prevent dendritic cells from producing killer T cells, and restrict effector $CD4^{+}$T cells' ability to fight tumors [31]. Additionally, $CD19^{+}CD24^{hi}CD38^{hi}$ immature B cells demonstrated immunosuppressive properties; upon CD40 stimulation, these cells blocked Th1 and Th17 development [32]. Br1 cells strongly inhibit the proliferation of antigen-specific T cells in an IL-10-dependent manner [33]. GrB^{+}B cells are another element that can prevent T cells from functioning [34]. It was recently discovered that $CD9^{+}$ B cells have regulatory roles and generate IL-10. Through direct B-T cell interaction, CD9 itself may exert an inhibiting effect on the in vitro T cell proliferation assay. This suggests that in order to suppress T cell growth, $CD9^{+}$ B cells may need to connect with T cells and produce IL-10. They caused effector T cells to undergo apoptosis in both people and animals, boosted the ratio of Treg to effector T cells, and inhibited inflammation mediated by Th2 and Th17 [35]. Plasma cells impair the immune system, decrease anti-tumor responses, and lower $CD4^{+}$T cell and macrophage counts [36]. TIM-1 is expressed on both human as well as mice $IL\text{-}10^{+}$ B cells. $Tim\text{-}1^{+}$ B cells can suppress Th1 and Th17 responses while promoting IL-10 release by Tregs [37]. The phenotypic of Breg cells differs significantly between humans and animals. Many studies have shown the properties of mouse and human B cell subsets that regulate the immune system. They do this by producing IL-10 or using other inhibitory methods.

Subpopulation of IL-10-dependent Bregs

We know that Bregs have a significant part in tumorigenesis and development, autoimmune diseases, allergy and transplant rejection. Bregs are primarily responsible for producing TGF-β, IL-10, and IL-35. We first describe the most commonly studied IL-10-secreting B10 Bregs. B10 cells are known for their unique $CD1d^{(hi)}CD5^{(+)}$ $CD19^{(hi)}$ phenotype, and as a predominantly IL-10-producing subpopulation of Bregs, B10 cells have a significant immunosuppressive function in immunomodulation. B10 cells can be differentiated into various developmental stages of B cells, such as transitional, mature B, and plasma cells. These are found in particular populations of B1 and B2 cells in lung tissues, spleen, mediastinal lymph nodes, and blood. They have different differentiation states [42]. Similarly, some immature cells can differentiate into B10 cells that secrete IL-10. These cells are transitional immature (TI) and marginal zone (MZ) B cells, which we call marginal zone precursor-like (MZP) cells. Mzps have a $CD19^{+}IgM^{hi}CD27^{+}CD1c^{+}CD21^{low}CD10^{+}$ phenotype, such as T2-MZP-B cells, MZ B cells and B-1a B cells, which present important regulatory B cell (Breg) characteristics and functions [43]. These cells can also perform positive selection concurrently, and higher BCR signaling intensity can further promote the development of B10 cells [44]. B10 cells are an IL-10-dependent Bregs subpopulation. By releasing IL-10, they can both adversely and positively influence the immune response in various autoimmune and infectious conditions. They also inhibit the immune reaction in chronic inflammatory diseases. It can promote $CD4^{+}CD25^{+}FoxP3^{+}$Treg and Tr1, and iNKT growth. But, it may prevent the cytotoxicity of Tfh, Th1, and Th17, and inhibit $CD8^{+}$CTL. This anti-inflammatory role also restricts macrophages and monocytes from releasing inflammatory cytokines. It significantly inhibits the anti-tumor immune response. Bregs can also cause apoptosis by binding to Fas on $CD4^{+}$ T, $CD8^{+}$ T, and B cells. In this process, B10 cells mainly recognize self-antigens and, in an antigen-specific way, inhibit immunological responses [45].

Bregs can, in the immune system's mutual support, release IL-10. This reduces inflammation. Their suppressive effect can further promote immune support. Thus, they create a beneficial coordination effect. However, Bregs may overexpress IL-10 under some circumstances. Bregs could express IL-10 in response to specific stimuli. These include long-term treatment with certain immunotherapeutic drugs, such as immunosuppressants or biologics. These drugs can cause Bregs to produce huge amounts of IL-10 to suppress inflammation. In some cases, the intestinal flora can cause Bregs to secrete IL-10. When the Bregs encounter antigens, they encourage T cells to produce TGF-β and IL-10. The Bregs can also synthesize and secrete IL-10. This creates a beneficial, coordinated effect. When Bregs encounter an antigen, they induce T cells to make TGF-β and IL-10. They can also simultaneously synthesize and secrete IL-10. This creates an "intestinal-regulatory B cell-T cell sandwich pattern." It enhances their regulatory role and prevents inflammation. They control the nearby immune cells in the intestinal mucosa. This preserves the balance of the intestinal immune system. In inflammatory bowel diseases, autoimmune diseases, and chronic infections, Bregs play a key role in immune regulation. They inhibit inflammatory reactions by significantly expressing IL-10. B10 cells inhibit the immune response. They secrete IL-10, which reduces

cytokine production, co-stimulatory molecule expression, and antigen presentation. IL-10 also directly inhibits Th17 cell production. IL-10-producing Breg cells have a key role in many autoimmune and infectious diseases. They help to modulate the immune system [46].

However, the variables that control the growth and maintenance of B10 cells are still poorly known. For the question of how B cells manufacture IL-10, the first thing we need to understand is that naïve B cells will not consistently express IL-10. It is stimulated by several receptors that produce IL-10. These include APRIL, PI3K class 1 p110δ isoforms, TLR, BCR, and cytokine receptors. The current study shows that IL-10 gene expression has a known regulatory sequence. We have now identified important transcription factors for IL-10 expression. TLR ligands are crucial for activating B10 Bregs. They are powerful stimulants of IL-10 production in B cells. However, overstimulation of TLR7 will decrease B10 cells. This shows TLR7's suppressive role in B10 cell production [47]. In a mouse model of experimental EAE, researchers found that NFATc1 deficiency led to the reduction of IL-17A, IL-17F, IL-21and IL-10 in vitro and the expansion of B10 cells [48]. However, another study revealed that, in comparison with non-B10 cells, B10 cells had higher expression levels of TLR1, IFNγR, and STAT10, demonstrating that the IFNγR-STAT1 pathway has a detrimental regulatory effect on TLR7-mediated development of B10 cells [49]. Additionally crucial for B cells producing IL-10 is STAT3, and CXCL13 can also promote the secretion of IL-10 by B cells. The expression of IL-10 is also regulated by various mechanisms. By focusing on the mRNA for transcription factors that govern IL-10 expression, miRNAs can regulate IL-10. They can also regulate epigenetic factors that affect the IL-10 gene's chromatin state. MicroRNA-21(miR-21) affects the IL-10 expression by directly impairing TLR-stimulated B cells. Mir-16 in miRNAs targets the mRNA of STAT3 to decrease the expression of STAT3 and IL-10 in B cells. The study found that miR-155 and IL-10 mRNA rose together. This suggests an interaction between the two factors [27]. In addition to this, blocking SLAMF5 in vivo can additionally increase the disease's severity by raising the quantity of B10 cells [28, 42, 46, 50–66].

Although the function of B10 cells has been thoroughly investigated, our understanding of the mechanism of how B cells develop into B10 cells has yet to be further explored, and more thorough research is required to clarify and describe their genesis and growth. In future studies, we need more research to understand the regulation mechanisms of B10 cells and the interactions with other regulatory cells, with a view to providing a more in-depth theoretical basis for immunotherapy. In conclusion, by secreting IL-10 to prevent the generation of pro-inflammatory cytokines, the expression of co-stimulatory molecules, the presentation of antigens, and the direct suppression of Th17 cell development, B10 cells play a significant role in immunomodulation. Further research is required to fully comprehend the processes underlying B10 cell formation and differentiation as well as how these cells interact with other immune cells, in order to deeper comprehend the mechanics of the role of B10 cells in immunomodulation.

Subpopulation of IL-10-independent Bregs

Ever since a population of Breg cells was discovered with immunomodulatory functions, numerous studies have been carried out on humans and mice by researchers to identify subpopulations of Breg cells with immunomodulatory functions. Although L-10 is a prominent molecule in the investigation of B cell immunomodulation mechanisms, it is not the only functional molecule and other subpopulations of Bregs with immunomodulatory functions that are not related to the secretion of IL-10 have been identified, for example, Bregs are immunomodulated by adenosine, TGF-β, IL-35, and IgM production. In the next section, we will describe these subgroups of Bregs that are not dependent on IL-10 for immunoregulation [47, 67].

IL-35^{+} Bregs The two subunits of IL-35, an immunosuppressive factor belonging to the IL-12 family, are p35 and EBV-induced gene 3 (EBI3). The heterodimeric nature of IL-35 and the variety of cell surface markers made it possible to characterize Breg cells that produce IL-35 [18, 63, 67–71].

Breg cells that produce IL-35 primarily come from CD138$^{(+)}$ plasma cells, and IL-35 produced by Breg cells is a potential therapeutic target for infectious and autoimmune disorders [47, 72]. In addition to being utilized to treat autoimmune and inflammatory illnesses and create autologous Bregs and IL-35$^{(+)}$ Breg cells, IL-35 has been demonstrated to function as a pro-tumorigenic agent in animal tumor models and its expression has been associated with lower clinical outcomes in a variety of human cancers (e.g., colorectal, pancreatic, or hepatocellular carcinoma) [59, 73–75]. Li S et al. [76] found that tumor growth was inhibited by anti-IL-35 inhibition and genetic ablation, and the STING-IL-35 axis dampened NK-driven anti-tumor responses and decreased the proliferation of natural killer (NK) cells. Huang A et al. found that diffuse large B cell lymphoma (DLBCL) is characterized by the overexpression of IL-35 by tumor cells, which phosphorylates STAT1 and STAT3 in B cells to inhibit the generation of IL-10 [69]. Additionally, it has been demonstrated that IL-35 stimulates the growth of regulatory T cells (Tregs) and Bregs [71]. Therefore, genetic ablation therapy or anti-IL-35 inhibition can slow the growth of tumors and show promise as anti-tumor therapeutics. All things considered, research on IL-35-producing Bregs could

lead to novel approaches to tumor treatment, and the study of IL-35-producing Breg cells can also be applied to the treatment of other immune-related diseases.

IL-27$^+$ Bregs Activated antigen-presenting cells release interleukin-27 (IL-27), a novel member of the IL-12 family that triggers several signaling cascades, including the p38 MAPK and JAK-STAT pathways. Research has indicated that IL-27 exhibits both pro- and anti-inflammatory properties in several autoimmune disorders; however, the underlying mechanisms for IL-27's dual function in inflammation and autoimmunity are not fully understood [52]. According to the studies of Pratumchai I et al. Bregs that produce IL-27 can influence antibody class switching and control of persistent viral infections by promoting IL-27 signaling on CD4$^+$ T cells, thereby facilitating infection control and driving cellular mechanisms of antiviral immunity and antibody responses [77]. A study by Meka RR et al. found an innate-like regulatory B-1a cell (i27-Bregs) that producesIL-27 in the peritoneal cavity and human umbilical cord blood. In contrast to other B cells, i27-Bregs can continue to secrete IL-27 in lymphoid tissues and the central nervous system while growing in vivo. Because i27-Bregs' inhibitory effects are neither antigen-specific nor disease-specific, they are consistent with their developmental origin and have broad applicability potential as an efficient immunotherapy for a variety of disorders [78]. Nowadays, autoimmune encephalomyelitis and uveitis are the main conditions treated by immunotherapy against i27-Bregs. This is achieved by transforming normal B cells into Bregs, which are capable of secreting IL-10 and IL-35 by upregulating inhibitory receptors (e.g., Lag3, PD-1), suppressing the Th17/Th1 response, and sending inhibitory signals to the brain, spinal cord, or eye. As a result, research on i27-Bregs has substantial theoretical and clinical implications and may yield novel therapeutic approaches for autoimmune disorders.

