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REVIEW ARTICLE

Regulatory B cells, A to Z

Kirstin Jansen[1] | Lacin Cevhertas[1,2,3] | Siyuan Ma[1,4] | Pattraporn Satitsuksanoa[1] | Mübeccel Akdis[1] | Willem van de Veen[1]

[1]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[2]Department of Medical Immunology, Institute of Health Sciences, Bursa Uludag University, Bursa, Turkey

[3]Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

[4]Department of Otolaryngology Head and Neck Surgery+, Beijing TongRen Hospital, Capital Medical University, Beijing, China

Correspondence
Willem van de Veen, Swiss institute of Allergy and Asthma Research (SIAF), University of Zurich, Herman-Burchard-Strasse 9, CH-7265 Davos-Wolfgang, Switzerland.
Email: willem.vandeveen@siaf.uzh.ch

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Abstract

B cells play a central role in the immune system through the production of antibodies. During the past two decades, it has become increasingly clear that B cells also have the capacity to regulate immune responses through mechanisms that extend beyond antibody production. Several types of human and murine regulatory B cells have been reported that suppress inflammatory responses in autoimmune disease, allergy, infection, transplantation, and cancer. Key suppressive molecules associated with regulatory B-cell function include the cytokines IL-10, IL-35, and TGF-β as well as cell membrane-bound molecules such as programmed death-ligand 1, CD39, CD73, and aryl hydrocarbon receptor. Regulatory B cells can be induced by a range of different stimuli, including microbial products such as TLR4 or TLR9 ligands, inflammatory cytokines such as IL-6, IL-1β, and IFN-α, as well as CD40 ligation. This review provides an overview of our current knowledge on regulatory B cells. We discuss different types of regulatory B cells, the mechanisms through which they exert their regulatory functions, factors that lead to induction of regulatory B cells and their role in the alteration of inflammatory responses in different diseases.

KEYWORDS
allergy, autoimmunity, Breg cells, IL-10, inflammation, suppression, tolerance

1 | INTRODUCTION

A healthy immune system is characterized by a fine balance between pro-inflammatory responses allowing efficient clearance of infections and killing of malignant cells and anti-inflammatory responses to prevent chronic inflammation. B cells contribute to immune responses through antibody production, antigen presentation, and cytokine production. The term regulatory B (Breg) cell was coined to describe B cells that have an anti-inflammatory function. During the past two decades, our knowledge of the phenotype and function of Breg cells has substantially increased. This review aims to provide an overview of the role of Breg cells in different pathophysiological conditions. We discuss different Breg cell types, their mechanisms of suppression, the factors that drive their development, and their role in different diseases.

2 | BREG CELL SUBSETS

Several subsets of B cells with immunoregulatory functions have been characterized in numerous studies in mice and humans; however, these B-cell subsets differ in their phenotypic characteristics and the suppressive molecules that they express, although some overlap exists as well. Here, we discuss the major types of Breg cells that have been identified in mice (Table 1) and humans (Table 2). It should be stressed that to date, there is no clear