TGF-β$^+$ Bregs TGF-β is a significant cytokine that comes in three isoforms: TGF-β1, TGF-β2, and TGF-β3. TGF-β1 is the typical member of the family. By binding to the TGF-β type II receptor (TGFβRII), phosphorylating the TGF-β type I receptor (TGFβRI), and controlling the expression of many genes, TGF-β activates the SMAD-dependent pathway [79]. Furthermore, TGF-β has the ability to control cellular processes via non-SMAD-dependent pathways (including ERK, JNK, p38, PI3K, and AKT). Poznansky SA et al. found that TGF-β is crucial for B cell growth and autoimmune control, and it can also be dominant in regulating Bregs immunological function by converting naïve CD4$^+$ T cells into Tregs, which suppresses immune responses [80]. The study by Huai G et al. on breast cancer models showed that tumor produced substances, such as leukotriene B, activate Bregs and stimulate Tregs to create TGF-β, which contributes to the negative regulation of immune responses. Furthermore, they discovered that transgenic mice lacking Bregs-derived TGF-β1 developed EAE more quickly in the EAE mouse model, which was correlated with the activation of the DC frequency in the CNS and the pathogenic CD4$^+$ T cell expansion in the CNS. Tumor-induced TGF-β secreted by Bregs can also increase the generation of reactive oxygen species and NO by bone marrow-derived suppressor cells, inhibit the proliferation of CD4$^+$ and CD8$^+$ T cells, and ultimately favor tumor metastasis [81]. In addition, Liu J et al. found that TGF-β-producing Bregs additionally have a significant impact on worm-infected mice, inhibiting Th1 and/or Th2-mediated colitis by cooperating with anti-inflammatory macrophages [82].

Therefore, further studies on the occurrence and regulatory mechanisms of TGF-β$^+$Bregs are of great significance for the management of autoimmune illnesses and malignancies.

PD-1$^+$ Bregs Tumor cells can express a variety of immunosuppressive signaling proteins that lead to immune cell malfunction and apoptosis, and immune evasion is a characteristic of malignancies. Programmed death ligand-1 (PD-L1) is one of these inhibitory substances; it inhibits anticancer immunity by binding to PD-1 expressed on T cells, B cells, DCs, and NK cells. Although B cell-mediated control helps to maintain tolerance, it could also perform a role in immunological dysfunction in cancer and infectious illnesses. Although uncommon in peripheral blood, Wang X et al. discovered that B cell subgroups with PD-1 expression were markedly elevated in differentiated thyroid cancers. Additionally, PD-L1 was expressed at noticeably greater levels in PD-1$^+$B cells. Anti-Ig/CD40 L stimulation that is ongoing rather than transient increased the expression of PD-1 and PD-L1 in B cells. PD-1$^+$ B cells were found to have a regulatory role in vitro, as evidenced by their considerable inhibition of CD4$^+$ and CD8$^+$ T cell growth and reduction in viability in response to CD3/CD28 stimulation. PD-1$^+$ B cells did not, however, express large quantities of IL-10, in contrast to other Breg cells subgroups that secrete IL-10. PD-L1 appeared to play a role in PD-1$^+$ B cell-mediated inhibition instead, since blocking PD-L1 markedly improved T cell survival and proliferation in co-culture. Taking everything into account, this study indicates that PD-1$^+$ B cells can control T cell reactions [83]. Mao Y et al. investigated how circulating exosomes in ESCC contributed to the formation of the PD-1$^+$ and IL-10 Bregs subpopulations, two of the major Bregs subpopulations. The findings demonstrated that, in comparison with healthy controls, ESCC patients had a higher percentage of B10 cells in peripheral circulation. The researchers then extracted and studied exosomes from ESCC cell lines and patient peripheral blood. It was discovered that exosomes from ESCC patients and cell lines

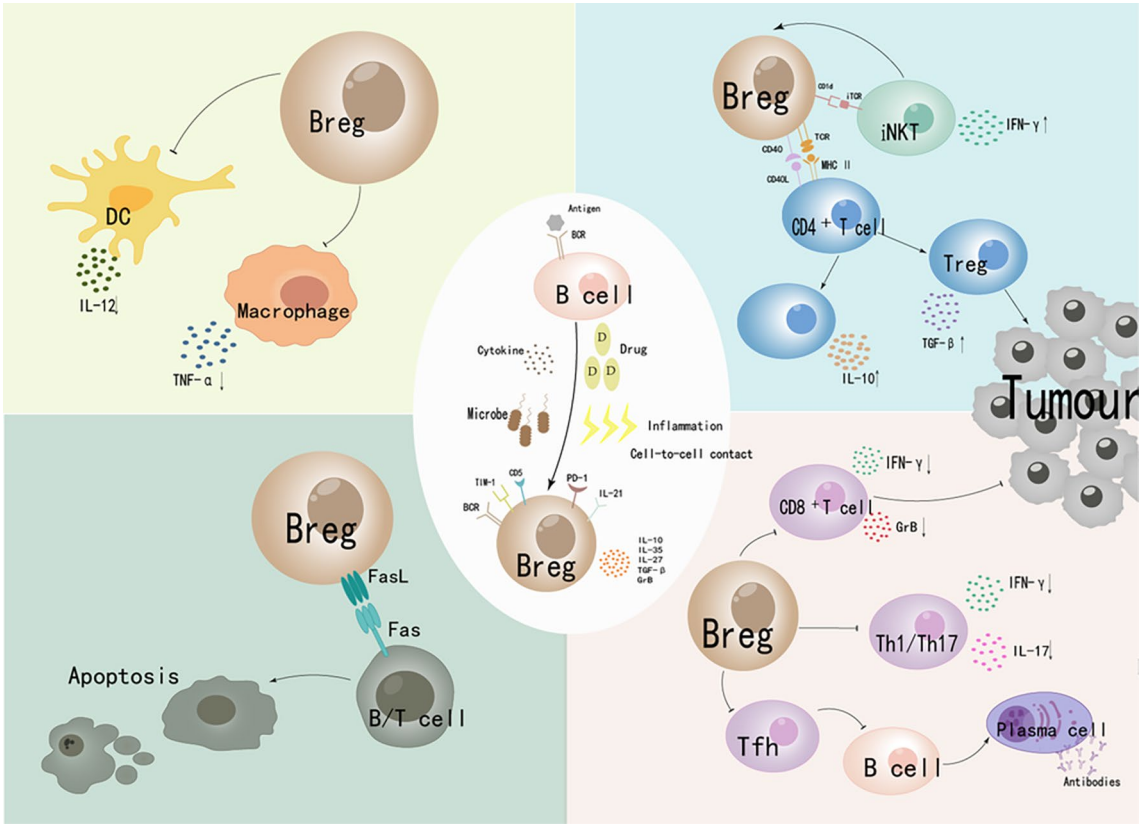

Fig. 2 Functions of Bregs. Breg, which is transformed from B cells under different stimuli, on the one hand promotes the transformation of naive $CD4^{+}$T cells into Tr1 and Treg cells to assist iNKT; On the other hand, it prevents the differentiation of Th17 cells and the Th1 cell response, and inhibits macrophage and DC cells functions. In addition, Bregs also participates in the process of apoptosis

inhibited B cell proliferation and stimulated the generation of PD-1^{hi} Bregs and B10 [84]. Xiao X et al. [85] found that 10% B cells in advanced hepatocellular carcinoma were members of a tumor-promoting subpopulation that constitutively expressed elevated levels of PD-1. The phenotype of these PD-$1^{(hi)}$ B cells is different from that of typical $CD24^{(hi)}CD38^{(hi)}$ peripherally Bregs; it is $CD5^{(hi)}CD24^{(-/+)}$ $CD27^{(hi/+)}$ $CD38^{(dim)}$. In HCC, environmental stimuli that induce PD-$1^{(hi)}$ B cells need TLR4-mediated overexpression of BCL6. This impact was reversed by phosphorylating STAT6 in response to IL-4. Importantly, PD-$1^{(hi)}$ B cells developed regulatory roles that inhibited tumor-specific T cell immunity and encouraged cancer growth via IL-10 signaling when coming into contact with PD-$L1^{(+)}$ cells or experiencing PD-1 triggering.

These results offer significant new understandings of immunosuppression caused by PD-1/PD-L1 and anticancer treatments for malignancies in humans.

Breg cell-targeted therapies are becoming more and more common in clinical practice, and in order to develop safer and more effective immunotherapies targeting Breg cells, a deeper and more precise understanding of the mechanisms governing Breg cell regulation is required.

Functions of immunoregulation by Breg

Bregs are essential for immune system homeostasis and are particularly useful when tissue injury, inflammation, or infection occur. Numerous factors, including cytokines (such as IL-1β, IL-2, IL-6, and IFN-α), environmental variables and cell–cell interactions can activate Bregs [86–93] (Fig. 2).

Bregs primarily secrete TGF-β, IL-35, and cytokines (mainly IL-10) to maintain immune system homeostasis and control the immune system [94–97]. Activation of macrophages, $CD4^{+}$ T cells, PD-1 T cells, DCs, and CTLs can all be inhibited by these cytokines [18, 27, 63, 98–101]. Bregs can also suppress the immune system by producing granzyme B, which stops $CD4^{+}$ T cell growth. Granzyme B, a serine protease that triggers apoptosis, is primarily produced by NK cells and CTLs. Bregs that produce Granzyme B are greatly enhanced in environments that are high in IL-21. Granzyme B^{+} Breg cells have been found in autoimmune disorders that can reduce Th1 and Th17 cells through downregulating the TCR zeta chain and causing T cell death. These malignancies may impede anti-tumor T cell responses [34, 102–108]. In addition, the $CD39^{hi}CD73^{+}$

phenotype of Breg cells exerts negative regulatory properties on the immune system by producing adenosine (ADO), a key enzyme molecule associated with the anti-inflammatory milieu, and by promoting the release of IL-6 and IL-10, which prevent effector T cells activation and proliferation [109].

Bregs can interact with other cells to modulate the immune system. One significant activation mechanism among them is cell–cell contact with T cells that is CD40 dependent. Bregs' ability to express CD40 can improve their ability to connect with T helper cells that express CD40L, which increases the likelihood that Bregs will become activated [6, 32, 110–116]; environmental variables that cause Bregs activation and IL-10 production include LPS and plasmacytoid DCs through IFN-α- and CD40-mediated stimulation. These environmental cues have the potential to activate Bregs, which in turn controls the immunological response via negative regulatory mechanisms, preserving the immune system's homeostasis.

Furthermore, Bregs possess the ability to independently control immunological responses in the absence of cytokines. Breg cells have the ability to produce TNF by depending on glucocorticoid-α related receptor ligand (GITRL) or other TNF family members, like membrane-bound TNF, GITR, and trail, to trigger immune regulation or contact-dependent apoptosis [117–125]. Bregs can also carry out immune regulation through the expression of PD-L1 along with Fas ligand (FasL) on Bregs. Bregs expressing high levels of PD-L1 can regulate humoral immunity through PD-1 ligation, which inhibits $CD4^+CXCR5^+PD\text{-}1^+$ Tfh cells [18, 83, 85, 93, 126–133]. Induced cell death is triggered and self-tolerance is maintained via FasL's connection to the Fas death receptor on activated T cells. Hence, on Breg cells, targeted deletion of FasL can induce autoantibody synthesis, T cell proliferation, and tolerance breaking. Human Breg cells expressing FasL were discovered in bone marrow, tonsil GCS, and plasma cells including various organs. When there is a bodily infection, FasL Bregs can prevent an inflammatory response from happening. Cytotoxic $CD8^+$ T lymphocytes can also undergo apoptosis when exposed to FasL Bregs. Furthermore, FasL B cells retrieved from tumor-draining lymph nodes can kill tumor cells in vitro and trigger death of nonimmune cells when inflammation is developed in the body. In conclusion, inflammation induces the production of FasL Bregs, which may be involved in the maintenance of peripheral tolerance and the regulation of exacerbation responses, as well as the formation of anti-tumor immunity and inflammation-induced damage [134–147].