consensus on the classification and definition of Breg cells. In mice, innate-immune like B cells or B-1a cells are characterized by the expression of CD5. These cells are considered innate-like since they are not dependent on T cell help for antibody production. Besides their role in the production of low-affinity natural IgM antibodies, they are a major source of IL-10.[1,2] Lundy et al. discovered that a subset of B-1a cells in the spleen expressed Fas ligand (FasL) and named these cells "killer B cells." Killer B cells induced $CD4^+$ T-cell death and suppressed arthritis in mice.[3] In a food allergy mouse model, intestinal mucosa-derived $CD5^+CD19^+CX3CR1^+$tolerogenic B cells (TolBCs) were reported.[4] These cells could induce Treg cells in the intestine, leading to suppression of food allergy-related type II inflammation. In 2011, Matsushita et al. showed that $CD5^+CD1d^{hi}$ B cells, which they termed B10 cells, isolated from the spleen secreted high amounts of IL-10 in response to stimulation with LPS, PMA, and ionomycin.[5] The immunosuppressive functions of B10 cells have been intensively characterized in different disease models such as allergic inflammation, intestinal inflammation, experimental autoimmune encephalomyelitis (EAE), arthritis, and lupus.[6–9] Subsequently, Evans et al. discovered that the murine transitional 2-marginal zone precursor (T2-MZP) B cells, which express high levels of CD21, CD23, and IgM, had potent immunosuppressive capacity.[10] These T2-MZP B cells displayed immune-modulating functions by production of IL-10 in various diseases including allergy, autoimmunity, cancer, and skin allograft rejection.[11–16] Another B-cell subset, called marginal zone (MZ) B cells, expresses high levels of CD1d and is enriched for IL-10-producing cells. Passive transfer of these MZ Bregs from apoptotic cell treated mice protected against collagen-induced arthritis.[17] Additionally, MZ Bregs abolished antigen-specific $CD8^+$ T-cell responses in mice with *Leishmania donovani* infection.[18] The immunosuppressive capacity of TIM-1^+ B cells was discovered using a Tim-1–mutant mouse (Tim-$1^{\Delta mucin}$). These mutant mice had a defect in IL-10 secretion and developed autoimmunity.[19] Tim-1-deficient B cells have impaired IL-10 production and increased production of the inflammatory cytokines IL-6, IL-1β, and IL-12 and thereby promote Th1 and Th17 responses and inhibit the generation of Treg cells which enhances the severity of EAE and stimulates allograft rejection.[20,21] Lastly, different types of plasma cells have regulatory functions. A subset of $CD138^+$ plasma cells could suppress dendritic cell function in pathogenic T-cell generation.[22] In a mouse model of Salmonella infection, plasma cells expressing the surface markers $sIgM^+CD138^{hi}$ $TACI^+CXCR4^+CD1d^{int}$ $Tim1^{int}$ produced both IL-10 and IL-35 to suppress inflammation.[23] A similar study showed that plasma cells were responsible for the suppression of inflammatory cytokine production of NK cells and neutrophils, which was MyD88 dependent.[24] And Lino et al. reported that LAG3+CD138hi plasma cells had immunosuppressive

TABLE 1 Murine B reg cell subsets and suppressor molecules

Types of Breg Cell	Phenotype	Suppressive cytokines	Functions
B1a cells	$CD19^+CD5^+$	IL–10	Suppress TLR-mediated inflammation.[155]
Killer B cells	$CD19^+CD5^+FasL^+$		Induce T-cell death.[3]
TolBC	$CD5^+CD19^+CX3CR1^+$	TGF-β	Induce Treg cells.[4]
B10 cells	$CD19^+CD5^+CD1d^{hi}$	IL–10	Suppress effector CD4+ T cells,[6,7,9,45,67,156] Th17 cells[8] and inflammation[5]
T2-MZP Cells	$CD19^+CD21^{hi}CD23^{hi}$ $CD24^{hi}$ ($IgM^{hi}IgD^+CD1d^+$)	IL–10	Suppress effector CD4+, CD8+ T cells and induce Treg cells.[10-15,157]
MZ cells	$CD19^+CD21^{hi}CD23^-$	IL–10	Regulate antigen-specific CD8+ T cell.[18]
Tim–1 + B Cells	Tim–1^+CD19^+	IL–10	Increase IL–10 production on Treg cells.[19,21,151] Regulate Th1 and Th17 cells during inflammation.[20,158]
Plasma cells	$CD138^+CD44^{hi}$	IL–10	Suppress DCs.[22]
	$CD19^+CD138^+$	IL–10	Suppress neutrophils and NK cells.[24]
	$IgM^+CD138^{hi}TACI^+$ $CXCR4^+CD1d^{int}$ $Tim1^{int}$	IL–10 and IL–35	Suppress CD4+ T cells and macrophages.[23,24]
	$LAG3^+CD138^{hi}$	IL–10	Decrease levels of IFNγ and TNF.[25]
$CD9^+$	$CD19^+CD9^+$	IL–10	suppress Th2 and Th17 inflammation [37]