In conclusion, the understanding of these mechanisms contributes to our in-depth understanding of the function and biological properties of Bregs, and it provide a foundation for the creation of Bregs-specific targeted treatments. Consequently, a thorough investigation of the activation mechanism and related signaling pathways of Bregs and exploration of mechanism of action and disease resistance in the immune system will offer fresh approaches to the management of autoimmune disorders and clinical cancer.

The role of Bregs in cancer prognosis

Current research shows that human cells from a range of malignant tumors, such as those in the pancreas, ovary, stomach, lung, colon, esophagus, bladder, and circulatory system, have been shown to contain Bregs. These results suggest a close relationship between Bregs and the clinicopathological features of tumors as well as the prognosis of cancer patients.

Breast cancer

One of the most prevalent malignancies in female patients is breast cancer. Although new treatment methods and strategies have been introduced, and the global breast cancer mortality is decreasing year by year, the downward trend of breast cancer mortality in China is not obvious. Determining the variables associated with the prognosis of breast cancer is therefore crucial. In order to look into the involvement of $CD19^+CD24^{hi}CD38^{hi}$Breg cells in breast cancer, Gheybi MK et al. examined blood samples from patients with invasive ductal breast cancer and healthy controls. The study's findings indicated a correlation between TGF-β1 in patients' serum with advanced disease and an increase in $CD19^+CD24^{hi}CD38^{hi}$Breg in peripheral blood, as well as a significant increase in the proportion of circulating CD4CD25Foxp3 Tregs and $CD19^+CD24^{hi}CD38^{hi}$Breg in breast cancer patients. These findings suggested that $CD19^+CD24^{hi}CD38^{hi}$Breg cells may be responsible for suppressing immunological reactions against breast cancer [148]. Ishigami E et al. undertook immunohistochemistry assessment of $CD25^+IL\text{-}10^+$Bregs and $Foxp3^+$Tregs in tumor-infiltrating lymphocyte aggregates (TILs) from breast cancer patients in order to better understand the clinical effects of the coexisting of Bregs and Tregs in cancer patients. Treg presence was closely associated. Subsequent multivariate analysis demonstrated a correlation between breast cancer patients' metastasis-free survival (MFS) as well as the presence of both Bregs and Tregs in TILs. Furthermore, the MFS was substantially worse for patients with both Tregs and Bregs in TIL than for patients with just Tregs and no Bregs. Put differently, Bregs were linked to distant breast cancer cell metastasis and the production of Tregs in TIL [149]. Not coincidentally, a study by Pati S

et al. revealed low serum IgG levels in patients with breast cancer despite having a higher number of Breg cells. They employed high-dimensional flow cytometry to examine the heterogeneity of the Breg cells population and discovered that the identified $CD39^{+}CD19\text{-}IL39^{+}$ Breg cells population both increased the production of naturally suppressive $CD1^{+}FOXP4^{+}$ Treg cells and limited the growth of Th cells and the survival of killer effector cells. These Breg cells hindered the growth of autologous T helper cells and reduced the production of IgG antibodies, which may have led to low IgG levels in breast cancer patients, which are linked to a poor prognosis [114]. Furthermore, while the percentage of $PD\text{-}1^{+}$ Breg cells was larger in patients with high-grade tumors, and the results showed a non-significant positive connection between the frequency of Bregs and the tumor grade. Shariati S et al.'s study looked at changes in the frequency of B cells in lymph nodes in breast cancer and discovered that the frequency of PD-L1 Breg cells was negatively correlated with the expression of estrogen and progesterone receptors [150]. Bregs are a significant predictive factor for breast cancer and could be a novel target for breast cancer patients' treatment and diagnosis in the future. Breg cells elimination may be a novel and exciting approach to treatment in the future to encourage antibody responses mediated by plasma B cells.

Melanoma

Melanoma is one of the deadliest cancers. The survival rate deteriorated significantly with the progression of staging. Therefore, finding the factors that affect the prognosis of melanoma is essential to improve the prognosis of melanoma and develop new treatment strategies. In recent years, researchers have extensively explored the relationship between Breg cells and melanoma. According to a research by Aira LE et al. melanoma patients with IL-10(B-1a) Breg cells preferentially accumulate, which promotes tumor growth by impeding the ability of tumor-infiltrating $CD8^{+}$ T cells to produce cytokines and other IL-10-dependent processes [151]. Wu H et al. focused on PD-L1 Breg cells in melanoma and discovered that circulating B cells from patients with melanoma expressed PD-L1 at much higher levels than those from healthy controls. The enhanced levels were also found to be positively connected with the stage of the tumor, with patients with stage IV bone metastases having the highest levels. The proportion of cells in bone metastases was found to be much higher than in primary tumors, indicating a tight relationship between PD-L1 Breg cells and advanced stage and metastasis of cancer [152]. To further understand the possible mechanisms of Breg's role in melanoma, Harris RJ et al. analyzed and investigated Bregs expressing pro-inflammatory cytokines in melanoma patients employing methods including B: T cell co-culture, transcriptome, immunofluorescence, flow cytometry, CyTOF, and single-cell RNA-seq. The peripheral circulation of melanoma patients showed decreased populations of $TNF\text{-}\alpha^{+}$Breg cells and increased populations of TGF-βand PD-L1 expressing Bregs; $TGF\text{-}\beta^{+}$ B cells aggregated in clusters in the microenvironment of melanoma tumors and interacted with T cells through recruiting lymphatic. Further research has revealed that reg cells in melanoma patients maintain autologous T helper cells to express IFN-γ and TNF-α and promote T helper cell proliferation in isolation, all while promoting FOXP3 Treg division through the expression of TGF-β. Furthermore, the above mechanism of action is further enhanced by the blockade of the anti-PD-1 checkpoint [98]. Not coincidentally, Kobayashi et al. also demonstrated that mice with melanoma growth-promoting B cell-specific PTEN abnormalities showed a large increase in the number of tumor-infiltrating Bregs and a significant decrease in the fraction of tumor-infiltrating $CD8^{+}$ T cells secreting IFN-γ and TNF-α. These findings imply that a higher Bregs level may be linked to a worse melanoma prognosis [153]. When considered collectively, these results demonstrate the critical part that Breg cells play in the genesis and progression of melanoma. These findings offer fresh perspectives and avenues for melanoma research, as well as new approaches to developing novel therapeutic approaches.

Gastric cancer

Among the most prevalent and deadly cancers is gastric cancer. Gastric cancer can arise and spread due to a variety of reasons, including chronic inflammation and bacterial virulence factors. Since $CD19^{+}IL\text{-}10^{+}$Breg cells have immunosuppressive functions, in addition to their significance in autoimmune and infectious illnesses, research by Nahid-Samiei M et al. raises the possibility that the pathophysiology of H. pylori infection may be significantly influenced by the increased quantity of Breg cells and their interactions with other cells. Thus, the scientists postulated that Breg cells might possibly be involved in the onset and spread of stomach cancer [154]. In a study examining the function of Bregs in gastric cancer, Zhuang H et al. demonstrated that patients with gastric cancer had higher numbers of Th1 cells, which can inhibit the growth of IL-10 Breg. This led to the inhibition of B10Breg, which in turn caused tumors and inflammation to develop [155]. Additionally, Murakami et al. discovered that Bregs are crucial for immune escape in patients with gastric cancer (GC). The findings demonstrated that GC patients had significantly higher peripheral blood Breg frequencies than healthy controls, and that GC tissues had significantly higher $CD19^{+}CD24^{hi}CD27^{+}$ Breg cells than both peripheral blood and healthy gastric tissues. Additionally, carboxyfluorescein succinimide levels were found in GC patients' peripheral. Additional

carboxyfluorescein succinimide labeling demonstrated that $CD19^{+}CD24^{+}CD27^{hi}$ B cells could decrease autologous $CD4^{+}$ T cell growth and $CD4^{+}$ T cells' production of INF-γ. Additionally, a multifactorial examination indicated that the frequency of Bregs were a separate prognostic factor for patients with GC [156]. Bregs connect not only with the clinical course, but also with the prognosis of gastric cancer. Li Wet al.'s work looked into the connection between the clinical outcomes of patients with gastric cancer treated with XELOX and the dynamic changes in circulating Breg cells. According to the study, patients with a longer progression-free survival (PFS) had a decreasing trend of $CD19^{+}CD24^{hi}CD27^{+}$ Breg cells compared to the initial value at the early stage of chemotherapy. This suggests that the frequency of Breg cells may be used to predict the effectiveness of chemotherapy and assist doctors in modifying the right course of treatment [157]. When considered collectively, these data imply that Bregs might be a significant factor in the incidence and progression of stomach cancer. Therefore, it is crucial to continue researching Bregs' function and mechanism in gastric cancer in order to create novel treatment approaches.

Liver cancer

B cells are a crucial component of tumor cells and are involved in many immunological responses, including inflammation, infection, and tumor formation. One of the main epigenetic regulators of B cells has been identified as ten-2 translocation-2 (tet5), which demethylates 5-methylcytosine to 5-hydroxymethylcytosine (5hmc) to control gene expression. A recent study investigated the potential clinical applications of tet10 and its involvement in the hepatocellular carcinoma-related generation of IL-10^{+}B cells. High levels of TET2, IL-10, and 5hmc have been linked to a poor prognosis for hepatocellular carcinoma patients, according to research by Lu Z et al. [57]. Bregs displayed greater levels of PD-1 and made up about 10% of total B cells in advanced hepatocellular carcinoma (HCC), according to a different study by Xiao X et al. which also revealed tumor-promoting subpopulations of B cells in hepatocellular carcinoma. With their distinct $CD5^{(hi)}CD24^{(-/+)}CD27^{(hi/+)}CD38^{(dim)}$ phenotype, these PD-$1^{(hi)}$ B cells have the ability to inhibit tumor-specific T cell immunity and stimulate tumor development via IL-10 signaling [85]. To sum everything up, Bregs are strongly associated with a dismal outcome for liver cancer. To give more useful and workable prediction and coping strategies for clinical practice, we should investigate this association further.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) patients have monoclonal expansion of $CD5^{+}CD23^{+}CD27^{+}CD19^{+\kappa/\lambda+}$ B lymphocytes, which are indicative of a B regulatory cell-like immune phenotype that produces large amounts of IL-10 and TGF-β, which turns naïve T cells into Tregs, which adversely impacts immunological response and T cell activation. Saulep-Easton D et al. found that B cell activating factor (BAFF) of the tumor necrosis factor family (TNF) activates IL-10-producing Breg cells in CLL patients, which promotes immune tolerance in CLL and is linked to the onset and progression of CLL [158]. Another study by Ringelstein-Harlev S et al. further identified and characterized Bregs properties in CLL cells: Toll-like receptor 10 (TLR9) or CD9 activators increased the frequency of $CD4^{+}$ $CD25^{hi}$ FOXp3 Tregs as well as inhibited the proliferation of autologous $CD4^{+}$ T cells. Additionally, they promoted the production of IL-10 in CLL cells, which intensified the inhibition of T cell proliferation. These findings imply that CLL cells employ Bregs properties to promote T cell regulation and thus influence tumorigenesis [159]. Mohr A et al. evaluated the Bregs-like capacity of CLL B cells that received Toll-like receptor 9 (TLR9) stimulation and found that with normal T cell sensitivity in all patients, only half of the patients' CLL B cells had Bregs properties, while the remaining patients' B cells were unable to develop Bregs function, implying that inherent CLL B cell shortage was the cause of the aberrant Bregs activity, and further studies on the relevance of Bregs function showed that CLL patients with efficient Bregs activity were more aggressive than those with defective Breg cells [160, 161]. Currently, ibrutinib, a common drug for the treatment of CLL, is a covalent inhibitor of Bruton's tyrosine kinase (BTK), and can be applicable to the treatment of individuals with primiparous or relapsed/refractory chronic lymphocytic leukemia (CLL). In a prospective study of peripheral blood samples, Kondo K et al. discovered that patients receiving ibrutinib mediated a persistent and selective down-regulation of PD-L1 through STAT3, in addition to inhibiting regulatory B cell function, which decreased the amount of IL-10 produced by CLL cells. Suggesting that ibrutinib can treat CLL by inhibiting Breg cell's function [162]. Therapeutic approaches to target Bregs include inhibition of BAFF signaling pathway and CD38 antibody therapy targeting CLL cells, and in an vivo xenograft model experiments, Manna A et al. validated the efficacy for anti-CD38 monoclonal antibody therapy, which alters the tumor microenvironment, increasing the percentage of Th17 as well as $CD8^{+}$ T cells while lowering Bregs, Tregs, and PD-$1^{+}CD38^{hi}CD8^{+}$ T cells, which strengthens the immune response to CLL [163]. The previously mentioned results demonstrate that a positive treatment impact is inversely correlated with the level of Bregs. Investigating

and learning more about Bregs in relation to CLL development is crucial. Future studies will provide a fresh perspective on how to suggest Bregs treatment plans that are more successful.