TABLE 2 Human Breg cells and suppressor molecules

Types of Breg Cell	Phenotype	Suppressor Cytokines	Functions
B10 cells	$CD24^{hi}CD27^{+}$	IL–10	Regulate TNF-α production by monocytes.[26]
Transitional B cells	$CD19^{+}CD24^{hi}CD38^{hi}$	IL–10	Restrain naïve T cell Differentiation into Th1 and Th17 cells.[28] Induce Treg cells.[85]
Br1 cells	$CD19^{+}CD25^{hi}CD71^{hi}$ $CD73^{-}$	IL–10	Suppress inflammatory responses Induce Treg cells and promote IgG4 production.[29]
Plasmablasts	$CD19^{+}CD27^{int}CD38^{+}$	IL–10	Inhibit DCs function to generate pathogenic T cells.[22]
	$IgA^{+}CD138^{+}PD\text{-}L1^{-}$ $IL\text{–}10^{+}$	TGF-β	Suppress cytotoxic T cells.[38]
GrB+B cell	$CD19^{+}CD38^{+}CD1d^{+}$ $IgM^{+}CD147^{+}$	Granzyme B	Degradation of T cell receptor.[35]
CD9+	$CD19^{+}CD9^{+}$	IL–10	Suppress Th2 and Th17 Inflammation.[37]
CD5+CD1d+	$CD19^{+}CD5+CD1d^{hi}$	IL–10	Suppress Th17 response.[119]

functions and produced IL-10.[25] In analogy to the mouse system, human immunosuppressive B-cell populations have been reported as well. B cells capable of producing IL-10 were enriched among circulating $CD24^{hi}CD27^{+}$ B cells, coined human B10 cells. These cells secreted IL-10 and suppressed TNF-α production by monocytes, after LPS and CpG stimulation. The frequency of these cells was markedly increased in patients with autoimmune diseases.[26,27] $CD19^{+}CD24^{hi}CD38^{hi}$ immature B cells also showed immunosuppressive capacity.[28] After CD40 stimulation, these cells inhibited Th1 and Th17 differentiation, a process that was dependent on IL-10, CD80, and CD86 expression. Such $CD19^{+}CD24^{hi}CD38^{hi}$ Breg cells isolated from peripheral blood of patients with systemic lupus erythematosus (SLE) produced less IL-10 and lacked suppressive capacity.[28] $CD19^{+}CD25^{+}CD71^{+}CD73^{-}$ inducible Breg cells, (Br1 cells), were identified in relation to allergen-specific immune tolerance studies.[29] These cells produced high amounts of IL-10 in response to stimulation with the Toll-like receptor (TLR) 9 agonist CpG and potently suppressed antigen-specific T-cell proliferation in an IL-10-dependent manner.[30–34] Another Breg cell subset that can suppress T cell functions is the granzyme B (GrB+) B cell. They are characterized by the surface markers $CD19^{+}CD38^{+}CD1d^{+}IgM^{+}CD147^{+}$ and express granzyme B in conjunction with IL-10, indoleamine-2,3-dioxygenase (IDO), and CD25.[35] Recently, $CD9^{+}$ B cells were found to produce IL-10 and have regulatory functions. They suppressed Th2- and Th17-mediated inflammation, increased the Treg/effector T-cell ratio, and induced apoptosis of effector T cells in both mice and humans.[36,37] Lastly, subsets of plasma cells and plasmablasts have immunosuppressive functions. Human $CD27^{int}CD38^{hi}$ plasmablasts produced IL-10 in response to CpG stimulation and displayed morphological maturation; they increased in size and developed eccentric nuclei and perinuclear haloes.[22] $IgA^{+}CD138^{+}PD\text{-}L1^{-}IL\text{-}10^{+}$ plasma cells may play a role in the suppression of anti-tumor responses.[38]

Taken together, the landscape of different B cells with immunosuppressive capacity is diverse and Breg cells do not comprise a single B cell subset.

3 | DEVELOPMENT AND INDUCTION OF BREG CELLS

Immature and mature B cells as well as plasmablasts can differentiate into Breg cells in response to antigen recognition and/or different stimuli (Figure 1).[39] CpG stimulation can induce the differentiation of B cells into plasmablasts that produce IL-10. When CpG stimulation was combined with IL-2, IL-6, and IFN-α, the IL-10 expression was significantly higher.[22] Similarly, another study showed that IFN-α, IL-1β, and IL-6 can drive the induction of IL-10 production and Breg cell differentiation[40] as well as the development of immature B cells into Breg cells, mature B cells, and plasma cells.[41] Furthermore, the production of IL-10 in human B cells can be induced via TLR signaling with or without BCR stimulation or CD40 ligation.[22] IL-10 production in B cells is controlled in part through the TLR-MyD88-STAT3 pathway.[42] Moreover, TLR signaling regulates IL-10 production through IFN-α, which enhances TLR7- or TLR8-induced IL-10 production in B cells.[42] IFN-α enhances CD38 expression on naïve B cells and induces plasma cell differentiation in a dose-dependent manner.[41] Furthermore, IRF8 and IRF4, which can be induced by TLR and BCR signals,[43] are involved in the secretion of IL-10 by regulating the transcription of the immune-suppressive genetic loci of IL-10 and IL-35 (*EBI3* and *IL12A*) in Breg cells.[44] In addition to BCR signaling, there are other molecules such as LPS, phorbol myristate ester, ionomycin,

facilitating access to the transcriptionally active conformation of the IL-10 gene.[45]

Additionally, plasmacytoid dendritic cells (pDCs) have a role in controlling B cell fate by inducing the generation of plasmablasts that express IL-10, IL-6, and TNF-α, and $CD19^{+}CD24^{hi}CD38^{hi}$ Breg cells.[41] Forced overexpression of IL-10 in primary B cells led to the induction of an immunosuppressive phenotype characterized by elevated expression of CD25, programmed death-ligand 1 (PD-L1), suppressor of cytokine signaling 3 (SOCS3), and glycoprotein A repetitions predominant (GARP).[46]