Acute myeloid leukemia

Hematologic malignancy with a heterogeneous appearance is acute myeloid leukemia (AML). Breg cells have negative immunoregulatory characteristics, which may contribute to the pathogenesis of AML even if many aspects of their immunological processes are yet unknown. Therefore, Dong Q et al. performed experimental analyses by flow cytometry, enzyme-linked immunosorbent assay, and RT-qPCR in three groups of freshly diagnosed individuals with AML, AML patients in total recovery, and normal controls to thoroughly evaluate the quantity and performance of Bregs and Treg cell subcategories in AML clients, as well as their possible roles in AML pathogenesis. The findings demonstrated that the frequency of Bregs were much higher and the quantity of Tregs increased in newly diagnosed AML patients. IL-10 and Foxp3 mRNA levels were higher in recently diagnosed individuals with AML, but not statistically different from those in complete remission or normal controls. These findings indicate that Bregs and Tregs are present at varying levels throughout the disease course in AML patients, implying that they may play distinct roles in AML pathogenesis. In contrast, the levels of Bregs and Tregs were not significantly different between patients in complete remission and healthy controls. Compared to healthy controls and AML patients in complete remission, newly diagnosed AML patients had higher plasma IL-10 levels but lower TGF-β [164]. The frequency of Breg cells and clinical data in AML patients were also investigated in the study by Lv Y et al. The findings suggested that individuals with AML had a greater incidence of Breg cells in peripheral and bone marrow compared to healthy donors (HD); patients with high leukocyte levels had higher frequency of Breg cells than patients with low leukocyte levels; patients at intermediate risk had higher frequency of Breg cells compared to low-risk patients; and patients with high WBCs and a high frequency of Breg cells had shorter overall survival. Comparably, the younger group of patients with low Breg cells frequency had a much longer overall life than the older group of patients with high Breg cells frequency. When combined, these findings suggest that patients with acute myeloid leukemia have a significantly higher frequency of Breg cells than healthy donors, and that higher expression of PD-L1 in Bregs are also linked to a poor prognosis. These findings suggest that increased Breg cells frequency in AML may also be associated with a poor prognosis [165].

In conclusion, these investigations indicate that the specific level of Breg cells in AML patients may be associated with the exacerbation of AML and the general survival rate for patients, which offers a new therapeutic target for the treatment of AML and also provides useful information for further exploring the pathogenesis of AML. Also, we can further detect the Bregs level of AML patients in the clinic to judge the possible prognosis, and timely intervention and treatment.

Breg and cancer immunotherapy

As mentioned earlier, there is growing evidence that regulatory B cells (Bregs) play an important role in suppressing the immune response to tumors. Immune checkpoint inhibitors (ICIs) are an immunotherapy that should not be overlooked in current cancer treatments. These drugs attack cancer cells by disarming immunosuppressive mechanisms in the tumor microenvironment and activating the patient's own immune system. However, despite the fact that ICIs have shown significant efficacy in a wide range of cancer types, a significant proportion of patients do not respond to or are resistant to single-agent treatment [166]. Since Breg cells express CD80/86 and PD-L1, theoretically, Breg would also be affected by anti-CTLA-4 and anti-PD-1/PD-L1 ICIs [167]. Therefore, we will next discuss the relationship between Breg and ICIs to provide new ideas for further exploration of ICI resistance mechanisms.

Oral squamous cell carcinoma

In a study of oral squamous cell carcinoma conducted by Piersiala, K et al. the researchers used flow cytometry to analyze tumor-draining lymph node (TDLN), non-tumor-draining lymph node (nTDLN), and metastatic lymph node specimens of 21 patients with oral squamous cell carcinoma in a subgroup comparative analysis. The results showed that the proportion of immunosuppressive regulatory B cells (Breg) present in patients with TDLN that developed metastases was significantly increased compared to patients without metastases. Meanwhile, the expression level of interleukin-10 (IL-10)-producing Breg was significantly higher in TDLN compared to nTDLNs. Further studies revealed that the immunosuppression triggered by the high accumulation of Breg in TDLN was closely associated with disease progression and drug resistance. This phenomenon is highly likely to be a potential impediment to effective response to novel cancer immunotherapy (ICI) in head and neck cancer patients. Therefore, Breg is expected to be a potential therapeutic target to enhance the anti-tumor response of TDLN. An in-depth investigation of the mechanism of Breg in TDLN is of great significance for optimizing ICI therapeutic strategies and improving the therapeutic efficacy of head and neck cancer patients [168].

Melanoma

The use of PD-1 and PD-L1 inhibitors has become a well-established therapeutic approach for patients with advanced melanoma, as reported by Wulfken, L.M., et al. Five years after the diagnosis of melanoma, the patient was treated with rituximab for pre-existing granulomatous polyangiitis, which resulted in complete depletion of B cells in his peripheral blood and tumor tissue. B cells in his peripheral blood and tumor tissue were completely depleted. In the absence of the b-raf mutation in the proto-oncogene, the patient was started on nivolumab and achieved a deep partial remission, which lasted for more than 14 months. Follow-up flow cytometry analysis of peripheral blood single nucleated cells revealed that 15% of these cells produced IL-10 and 14% were regulatory B cells (Breg) that were double positive for CD24 and CD38. The exceptional clinical response shown by this B cell depleted patient to monotherapy provides a new direction for research on the role of B cells in modulating the immune response in melanoma. This suggests that depletion of regulatory B cells may contribute to enhancing the therapeutic efficacy of immune checkpoint inhibitors (ICIs), and that there is a strong link between the two. Further in-depth study of the relationship between Breg and ICI is important for optimizing immunotherapy strategies for melanoma [169].

Breast cancer

The axillary lymph node (LN), as a major metastatic site of breast cancer, occupies a key position in the developmental process of breast cancer. However, the mechanism of interaction between tumor cells and immune cells within metastatic lymph nodes (mLN) remains poorly elucidated and many unknowns exist. The study conducted by Huang, H et al. focused on the regulatory impact of $CD24^{hi}CD27^{+}$ regulatory B cells (Breg) within the mLN on the drug resistance of breast cancer cells. The results showed a strong association between activated $CD24^{hi}CD27^{+}$ Bregs and the spatial distribution of residual tumor cells within the mLN in breast cancer patients receiving NAT. In terms of mechanism of action, $CD24^{hi}CD27^{+}$Bregs were able to significantly enhance the multidrug resistance of breast cancer cells and contribute to the acquisition of stem cell-like features through the secretion of IL-6 and TNF-α. More critically, breast cancer cells could further activate $CD24^{hi}CD27^{+}$Bregs through CD40L-dependent and PD-L1-dependent proximal signaling pathways, thus forming a positive feedback regulatory mechanism and exacerbating the process of tumor drug resistance. Notably, PD-L1 blockers were able to significantly attenuate $CD24^{hi}CD27^{+}$Bregs-induced drug resistance in breast cancer cells, and the addition of anti-PD-L1 antibodies to the chemotherapy regimen effectively improved the remission of tumor cells in mLN. This study clearly reveals the key mechanism of action by which $CD24^{hi}CD27^{+}$Bregs interact with breast cancer cells within the mLN and thus promote tumor resistance. This result provides a new theoretical basis for optimizing the chemo-immunotherapy strategy for breast cancer patients with mLN metastasis, and lays the foundation for further exploring the synergistic therapeutic regimen of targeted Bregs and immune checkpoint inhibitors (ICIs), which is of great significance in enhancing the clinical outcome of breast cancer treatment [170]. It is not the only case, Li, X., et al. Aiming to investigate the role of soluble programmed death ligand 1 (sPD-L1) in the pathogenesis of human breast cancer, serum levels of sPD-L1 and interleukin-10 (IL-10) in patients with breast tumors, as well as the patients' peripheral blood levels of B cells, programmed death receptor 1-positive B cells (PD-1 B cells), regulatory B cells (Bregs) and the proportion of PD-1 Bregs were examined, and the association between these metrics and sPD-L1 was assessed. It was found that serum levels of sPD-L1 and IL-10 in patients with invasive breast cancer (IBCa) were significantly higher than in patients with fibroadenoma of the breast (FIBma). Also, the proportion and absolute number of Bregs and PD-1 Bregs in the peripheral blood of IBCa patients were significantly higher than those of FIBma patients. In addition, positive correlations between sPD-L1 and IL-10, IL-10 and PD-1 Bregs, and sPD-L1 and PD-1 Bregs were observed in IBCa patients. The researchers further confirmed through in vitro experiments that sPD-L1 was able to induce Breg differentiation, IL-10 secretion, and IL-10 mRNA expression in a dose-dependent manner. In addition, the study also found that Bregs could inhibit anti-tumor responses, which was further supported by experiments on the induction of regulatory T cells, as well as indicating that PD-L1 blockade therapy could promote tumor cell apoptosis. Taken together, these findings suggest that sPD-L1 is able to mediate the differentiation of Bregs, contribute to the expansion of $CD4^{+}$ regulatory T cells, and thus impair the anti-tumor activity of $CD4^{+}$ T cells. This implies that PD-L1/PD-1 blockade therapy is expected to be an effective therapeutic strategy for IBCa patients, especially for TNBC patients with high levels of PD-1 Bregs. The research results provide a new theoretical basis and potential therapeutic direction for the treatment of IBCa, and further reveal the close connection between Bregs and immune checkpoint inhibitors, which is of great significance for optimizing the immunotherapeutic regimen of breast cancer [171].

Thyroid cancer

Regulatory B cells (Bregs) can inhibit the function and proliferation of T cells by overexpressing negative immune checkpoints, ultimately leading to immune escape of tumor

cells. Based on this, Bregs play a negative role in inducing tumor immune escape. Targeting Bregs immune checkpoints is a potential therapeutic strategy to address this situation [172]. A recent study by Wang, X., et al. showed that in thyroid cancer, Breg cells with high expression of programmed death receptor 1 (PD-1) significantly inhibited T cell proliferation. And after targeting PD-1 for blockade, the proliferative capacity of T cells was significantly enhanced, and the survival rate of $CD4^+$ and $CD8^+$ T cells was also significantly increased. In addition, surgical treatment with radioactive iodine therapy was able to substantially reduce the frequency of PD-1^+ B cells. This shows that blockers targeting PD-1 in immune checkpoint inhibitors (ICIs) will be more helpful in achieving the desired therapeutic effect if they are used in combination with other cancer treatments. This study reveals the potential connection between the immunosuppressive mechanism of Bregs and ICI therapy, which provides a new idea for the treatment of thyroid cancer and other related tumors, i.e., to enhance the efficacy of ICI by inhibiting Bregs-mediated immune escape, and thus improve the prognosis of patients [83].