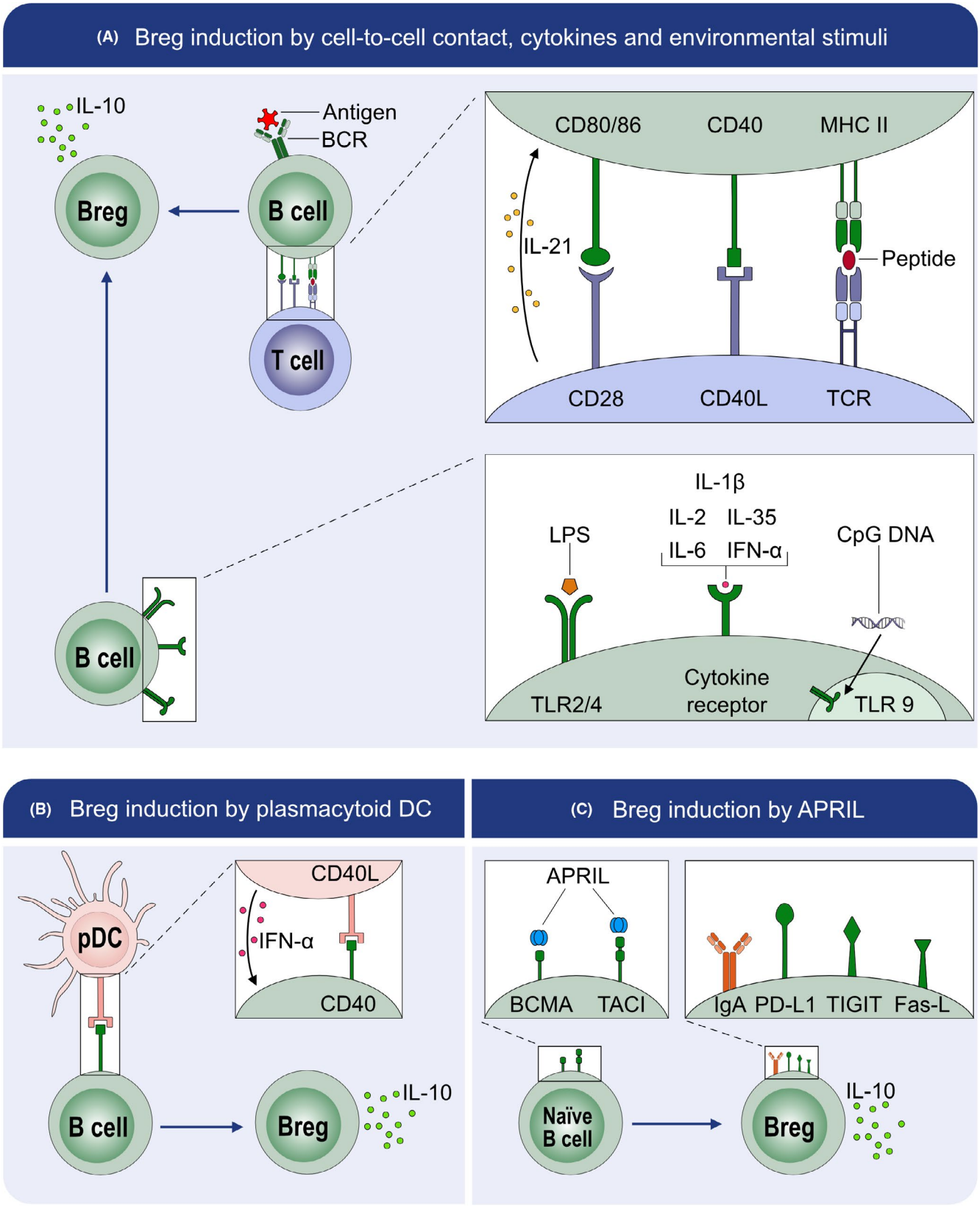

FIGURE 1 Mechanisms of induction and development of Breg cells. Breg cells can be induced through cell-cell contact, cytokines, and various environmental stimuli. (A) Antigen-specific recognition by BCR, CD40 ligation and the activation of PRRs, acute inflammation are major inducers of Breg cells and IL-10 production. While CD40-dependent cognate interactions with T cells[45] as well as CD80 and CD86-mediated co-stimluation[28] have been shown to induce IL-10 production in B cells, pro-inflammatory cytokines, including IL-1β, IL-2, IL-6, and IFN-α, help to induce Bregs in a dose-dependent manner.[40] IL-35 can also induce IL-10 production by B cells.[51,52] *Salmonella typhimurium* can induce IL-10 production by B cells via TLR-2/4 and the Myd88 pathway.[23] (B) Development of IL-10-producing Bregs can be driven by plasmacytoid dendritic cells via IFN-α and CD40 engagement. (C) APRIL promotes the differentiation of naïve B cells to IgA^+ IL-10-producing B cells and induces PD-L1, TIGIT and Fas-ligand expression.[49] APRIL, A proliferation-inducing ligand; BCR, B-cell receptor; IFN-α, Interferon-α; IL, interleukin; LPS, lipopolysaccharide; Myd88, myeloid differentiation primary response gene 88; PMA, phorbol myristate ester; PRRs, pattern-recognition receptors; PD-L1, Programmed death-ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TLR, Toll-like receptor

Another molecular mechanism involved in the induction and controlling of B-cell differentiation and lineage commitment is the activation of the aryl hydrocarbon receptor (AhR), which prevents the differentiation of mature B cells into plasmablasts.[47] In contrast, AhR expressing IL-10-producing $CD19^+CD21^{hi}CD24^{hi}$ B cells can promote and sustain the immunosuppressive state of splenic Bregs.[48] Additionally, a proliferation-inducing ligand (APRIL), contributes to IL-10 production in human B cells, promoting the differentiation of naïve B cells to IL-10-producing IgA^+ B cells.[49]

A recent study suggested a function for ILC3 cells in Breg cell differentiation. $CD40L^+$ILC3 cells could induce IL-10-secreting immature transitional Breg cells via CD40L and BAFF, which implied an innate immunoregulatory mechanism for immune tolerance.[50]

The inhibitory activities of B cells involve IL-10 but also IL-35. Breg cells are capable of releasing IL-35 containing exosomes.[51] IL-35-induced Bregs show their suppressive mechanism through the activation of STAT1/STAT3 pathways by the IL-35 receptor.[52] Moreover, IL-35 induces the conversion of Breg-cells into $IL\text{-}35^+$ Bregs or B cells to Breg cells.[51] Additionally, *Salmonella typhimurium* infection also can induce splenic $CD138^+$ plasma cells to produce IL-10 and IL-35 in mice.[23]

Breg cells are found among B-cell populations of different maturation and differentiation stages, indicating that multiple distinct lineages can be induced to adopt a regulatory function in response to various environmental factors. Due to the heterogeneity of Breg cell subsets, the identification of a Breg cell-specific transcription factor has thus far been unsuccessful. It is therefore likely that Breg cells do not represent a distinct lineage of B cells and that a regulatory phenotype and function can be induced in a range of different B cell subsets.

4 | BREG SUPPRESSOR MOLECULES

Breg cells can produce different types of suppressive cytokines such as IL-10, TGF-β, and IL-35, and express other suppressive molecules such as programmed death-ligand 1 (PD-L1), granzyme B, CD39 and CD73, and aryl hydrocarbon receptor (AhR) (Figure 2).

IL-10 has a suppressive effect on a wide range of inflammatory conditions including allergic disease, autoimmunity, organ transplantation, and tumor tolerance.[53] The positive regulation of IL-10 has an important effect on survival of B cells, class switch recombination, and plasma cell differentiation.[54] TGF-β controls the differentiation of $CD4^+$ T cells to Treg cells and plays a dominant role in tissue remodeling and wound healing processes. A study reported that transplantation tolerance is promoted by both TGF-β-producing Breg cells and Treg cells.[55] The third immunosuppressive cytokine that is produced by Breg cells is IL-35.[56] In a murine model of experimental autoimmune uveitis, Breg cells induced by IL-35 significantly suppressed symptoms by inhibiting pathogenic Th17 and Th1 cells.[52] Additionally, pathogenic T cells in autoimmune diseases are mainly controlled by IL-35 secreting Breg cells.[57]

Besides the production of anti-inflammatory cytokines, Breg cells also express other anti-inflammatory molecules. PD-L1 is a transmembrane protein and associated with B cell–mediated immunosuppression. $PD\text{-}L1^{hi}$ B cells control humoral immunity by suppressing $CD4^+CXCR5^+PD\text{-}1^+$ follicular helper T cells via PD-1 ligation.[58]

Granzyme B is a serine protease released by natural killer cells (NK cells) and cytotoxic T cells, that can induce apoptosis. Granzyme B-expressing B cells were detected in tumors and may suppress anti-tumor T-cell responses.[35]

CD39 and CD73 are crucial enzymatic molecules that convert ATP, which is associated with a pro-inflammatory environment, to AMP, to adenosine (ADO), which is associated with an anti-inflammatory environment. A study showed that *in vitro*–activated $CD39^+CD73^+$B cells produced 5′-AMP and inhibited T-cell proliferation and cytokine production.[59] Additionally, the subpopulation of ADO-producing $CD39^+CD73^+$ B cells showed regulatory properties.[60]

The Aryl hydrocarbon receptor (AhR) is a cytoplasmic receptor and transcription factor that can be induced by xenobiotic ligands and compounds derived from the microbiome or host metabolism. It regulates several immune cells including Treg cells, Th17, dendritic cells, and stem cells.[61] AhR is expressed by $IL\text{-}10^+CD19^+CD21^{hi}CD24^{hi}$ Breg cells.[62]

Thus, the suppressive molecules that are employed by B cells to regulate immune responses range from secreted cytokines to surfaces-expressed molecules with direct suppressive capacity as well as surface-expressed enzymes that catalyze immunosuppression.