Hepatocellular carcinoma

The findings of Lu, Z., et al. present a TET2-dependent epigenetic intervention strategy for targeting IL-10^+ B cell production during hepatocellular carcinoma (HCC) progression and clearly indicate that inhibition of TET2 activity is a highly promising, combinable treatment for HCC with immune checkpoint inhibitors. Currently, nivolumab, a second-line therapeutic agent for HCC, has failed to significantly improve the overall survival of HCC patients due to a limited anti-PD-1 response rate and has not met the predefined criterion for statistically significant improvement. It was found that the combination of TET2 deletion in $CD8^+$ T cells with anti-PD-L1 therapy also failed to further enhance anti-tumor efficacy. And the study confirmed that eliminating TET2-mediated immunosuppression in B cells is expected to improve the body's response rate to anti-PD-1 therapy. The researchers found experimentally that the use of Bobcat339 (an inhibitor of TET1 and TET2) in combination with anti-PD-1 therapy to pretreat B cells followed by overtransfer showed that there was a synergistic effect between Bobcat339 and the anti-PD-1 therapy, and that this synergistic effect was at least partially realized by reducing IL-10 secreted by the B cells. This suggests that IL-10 secreted by regulatory B cells (Breg) plays a key role in the process of immunosuppression, and that inhibition of TET2 can affect Breg function and enhance the effect of anti-PD-1 therapy. The effectiveness of Bobcat339 treatment lays the groundwork for subsequent in-depth study of TET2 inhibitors, which is expected to be optimized by optimizing the combination of TET2 inhibitors with immune checkpoint inhibitors (ICIs, such as anti-PD-1 therapies) combination treatment regimen, which is expected to bring greater clinical benefits to HCC patients. This research not only reveals the intrinsic connection between Breg, TET2 and ICI, but also opens up a new direction for the clinical treatment of HCC, which is of great significance for the improvement of HCC treatment [57].

Non-small cell lung cancer

Regulatory B cells (Bregs) inhibit autoimmune responses by directly suppressing self-reactive T cells, as well as inhibiting the production of follicular helper T cells (TFH cells), thereby limiting the activity of self-reactive B cells. Anti-PD-1 therapy might be able to directly impair the suppressive function of PD-1^+ and PD-$L1^+$ Bregs. Consistent with this scenario, patients who developed a toxic response after receiving immune checkpoint blockade therapy had significant defects in their functional B cell pools at the time of disease diagnosis, with a marked reduction in the subpopulation of B cells expressing IL-10 alone, a subpopulation that is closely related to the subpopulation of Bregs described in the literature. In the treatment of advanced non-small cell lung cancer, immune checkpoint blockade with Pembrolizumab has demonstrated durable clinical efficacy. However, some patients experience high-grade immune-related adverse events (irAE), which offset the therapeutic efficacy to a certain extent. Patel, A.J., et al. demonstrated that in these patients, the immune checkpoint function of Bregs are defective, which is unable to limit the enhancement of autoreactive T cell activity and the formation of autoantibodies after PD-1/PD-L1 blockade, leading to severe autoantibody formation. Formation, ultimately leading to severe autoinflammatory sequelae. Through functional in vitro assays and in-depth phenotypic mass spectrometry flow cytometry analysis, it was found that dysfunctional IL-10-producing regulatory B cells are a critical and important feature of patients who develop high-grade irAEs when treated with anti-PD-1/PD-L1 checkpoint blockade. Currently, there is a lack of clinical biomarkers capable of identifying patients most likely to develop severe autoinflammatory syndromes, and pre-treatment analysis of B cells may be an important tool for identifying lung cancer patients at high risk of developing severe irAEs while receiving immune checkpoint blockade therapy. This finding not only highlights the important role of Bregs in immune regulation, but also reveals a strong link between them and the therapeutic efficacy of immune checkpoint inhibitors (ICIs) and the associated adverse effects, which provides an important basis for optimizing immunotherapy strategies for lung cancer [173].

Therapeutic potential

Considering the dual function of B cells as immunomodulators, two possible therapeutic strategies have been proposed, aiming at activation and depletion of B cells, respectively. Moreover, there is growing evidence that tailoring therapy to the function of Bregs has excellent clinical relevance in cancer treatment.

T cell Ig structural domain and adhesion molecule structural domain protein 1 (TIM-1) have been identified by Ding Q et al. as co-stimulatory molecules that influence immune response by controlling $CD4^+$ T cell effector development. Most IL-10-expressing Bregs, including as transition zone, marginal zone, and follicular B cells, as well as B cell populations that have $CD1d^{(hi)}$ $CD5^+$ B cell populations, have high expression of TIM-1, IL-4 and IL-10 which is concentrated in TIM-1^+ B cells, and this stimulates a Th2 response that can transfer allograft tolerance directly. TIM-1-specific antibodies, which rely on IL-4 signaling, stimulate both cytokine production and the quantity of TIM-1^+ Bregs. As a result, TIM-1 is an inclusive marker for IL-10^+ Bregs, and TIM-1 attachment can cause the formation of these Bregs [37]. These results shed light on the signaling involved in the generation and activation of Bregs and imply that TIM-1 may be a novel therapeutic target for controlling immunological responses. Thus, TIM-1 may have potential therapeutic applications in immune cell induction, differentiation, and regulation in B cell-related therapy and vaccine development. In the future, we must investigate the precise methods by which TIM-1 regulates Bregs' actions in more detail and assess the possibility of using it to treat immune-related illnesses like cancer. Furthermore, combining immunotherapy with IL-35 inhibition could be a further therapeutic option to investigate. Apart from manipulating the quantity of Breg cells and focusing on cell surface markers, particular antigens or ligands may be utilized to stimulate Breg cells, thereby enhancing their differentiation and functionality. Alternatively, the quantity and function of Breg cells can be boosted for therapeutic purposes by cultivating and multiplying them in vitro and then transferring them to patients. This strategy has been explored in clinical trials.

Li, S., et al. showed that resistance to systemic therapy with STING agonists is partly due to the expansion of immunosuppressive B cells that impede NK cell function. STING activates the regulatory function of B cells by inducing IL-35, which in turn inhibits the NK cell response. And this negative regulatory circuit can be broken during cGAMP treatment by blocking the specific secretion of IL-35 by B cells, which provides a potential therapeutic strategy for tumor control. Regulatory B cells (Breg) play a key role in this process, and blocking the secretion of IL-35 by B cells can inhibit the immunosuppressive function of Breg and restore the anti-tumor activity of NK cells, which is expected to be a new way to improve the efficacy of tumor treatment [76].

Autologous i35—regulatory B cell (i35—Breg) administration is promising as a potentially effective immunotherapy for autoimmune and neurodegenerative disorders of the central nervous system (CNS), but there are still many challenges to overcome before it can be applied in the clinic. One of the major challenges facing i35—Breg therapy is the difficulty in accurately determining the i35—Breg-secreted IL-35 bioavailability. This uncertainty affects the assessment of therapeutic efficacy and the optimization of treatment regimens. Another obstacle is that the transport of cells (including lymphocytes) to the brain, retina or spinal cord is severely limited by the blood–brain barrier (BBB) and the blood-eye barrier (BOB) [19]. Of interest, a recent report by Kang, M., et al. suggests that IL-35-containing exosomes (i35—Exosomes) released by i35—Bregs provide a new pathway for the delivery of IL-35 to the CNS. The study found that mice treated with i35—Exosomes were effectively protected against severe uveitis and that the treatment triggered the expansion of IL-10 and IL-35 secreting regulatory T cells (Treg) and suppressed the Th17 response, resulting in disease protection. This finding highlights the importance of i35-Exosomes in immunomodulation and suggests their potential value in the treatment of CNS-related diseases. In the future, in-depth study of the mechanism of action of i35—Exosomes and optimization of their preparation and delivery methods are expected to overcome some of the difficulties faced by i35—Breg therapy, and further explore the potential of i35—Breg in the treatment of CNS autoimmune and neurodegenerative diseases, and to bring more effective treatments to patients [174].

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, which is characterized by high mortality and poor prognosis. B cells play a dual role in the tumor microenvironment of PDAC, and the regulatory B cells (Bregs) dispersed within the TME inhibit anti-tumor immune responses by secretion of anti-inflammatory cytokines (IL-10 and IL-35) to promote tumor growth and metastasis. Targeted regulation of this cell subpopulation is expected to improve the state of immune tolerance in the immune microenvironment of PDAC, thereby breaking the barrier of tumor immune escape and enhancing the body's immune attack ability against tumor cells [175]. Neutralizing interleukin-35 (IL-35) demonstrated significant therapeutic effects in pancreatic cancer mouse model studies. It was able to reduce the frequency of PD-$L1^+$ Breg cells and stimulate the production of $CD8^+CXCR3^+CCR5^+$ T cells, which in turn overcame resistance to anti-PD-1 immunotherapy in pancreatic cancer mice. This suggests that targeting Breg cell-associated cytokines (e.g., IL-35) has the potential to reshape the tumor immune microenvironment and enhance

the efficacy of immune checkpoint inhibitors (e.g., anti-PD-1 immunotherapies), which will bring new hope for the treatment of refractory tumors such as pancreatic cancer [93].

Zhu, H., et al. in PDAC found that infiltration of $CD38^+$ B cells with regulatory B cell-like properties was an independent factor affecting the prognosis of PDAC. This finding suggests that $CD38^+$ B cells play an important role in the disease progression of PDAC and that their infiltration is closely related to the prognosis of patients. In this study, we observed that $CD38^+CD19^+$ B cells were able to hinder the cytotoxic function of NK cells by secreting the inhibitory cytokine IL-10. For the first time, it was demonstrated that $CD38^+CD19^+$ B cells may exercise the function of regulatory B cells (Breg) in PDAC. In-depth investigation of the specific mechanism of the role of this cell subpopulation in the highly immunosuppressive pancreatic immune microenvironment and the development of precise targeted therapeutic strategies accordingly are of great clinical significance to enhance the efficacy of immunotherapy for PDAC and to improve the prognosis of patients. Future studies should focus on how to more effectively target $CD38^+CD19^+$ B cells to inhibit their immunosuppressive function and at the same time enhance the body's anti-tumor immune response, so as to bring more therapeutic choices and better hope of survival for PDAC patients [176].

In the therapeutic field of solid cancers, traditional B cell depletion therapies have obvious limitations. The CD20 antagonist rituximab, for example, is ineffective and almost difficult to apply in the treatment of solid cancers due to its lack of more precise targeting. Not only that, rituximab may instead promote cancer progression and metastasis by inducing CD20-inexpressing regulatory B cells (Breg), negatively impacting patient care. In contrast, exploring alternative Breg-specific markers has become a more promising direction for Breg depletion therapy. Among them, CD200, a type I membrane-associated glycoprotein closely associated with immunoregulatory signaling pathways, has been detected in a variety of hematological malignancies and solid cancers. For example, Breg cells expressing $CD200^+$ have been found in human papillomavirus-positive (HPV^+) head and neck squamous cell carcinoma (HNSCC) patients [177]. Based on this, the researchers tried the treatment with the anti-CD200 monoclonal antibody Samalizumab. The antibody was tested in the treatment of both hematologic malignancies as well as solid cancers. Unfortunately, the results of the trials were not favorable, and patients experienced a variety of adverse outcomes, including skin rashes, joint stiffness or pain, headaches, and blood disorders. This is largely due to the fact that CD200 is widely expressed in normal cells of hematopoietic and non-hematopoietic origin, leading to the inevitable potential toxicity triggered by the use of anti-CD200 monoclonal antibodies. In summary, caution must be exercised when utilizing Breg cell depletion therapy. On the one hand, traditional B cell depletion therapies have serious drawbacks in the treatment of solid cancers; on the other hand, newly explored Breg depletion therapies based on specific markers (e.g., CD200) face many problems. In the future, when promoting the clinical application of Breg cell depletion therapy, it is necessary to conduct more in-depth research on Breg-specific markers and develop more accurate and safe treatment strategies, so as to fully utilize the potential value of Breg cell depletion therapy in cancer treatment and minimize the harm of adverse effects on patients [79].

There has been some progress in the study of potential therapies to prevent or reverse the regulatory B cell (Breg) phenotype. In a variety of mouse cancer model experiments, researchers have found that lipoxin A4, an arachidonic acid metabolite with anti-inflammatory properties, selectively inhibits the process of B10 Breg induction. During this process, the number of regulatory T cells (Treg) in tumor tissues and draining lymph nodes was reduced, while the proliferation, differentiation, and germinal center (GC) formation of effector B cells were preserved. This finding implies that lipoxin A4 has a unique role in regulating the immune microenvironment, and is expected to break the balance of tumor immune escape by regulating the number and function of Breg and Treg cells, opening a new pathway for cancer treatment [178].

In the study by Zhou, J., et al. the mechanism of regulatory B cells (Bregs) in bladder cancer (BLCA) was explored in depth. The findings clearly showed a significant correlation between the percentage of Bregs infiltration and advanced tumor stage. Further, the researchers constructed a gene signature associated with Bregs, which was shown to be strongly correlated with the prognosis of BLCA as well as the infiltration level of Bregs. Based on this, three key genes, CD96, OAS1 and CSH1, were targeted, which play an important role in the prognosis of BLCA as well as the level of Bregs infiltration. A more in-depth experimental validation of CSH1 revealed that when CSH1 was co-incubated with BLCA cells, it was able to significantly promote the amplification of Bregs, which in turn affects the progression of BLCA. The study also explored the relationship between this gene signature and $CD8^+$ T cells, and found that there is a strong link between the two, which suggests that this gene signature has the potential to serve as an indicator of the abundance and function of effector T cells, and provides a new perspective for evaluating the tumor immune microenvironment. Particularly importantly, this gene signature became an important predictor of immunotherapy sensitivity in the cohort receiving anti-PD-1/PD-L1 therapy. This means that by detecting this gene signature, it is possible to predict patients' response to immunotherapy in advance, providing a strong basis for precise selection of immunotherapy regimens. In summary, this study identified a new

biomarker, BREGRS, which showed great potential in predicting prognosis and immunotherapy response in BLCA. This result can help guide the personalized treatment of BLCA, and targeting CSH1 in Bregs are expected to be a promising therapeutic strategy for BLCA, opening a new direction for the future treatment of BLCA [179].

In conclusion, therapeutic strategies for Breg cells are still evolving and improving, and more new methods and drugs will emerge in the future to meet the needs of clinical treatment.

Discussion

Numerous investigations on the role of Breg cells in immunological control have been conducted over the past 20 years, and several important advancements have been made. There are now a number of surface markers that can be used to recognize the immunosuppressive B cell population, but no particular markers that can be used to fully identify and categorize Breg cells have been discovered. Breg cells are important in determining the prognosis of many tumors and have demonstrated significant promise in the treatment of immune system abnormalities, allergy diseases, and other illnesses. It is important to note that Breg cells may suppress immunological responses related to infection or cancer if they become overactivated, which could worsen the illness.

Although Breg cells targeted therapy has not yet been put to the test in clinical trials, the latest research shows that there is a certain amount of evidence that it is helpful to increase the effectiveness on tumor immunotherapy by reasonably regulating the function of B cells. Therefore, how to balance the B cell responses of promoting and inhibiting tumors, how to deeply study the relevant factors that stimulate and regulate B cells' differentiation into Bregs, alone with how to understand the impact of the human microenvironment on B cell responses are issues that must be further explored.

Therefore, we should continue to deeply study the potential mechanism of Breg cells induction, differentiation and expansion, in order to establish a new treatment scheme based on Bregs, so as to better treat cancer and other immune-related diseases and make important contributions to human health.

Author contributions Ruyu Ye, Li Li and Sijia Li wrote the main manuscript text, and Yuxiao Li and Kaixin Shi prepared Figs. 1–2. All authors reviewed the manuscript.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Katz SI, Parker D, Turk JL (1974) B-cell suppression of delayed hypersensitivity reactions. Nature 251(5475):550–551
2. Aybar LT et al (2015) Reduced CD5$^{(+)}$ CD24$^{(hi)}$ CD38$^{(hi)}$ and interleukin-10$^{(+)}$ regulatory B cells in active anti-neutrophil cytoplasmic autoantibody-associated vasculitis permit increased circulating autoantibodies. Clin Exp Immunol 180(2):178–188
3. Cencioni MT et al (2021) Defective CD19^{+}CD24$^{(hi)}$CD38$^{(hi)}$ transitional B-cell function in patients with relapsing-remitting MS. Mult Scler 27(8):1187–1197
4. Fang Q et al (2020) CD19$^{(+)}$CD24$^{(hi)}$CD38$^{(hi)}$ regulatory B cells: a potential immune predictive marker of severity and therapeutic responsiveness of hepatitis C. Am J Transl Res 12(3):889–900
5. Gu Y et al (2020) Characterization of CD19$^{(+)}$ CD24$^{(hi)}$ CD38$^{(hi)}$ B cells in Chinese adult patients with atopic dermatitis. J Eur Acad Dermatol Venereol 34(12):2863–2870
6. Piper CJM et al (2018) CD19$^{(+)}$CD24$^{(hi)}$CD38$^{(hi)}$ B cells are expanded in juvenile dermatomyositis and exhibit a pro-inflammatory phenotype after activation through toll-like receptor 7 and interferon-α. Front Immunol 9:1372
7. Wang C et al (2022) CD19$^{(+)}$CD24$^{(hi)}$CD38$^{(hi)}$ regulatory B cells deficiency revealed severity and poor prognosis in patients with sepsis. BMC Immunol 23(1):54
8. Zhu HQ et al (2015) Impaired function of CD19$^{(+)}$ CD24$^{(hi)}$ CD38$^{(hi)}$ regulatory B cells in patients with pemphigus. Br J Dermatol 172(1):101–110
9. Xu C et al (2019) CD24$^{(hi)}$CD38$^{(hi)}$ B regulatory cells from patients with end plate inflammation presented reduced functional potency. Int Immunopharmacol 70:295–301
10. Zaimoku Y et al (2020) Deficit of circulating CD19$^{(+)}$ CD24$^{(hi)}$ CD38$^{(hi)}$ regulatory B cells in severe aplastic anaemia. Br J Haematol 190(4):610–617
11. Zhao Q, Jung LK (2018) Frequency of CD19$^{(+)}$CD24$^{(hi)}$CD38$^{(hi)}$ regulatory B cells is decreased in peripheral blood and synovial fluid of patients with juvenile idiopathic arthritis: a preliminary study. Pediatr Rheumatol Online J 16(1):44
12. Zhou H et al (2019) The proportion of CD19$^{(+)}$CD24$^{(hi)}$CD27$^{(+)}$ regulatory B cells predicts the occurrence of acute allograft rejection in liver transplantation. Ann Transl Med 7(18):465
13. Hardy RR, Hayakawa K (2001) B cell development pathways. Annu Rev Immunol 19:595–621

14. Hardy RR et al (2000) B-cell commitment, development and selection. Immunol Rev 175:23–32
15. Alhabbab RY et al (2019) Regulatory B cells: development, phenotypes, functions, and role in transplantation. Immunol Rev 292(1):164–179
16. Baba Y, Matsumoto M, Kurosaki T (2015) Signals controlling the development and activity of regulatory B-lineage cells. Int Immunol 27(10):487–493
17. Bing X, Linlang L, Keyan C (2018) Decreased Breg/Th17 ratio improved the prognosis of patients with ulcerative colitis. Can J Gastroenterol Hepatol 2018:5760849
18. Catalán D et al (2021) Immunosuppressive mechanisms of regulatory B cells. Front Immunol 12:611795
19. Choi JK, Egwuagu CE (2021) Interleukin 35 regulatory B cells. J Mol Biol 433(1):166607
20. Horowitz MC et al (2005) B cells and osteoblast and osteoclast development. Immunol Rev 208:141–153
21. LeBien TW, Tedder TF (2008) B lymphocytes: how they develop and function. Blood 112(5):1570–1580
22. Lykken JM, Candando KM, Tedder TF (2015) Regulatory B10 cell development and function. Int Immunol 27(10):471–477
23. Moore DK, Loxton AG (2019) Regulatory B lymphocytes: development and modulation of the host immune response during disease. Immunotherapy 11(8):691–704
24. Palomares O et al (2017) Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. Immunol Rev 278(1):219–236
25. Wang M et al (2019) Changes among TGF-$\beta1^{(+)}$ Breg cells and helper T cell subsets in a murine model of allergic rhinitis with prolonged OVA challenge. Int Immunopharmacol 69:347–357
26. Xiang W, Xie C, Guan Y (2021) The identification, development and therapeutic potential of IL-10-producing regulatory B cells in multiple sclerosis. J Neuroimmunol 354:577520
27. Yang SY et al (2021) Characterization of organ-specific regulatory B cells using single-cell RNA sequencing. Front Immunol 12:711980
28. Sarvaria A, Madrigal JA, Saudemont A (2017) B cell regulation in cancer and anti-tumor immunity. Cell Mol Immunol 14(8):662–674
29. Yanaba K et al (2008) A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. Immunity 28(5):639–650
30. Blair PA et al (2009) Selective targeting of B cells with agonistic anti-CD40 is an efficacious strategy for the generation of induced regulatory T2-like B cells and for the suppression of lupus in MRL/lpr mice. J Immunol 182(6):3492–3502
31. Matsumoto M et al (2014) Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation. Immunity 41(6):1040–1051
32. Flores-Borja F et al (2013) $CD19^{+}CD24^{hi}CD38^{hi}$ B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation. Sci Transl Med 5(173):173ra23
33. van de Veen W et al (2013) IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol 131(4):1204–1212
34. Lindner S et al (2013) Interleukin 21-induced granzyme B-expressing B cells infiltrate tumors and regulate T cells. Cancer Res 73(8):2468–2479
35. Brosseau C et al (2018) $CD9^{(+)}$ regulatory B cells induce T cell apoptosis via IL-10 and are reduced in severe asthmatic patients. Front Immunol 9:3034
36. Shalapour S et al (2015) Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature 521(7550):94–98
37. Ding Q et al (2011) Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. J Clin Invest 121(9):3645–3656
38. Bankoti R et al (2012) Marginal zone B cells regulate antigen-specific T cell responses during infection. J Immunol 188(8):3961–3971
39. Kaku H et al (2014) A novel mechanism of B cell-mediated immune suppression through CD73 expression and adenosine production. J Immunol 193(12):5904–5913
40. Khan AR et al (2015) PD-L1hi B cells are critical regulators of humoral immunity. Nat Commun 6:5997
41. Zhang M et al (2014) Anti-tuberculosis treatment enhances the production of IL-22 through reducing the frequencies of regulatory B cell. Tuberculosis (Edinb) 94(3):238–244
42. Milburn JV et al (2022) Identification of IL-10 competent B cells in swine. Dev Comp Immunol 135:104488
43. Doyon-Laliberté K et al (2022) Marginal zone B-cell populations and their regulatory potential in the context of HIV and other chronic inflammatory conditions. Int J Mol Sci 23(6):3372
44. Zhang J et al (2016) Positive selection of B10 cells is determined by BCR specificity and signaling strength. Cell Immunol 304–305:27–34
45. Matsushita T, Tedder TF (2011) Identifying regulatory B cells (B10 cells) that produce IL-10 in mice. Methods Mol Biol 677:99–111
46. Floudas A, Amu S, Fallon PG (2016) New insights into IL-10 dependent and IL-10 independent mechanisms of regulatory B cell immune suppression. J Clin Immunol 36(Suppl 1):25–33
47. Ray A, Wang L, Dittel BN (2015) IL-10-independent regulatory B-cell subsets and mechanisms of action. Int Immunol 27(10):531–536
48. Reppert S et al (2015) NFATc1 deficiency in T cells protects mice from experimental autoimmune encephalomyelitis. Eur J Immunol 45(5):1426–1440
49. Chodisetti SB et al (2020) TLR7 negatively regulates B10 cells predominantly in an IFNγ signaling dependent manner. Front Immunol 11:1632
50. Cerqueira C, Manfroi B, Fillatreau S (2019) IL-10-producing regulatory B cells and plasmocytes: molecular mechanisms and disease relevance. Semin Immunol 44:101323
51. Cherukuri A, Mohib K, Rothstein DM (2021) Regulatory B cells: TIM-1, transplant tolerance, and rejection. Immunol Rev 299(1):31–44
52. Choi JK et al (2021) IL-27-producing B-1a cells suppress neuroinflammation and CNS autoimmune diseases. Proc Natl Acad Sci U S A 118(47):e2109548118
53. Hu HT et al (2019) Characterization of intratumoral and circulating IL-10-producing B cells in gastric cancer. Exp Cell Res 384(2):111652
54. Levast B, Li Z, Madrenas J (2015) The role of IL-10 in microbiome-associated immune modulation and disease tolerance. Cytokine 75(2):291–301
55. Lin F et al (2022) Characterization of IL-10-producing regulatory B cells in thymoma. Autoimmunity 55(6):351–359
56. Lin X, Wang X, Lu L (2021) Detection of IL-10 in murine B cells: in vitro and in vivo techniques. Methods Mol Biol 2270:93–111
57. Lu Z et al (2023) Ten-eleven translocation-2 inactivation restrains IL-10-producing regulatory B cells to enable antitumor immunity in hepatocellular carcinoma. Hepatology 77(3):745–759
58. Luo Y et al (2020) Elevated circulating IL-10 producing Breg, but not regulatory B cell levels, restrain antibody-mediated rejection after kidney transplantation. Front Immunol 11:627496
59. Matsushita T (2019) Regulatory and effector B cells: friends or foes? J Dermatol Sci 93(1):2–7