5 | BREG CELLS IN AUTOIMMUNE DISORDERS

Support for a protective role for B cells in autoimmune diseases came from reports of de novo onset and exacerbation of several autoimmune diseases after the use of B cell–depleting therapies.[63–65] However, besides pathogenic effects, B cells can also have regulatory capacities in these diseases. In 1996 B cells were identified as having a possible suppressive role in EAE, a mouse model for multiple

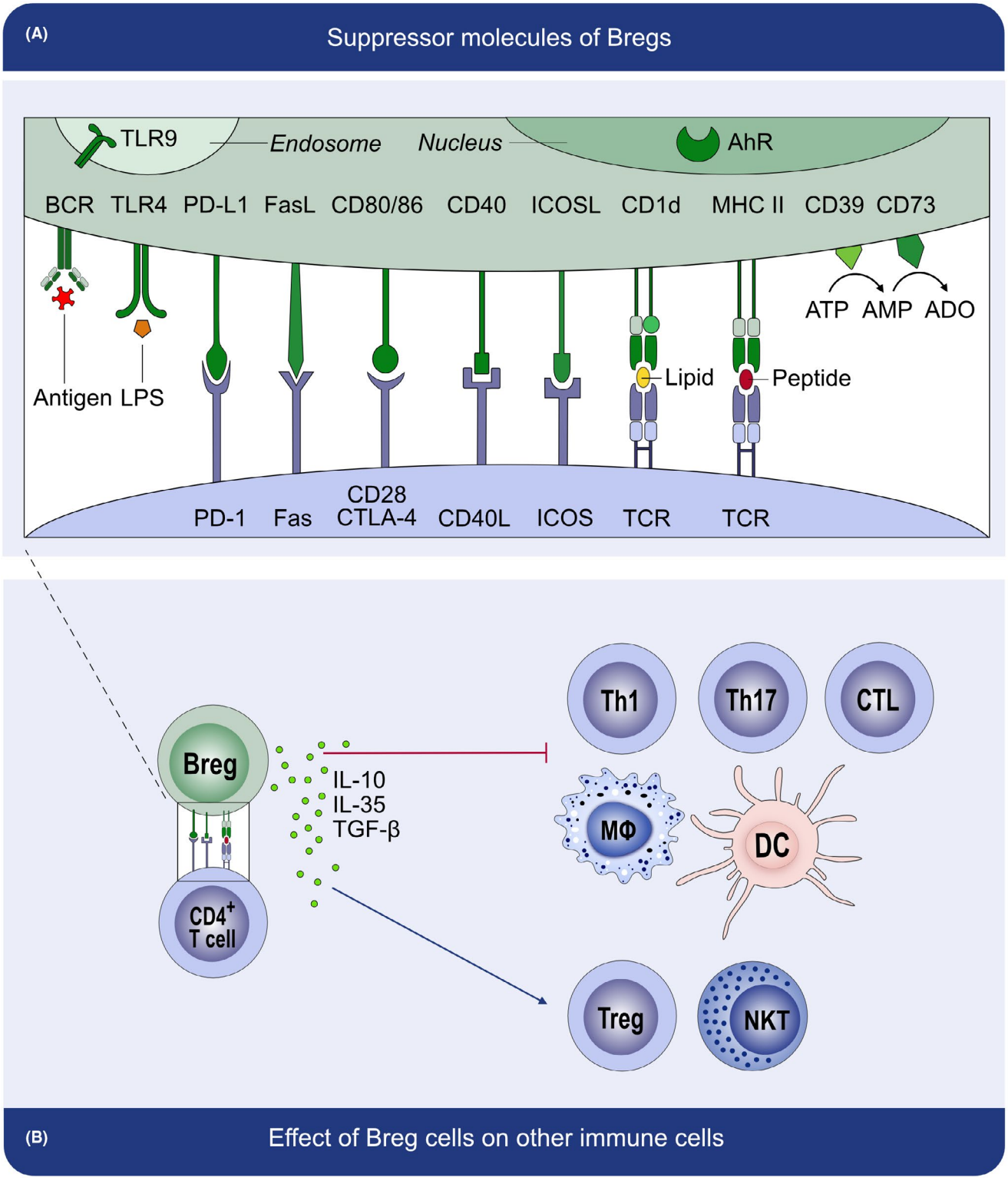

FIGURE 2 Breg cells and their suppressor molecules. (A) TLR ligation by the TLR4 ligand LPS and the TLR9 ligand CpG, as well as antigen-mediated BCR triggering and CD40 ligation can lead to Breg cell activation and the secretion of suppressive cytokines such as IL-10, IL-35, and TGF-β. Molecules expressed by Breg cells include BCR, CD80, CD86, PD-L1, CD40, FasL, ICOS-L, CD1d, MHC II, AHR, TLR9, and TLR4. Moreover, CD39 and CD73 are crucial enzymatic molecules in the ADO pathway and may contribute to the suppressive capacity of B cells. (B) The activation of macrophages and DCs is suppressed by Breg cells via the secretion of IL-10. Breg cells can also suppress Th1, Th17, and CTL responses. In contrast, Breg cells induce Treg cell expansion through the secretion of IL-10, TGF-β, and IL-35. In addition, CD1d which is expressed by certain Breg cells, activates NKT cells with a suppressive function. TLR, Toll-like receptor; LPS, lipopolysaccharide; PD-L1, Programmed death-ligand 1; BCR, B cell receptor; ICOS-L, inducible costimulator ligand; FasL, Fas ligand; MHC II, Major histocompatibility complex II; AHR, aryl hydrocarbon receptor; ADO, adenosine; DC, Dendritic cells; CTL, cytotoxic T lymphocyte; NKT, natural killer T cell

sclerosis (MS).[66] Since then, many studies have been published on the role that Breg cells can play in autoimmune diseases (Table 3).

5.1 | MULTIPLE SCLEROSIS

The role of Breg cells has been extensively studied in mouse models of MS, in particular the EAE model. B cell depletion using anti-CD20, before the induction of EAE, exacerbated the disease and increased the number of autoreactive T cells.[6] Adoptive transfer of B10 cells was able to reduce EAE initiation.[67] Likewise, the depletion of B10 cells in mice resulted in increased T-cell infiltration into the central nervous system and worsened EAE symptom severity.