60. Michée-Cospolite M et al (2022) Molecular mechanisms driving IL-10- producing B cells functions: STAT3 and c-MAF as underestimated central key regulators? Front Immunol 13:818814
61. Mion F et al (2021) Purification of murine and human IL-10-producing B cells from different anatomical compartments. Methods Mol Biol 2270:61–76
62. Radomir L et al (2021) The survival and function of IL-10-producing regulatory B cells are negatively controlled by SLAMF5. Nat Commun 12(1):1893
63. Rosser EC, Mauri C (2015) Regulatory B cells: origin, phenotype, and function. Immunity 42(4):607–612
64. Tonon S et al (2021) il-10 gene locus DNA methylation in regulatory B cells. Methods Mol Biol 2270:323–339
65. Wang L, Fu Y, Chu Y (2020) Regulatory B cells. Adv Exp Med Biol 1254:87–103
66. Rempenault C et al (2022) CXCR5/CXCL13 pathway, a key driver for migration of regulatory B10 cells, is defective in patients with rheumatoid arthritis. Rheumatology (Oxford) 61(5):2185–2196
67. Sullivan JA et al (2020) Treg-cell-derived IL-35-coated extracellular vesicles promote infectious tolerance. Cell Rep 30(4):1039-1051.e5
68. Huang A et al (2017) Interleukin-35 on B cell and T cell induction and regulation. J Inflamm (Lond) 14:16
69. Larousserie F et al (2019) Evidence for IL-35 expression in diffuse large B-cell lymphoma and impact on the patient's prognosis. Front Oncol 9:563
70. Michaud D et al (2021) Regulatory B cells in cancer. Immunol Rev 299(1):74–92
71. Zhu Z et al (2018) IL-35 promoted STAT3 phosphorylation and IL-10 production in B cells, but its production was reduced in patients with coronary artery diseases. Hum Immunol 79(12):869–875
72. Shen P et al (2014) IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 507(7492):366–370
73. Horii M, Matsushita T (2021) Regulatory B cells and T cell regulation in cancer. J Mol Biol 433(1):166685
74. Jansen K et al (2021) Regulatory B cells. A to Z Allergy 76(9):2699–2715
75. Wang RX et al (2014) Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nat Med 20(6):633–641
76. Li S et al (2022) STING-induced regulatory B cells compromise NK function in cancer immunity. Nature 610(7931):373–380
77. Pratumchai I et al (2022) B cell-derived IL-27 promotes control of persistent LCMV infection. Proc Natl Acad Sci U S A 119(3):e2116741119
78. Meka RR et al (2015) IL-27-induced modulation of autoimmunity and its therapeutic potential. Autoimmun Rev 14(12):1131–1141
79. Bao J et al (2023) Exploring the dual role of B cells in solid tumors: implications for head and neck squamous cell carcinoma. Front Immunol 14:1233085
80. Poznansky SA et al (2023) Leveraging the tolerogenic potential of TNF-α and regulatory B cells in organ transplantation. Front Immunol 14:1173672
81. Huai G et al (2021) TGF-β-secreting regulatory B cells: unsung players in immune regulation. Clin Transl Immunology 10(4):e1270
82. Liu J et al (2022) Intraperitoneally delivered mesenchymal stem cells alleviate experimental colitis through THBS1-mediated induction of IL-10-competent regulatory B cells. Front Immunol 13:853894
83. Wang X et al (2019) PD-1-expressing B cells suppress $CD4^{(+)}$ and $CD8^{(+)}$ T cells via PD-1/PD-L1-dependent pathway. Mol Immunol 109:20–26
84. Mao Y et al (2019) Circulating exosomes from esophageal squamous cell carcinoma mediate the generation of B10 and PD-1(high) Breg cells. Cancer Sci 110(9):2700–2710
85. Xiao X et al (2016) PD-1hi identifies a novel regulatory B-cell population in human hepatoma that promotes disease progression. Cancer Discov 6(5):546–559
86. Aydin F et al (2002) Correlation of serum IL-2, IL-6 and IL-10 levels with International Prognostic Index in patients with aggressive non-Hodgkin's lymphoma. Am J Clin Oncol 25(6):570–572
87. Cuellar-Núñez ML, Gonzalez de Mejia E, Loarca-Piña G (2021) Moringa oleifera leaves alleviated inflammation through downregulation of IL-2, IL-6, and TNF-α in a colitis-associated colorectal cancer model. Food Res Int 144:110318
88. Holsti MA, Raulet DH (1989) IL-6 and IL-1 synergize to stimulate IL-2 production and proliferation of peripheral T cells. J Immunol 143(8):2514–2519
89. Huang C et al (2022) Low-dose IL-2 attenuated depression-like behaviors and pathological changes through restoring the balances between IL-6 and TGF-β and between Th17 and Treg in a chronic stress-induced mouse model of depression. Int J Mol Sci 23(22):13856
90. Panzer S, Madden M, Matsuki K (1993) Interaction of IL-1 beta, IL-6 and tumour necrosis factor-alpha (TNF-alpha) in human T cells activated by murine antigens. Clin Exp Immunol 93(3):471–478
91. Papillion A et al (2019) Inhibition of IL-2 responsiveness by IL-6 is required for the generation of GC-T(FH) cells. Sci Immunol 4(39):eaaw7636
92. Pereda MP et al (1996) Interleukin-2 (IL-2) and IL-6 regulate c-fos protooncogene expression in human pituitary adenoma explants. Mol Cell Endocrinol 124(1–2):33–42
93. Takahashi R et al (2021) Interleukin-1β-induced pancreatitis promotes pancreatic ductal adenocarcinoma via B lymphocyte-mediated immune suppression. Gut 70(2):330–341
94. Dalloul A (2009) CD5: a safeguard against autoimmunity and a shield for cancer cells. Autoimmun Rev 8(4):349–353
95. Fillatreau S et al (2002) B cells regulate autoimmunity by provision of IL-10. Nat Immunol 3(10):944–950
96. Hilgenberg E et al (2014) Interleukin-10-producing B cells and the regulation of immunity. Curr Top Microbiol Immunol 380:69–92
97. Yoshizaki A et al (2012) Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions. Nature 491(7423):264–268
98. Harris RJ et al (2022) Enriched circulating and tumor-resident TGF-$\beta^{(+)}$ regulatory B cells in patients with melanoma promote $FOXP3^{(+)}$ Tregs. Oncoimmunology 11(1):2104426
99. Sanjabi S, Oh SA, Li MO (2017) Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. Cold Spring Harb Perspect Biol 9(6):a022236
100. Turner JA et al (2020) Regulatory T cell-derived TGF-β1 controls multiple checkpoints governing allergy and autoimmunity. Immunity 53(6):1202-1214.e6
101. Xiao Q et al (2021) Biological drug and drug delivery-mediated immunotherapy. Acta Pharm Sin B 11(4):941–960
102. Bai M et al (2021) Impaired granzyme B-producing regulatory B cells in systemic lupus erythematosus. Mol Immunol 140:217–224
103. Ma X et al (2022) Chloroquine suppresses effector B-cell functions and has differential impact on regulatory B-cell subsets. Front Immunol 13:818704
104. Papp G et al (2016) Increased IL-21 expression induces granzyme B in peripheral $CD5^{(+)}$ B cells as a potential counter-regulatory effect in primary sjögren's syndrome. Mediators Inflamm 2016:4328372

105. Salmi S et al (2022) The association of CD8+ cytotoxic T cells and granzyme B+ lymphocytes with immunosuppressive factors, tumor stage and prognosis in cutaneous melanoma. Biomedicines 10(12):3209
106. Tabanelli V et al (2017) Cytotoxic epstein-barr virus-positive large B cell lymphoma: a regulatory B cell-derived neoplasia? Histopathology 70(4):650–656
107. Xu L et al (2017) Impairment of granzyme B-producing regulatory B cells correlates with exacerbated rheumatoid arthritis. Front Immunol 8:768
108. Zhu J et al (2017) Granzyme B producing B-cells in renal transplant patients. Clin Immunol 184:48–53
109. Figueiró F et al (2016) Phenotypic and functional characteristics of CD39(high) human regulatory B cells (Breg). Oncoimmunology 5(2):e1082703
110. Fortea-Gordo P et al (2020) Circulating $CD19^{+}CD24^{hi}CD38_{hi}$ regulatory B cells as biomarkers of response to methotrexate in early rheumatoid arthritis. Rheumatology (Oxford) 59(10):3081–3091
111. Lemarquis AL et al (2018) Transitional B cells and TLR9 responses are defective in selective IgA deficiency. Front Immunol 9:909
112. Liu Y et al (2020) Correlation of $CD19^{+}CD24^{hi}CD38^{hi}$ B cells in coronary artery disease with severity of atherosclerosis. Chin Med J (Engl) 133(10):1257–1258
113. Liu Y et al (2021) Regulatory B cells dysregulated T cell function in an IL-35-dependent way in patients with chronic hepatitis B. Front Immunol 12:653198
114. Pati S et al (2023) Tumor-associated $CD19^{+}CD39^{-}$ B regulatory cells deregulate class-switch recombination to suppress antibody responses. Cancer Immunol Res 11(3):364–380
115. Wang WW et al (2015) $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs involved in downregulate helper T cells and upregulate regulatory T cells in gastric cancer. Oncotarget 6(32):33486–33499
116. Zhang Y et al (2022) The regulation between $CD4^{(+)}CXCR5^{(+)}$ follicular helper T (Tfh) cells and $CD19^{(+)}CD24^{(hi)}CD38^{(hi)}$ regulatory B (Breg) cells in gastric cancer. J Immunol Res 2022:9003902
117. Chien CH, Chiang BL (2017) Regulatory T cells induced by B cells: a novel subpopulation of regulatory T cells. J Biomed Sci 24(1):86
118. Clouthier DL, Watts TH (2014) Cell-specific and context-dependent effects of GITR in cancer, autoimmunity, and infection. Cytokine Growth Factor Rev 25(2):91–106
119. Costa FR et al (2016) GITR activation positively regulates immune responses against toxoplasma gondii. PLoS ONE 11(3):e0152622
120. Moore TC et al (2017) B cell requirement for robust regulatory T cell responses to friend retrovirus infection. MBio 8(4):10–1128
121. Moore TC, Hasenkrug KJ (2021) B-cell control of regulatory T cells in friend virus infection. J Mol Biol 433(1):166583
122. Oja AE et al (2020) GITR shapes humoral immunity by controlling the balance between follicular T helper cells and regulatory T follicular cells. Immunol Lett 222:73–79
123. Satoguina JS et al (2008) Tr1 and naturally occurring regulatory T cells induce IgG4 in B cells through GITR/GITR-L interaction, IL-10 and TGF-beta. Eur J Immunol 38(11):3101–3113
124. van Beek AA et al (2019) GITR ligation enhances functionality of tumor-infiltrating T cells in hepatocellular carcinoma. Int J Cancer 145(4):1111–1124
125. Zhou P et al (2007) Pivotal roles of $CD4^{+}$ effector T cells in mediating agonistic anti-GITR mAb-induced-immune activation and tumor immunity in CT26 tumors. J Immunol 179(11):7365–7375
126. Chen J et al (2016) Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann Oncol 27(3):409–416
127. Dasgupta S, Dasgupta S, Bandyopadhyay M (2020) Regulatory B cells in infection, inflammation, and autoimmunity. Cell Immunol 352:104076
128. Garcia-Lacarte M et al (2021) The PD-1/PD-L1 checkpoint in normal germinal centers and diffuse large B-cell lymphomas. Cancers (Basel) 13(18):4683
129. Good-Jacobson KL et al (2010) PD-1 regulates germinal center B cell survival and the formation and affinity of long-lived plasma cells. Nat Immunol 11(6):535–542
130. Lino AC et al (2018) LAG-3 inhibitory receptor expression identifies immunosuppressive natural regulatory plasma cells. Immunity 49(1):120-133.e9
131. Mi Y et al (2021) Role of the PD-1/PD-L1 signaling in multiple sclerosis and experimental autoimmune encephalomyelitis: recent insights and future directions. Mol Neurobiol 58(12):6249–6271
132. Sage PT et al (2018) Dendritic cell PD-L1 limits autoimmunity and follicular T cell differentiation and function. J Immunol 200(8):2592–2602
133. Shi Y, Liu Z, Wang H (2022) Expression of PD-L1 on regulatory B cells in patients with acute myeloid leukaemia and its effect on prognosis. J Cell Mol Med 26(12):3506–3512
134. Boggio E et al (2017) Decreased function of Fas and variations of the perforin gene in adult patients with primary immune thrombocytopenia. Br J Haematol 176(2):258–267
135. Huo J, Xu S, Lam KP (2019) FAIM: an antagonist of Fas-killing and beyond. Cells 8(6):541
136. Hutcheson J et al (2008) Combined deficiency of proapoptotic regulators Bim and Fas results in the early onset of systemic autoimmunity. Immunity 28(2):206–217
137. Ju ST, Matsui K, Ozdemirli M (1999) Molecular and cellular mechanisms regulating T and B cell apoptosis through Fas/FasL interaction. Int Rev Immunol 18(5–6):485–513
138. Kaku H, Rothstein TL (2009) Fas apoptosis inhibitory molecule enhances CD40 signaling in B cells and augments the plasma cell compartment. J Immunol 183(3):1667–1674
139. Klinker MW, Lundy SK (2012) Multiple mechanisms of immune suppression by B lymphocytes. Mol Med 18(1):123–137
140. Kojima Y et al (2006) Fas and Fas ligand expression on germinal center type-diffuse large B-cell lymphoma is associated with the clinical outcome. Eur J Haematol 76(6):465–472
141. Loxton AG, van Rensburg IC (2021) FasL regulatory B-cells during Mycobacterium tuberculosis infection and TB disease. J Mol Biol 433(13):166984
142. Lundy SK, Klinker MW (2014) Characterization and activity of Fas ligand producing $CD5^{+}$ B cells. Methods Mol Biol 1190:81–102
143. Lundy SK, Taitano SH, van der Vlugt L (2021) Characterization and activation of Fas ligand-producing mouse B cells and their killer exosomes. Methods Mol Biol 2270:149–178
144. Meynier S, Rieux-Laucat F (2019) FAS and RAS related apoptosis defects: From autoimmunity to leukemia. Immunol Rev 287(1):50–61
145. Ols ML et al (2016) Dendritic cells regulate extrafollicular autoreactive B cells via T cells expressing Fas and Fas ligand. Immunity 45(5):1052–1065
146. Rothstein TL et al (2000) Receptor-specific regulation of B-cell susceptibility to Fas-mediated apoptosis and a novel Fas apoptosis inhibitory molecule. Immunol Rev 176:116–133
147. Yoshino T et al (1994) Inverse expression of bcl-2 protein and Fas antigen in lymphoblasts in peripheral lymph nodes and activated peripheral blood T and B lymphocytes. Blood 83(7):1856–1861
148. Gheybi MK et al (2017) The correlation of $CD19^{+}CD24^{+}CD38^{+}$B cells and other clinicopathological variables with the proportion

of circulating Tregs in breast cancer patients. Breast Cancer 24(6):756–764
149. Ishigami E et al (2019) Coexistence of regulatory B cells and regulatory T cells in tumor-infiltrating lymphocyte aggregates is a prognostic factor in patients with breast cancer. Breast Cancer 26(2):180–189
150. Shariati S et al (2020) The balance of regulatory and stimulatory B cell subsets in breast cancer draining lymph nodes correlates with tumor prognostic factors. Life Sci 257:118117
151. Aira LE, Debes GF (2019) B cells and melanoma pathogenesis. J Invest Dermatol 139(7):1422–1424
152. Wu H et al (2020) PD-L1$^{(+)}$ regulatory B cells act as a T cell suppressor in a PD-L1-dependent manner in melanoma patients with bone metastasis. Mol Immunol 119:83–91
153. Kobayashi T et al (2019) Regulatory B1a cells suppress melanoma tumor immunity via IL-10 production and inhibiting T helper type 1 cytokine production in tumor-infiltrating CD8$^{(+)}$ T cells. J Invest Dermatol 139(7):1535-1544.e1
154. Nahid-Samiei M et al (2020) Enhanced frequency of CD19$^{(+)}$IL-10$^{(+)}$B cells in human gastric mucosa infected by helicobacter pylori. Am J Med Sci 359(6):347–353
155. Zhang H et al (2017) Proinflammatory follicular helper T cells promote immunoglobulin G secretion, suppress regulatory B cell development, and correlate with worse clinical outcomes in gastric cancer. Tumour Biol 39(6):1010428317705747
156. Li W et al (2017) Reduction in peripheral CD19^{+}CD24^{h}CD27^{+} B cell frequency predicts favourable clinical course in XELOX-treated patients with advanced gastric cancer. Cell Physiol Biochem 41(5):2045–2052
157. Murakami Y et al (2019) Increased regulatory B cells are involved in immune evasion in patients with gastric cancer. Sci Rep 9(1):13083
158. Saulep-Easton D et al (2016) The BAFF receptor TACI controls IL-10 production by regulatory B cells and CLL B cells. Leukemia 30(1):163–172
159. Ringelstein-Harlev S et al (2018) Chronic lymphocytic leukemia cells acquire regulatory B-cell properties in response to TLR9 and CD40 activation. Cancer Immunol Immunother 67(5):739–748
160. Mohr A et al (2019) The regulatory capacity of B cells directs the aggressiveness of CLL. Oncoimmunology 8(3):1554968
161. Mohr A et al (2016) Regulatory B lymphocyte functions should be considered in chronic lymphocytic leukemia. Oncoimmunology 5(5):e1132977
162. Kondo K et al (2018) Ibrutinib modulates the immunosuppressive CLL microenvironment through STAT3-mediated suppression of regulatory B-cell function and inhibition of the PD-1/PD-L1 pathway. Leukemia 32(4):960–970
163. Manna A et al (2020) Targeting CD38 is lethal to Breg-like chronic lymphocytic leukemia cells and Tregs, but restores CD8^{+} T-cell responses. Blood Adv 4(10):2143–2157
164. Dong Q et al (2020) Levels and clinical significance of regulatory B cells and T cells in acute myeloid leukemia. Biomed Res Int 2020:7023168
165. Lv Y, Wang H, Liu Z (2019) The role of regulatory B cells in patients with acute myeloid leukemia. Med Sci Monit 25:3026–3031
166. Ji K et al (2024) New insight in immunotherapy and combine therapy in colorectal cancer. Front Cell Dev Biol 12:1453630
167. Kim SS et al (2021) Role of B cells in responses to checkpoint blockade immunotherapy and overall survival of cancer patients. Clin Cancer Res 27(22):6075–6082
168. Piersiala K et al (2023) Regulatory B cells producing IL-10 are increased in human tumor draining lymph nodes. Int J Cancer 153(4):854–866
169. Wulfken LM et al (2021) Case report: sustained remission due to PD-1-inhibition in a metastatic melanoma patient with depleted B cells. Front Immunol 12:733961
170. Huang H et al (2023) CD24hiCD27+ Bregs within metastatic lymph nodes promote multidrug resistance in breast cancer. Clin Cancer Res 29(24):5227–5243
171. Li X et al (2022) The interaction between the soluble programmed death ligand-1 (sPD-L1) and PD-1$^{(+)}$ regulator B cells mediates immunosuppression in triple-negative breast cancer. Front Immunol 13:830606
172. Alemohammad H et al (2022) The importance of immune checkpoints in immune monitoring: a future paradigm shift in the treatment of cancer. Biomed Pharmacother 146:112516
173. Patel AJ et al (2022) Regulatory B cell repertoire defects predispose lung cancer patients to immune-related toxicity following checkpoint blockade. Nat Commun 13(1):3148
174. Kang M et al (2020) Interleukin 35-producing exosomes suppress neuroinflammation and autoimmune uveitis. Front Immunol 11:1051
175. Senturk ZN et al (2023) Pancreatic cancer: emerging field of regulatory B-cell-targeted immunotherapies. Front Immunol 14:1152551
176. Zhu H et al (2024) Intratumoral CD38$^{(+)}$CD19$^{(+)}$B cells associate with poor clinical outcomes and immunosuppression in patients with pancreatic ductal adenocarcinoma. EBioMedicine 103:105098
177. Shao A, Owens DM (2023) The immunoregulatory protein CD200 as a potentially lucrative yet elusive target for cancer therapy. Oncotarget 14:96–103
178. Wang Z et al (2015) Lipid mediator lipoxin A4 inhibits tumor growth by targeting IL-10-producing regulatory B (Breg) cells. Cancer Lett 364(2):118–124
179. Zhou J et al (2024) Investigating the impact of regulatory B cells and regulatory B cell-related genes on bladder cancer progression and immunotherapeutic sensitivity. J Exp Clin Cancer Res 43(1):101