[6] Another study showed that Breg cells are also important for the recovery phase. The absence of IL-10-producing B cells caused the persistence of pro-inflammatory type 1 immune responses in EAE and mice could not recover from the disease.[68] Similarly, CD19-deficient mice showed increased severity and prolonged recovery time of EAE.[69] Furthermore, a recent study showed that IL-10$^+$CD1d$^+$CD5$^+$B cells can polarize M2 macrophages, promote oligodendrocytes, and increase remyelination and thereby reduce EAE in mice.[70]

In MS patients, it is not clearly established whether frequencies of Breg cells are altered. One study reported normal Breg frequencies in MS patients.[71] However, other studies have reported a decreased amount of Breg cells in MS patients,[72,73] or decreased IL-10 production after *ex vivo* stimulation.[74,75]

Inducing Breg cells may have therapeutic effects in MS patients. It has been reported that Glatiramer acetate, an approved drug for MS treatment, can increase Breg cell frequencies and enhance Breg functions.[76,77] Similarly, Alemtuzumab, an antibody that binds CD52 of T and B cells and causes apoptosis or cell lysis, increases the frequency of CD19$^+$CD24^{hi}CD38^{hi} Breg cells in patients with relapsing MS.[72] Thymosin-α1 induced the expansion of regulatory plasma cells, which likely inhibit IL-17 and IFN-γ production.[73] B cells from patients treated with Fingolimod, a drug that prevents lymphocytes that express CCR7, from leaving lymph nodes, increased TGF-β expression, and reduced pro-inflammatory cytokines in T cells *in vitro*.[78] Lastly, DC targeted interferon therapy was able to induce IL-10 and TGF-β expression in B cells and conferred protection against EAE.[79] Thus, many approved or potential therapies for MS seem to induce and restore Breg functions, but it is not yet known if inducing Breg cells alone is enough to prevent relapses of MS.

The main reported mechanism of Bregs reducing EAE and MS is via IL-10, TGF-β, and IL-35 production.[68,80] However, recently it was shown that also in the absence of IL-10, B cells can reduce EAE by inducing the proliferation of Tregs, via glucocorticoid-induced TNF ligand.[81]

5.2 | RHEUMATOID ARTHRITIS

Deficiency of Breg cells could play a role in the pathogenesis of RA. Patients with RA have reduced numbers of IL-10-producing B cells.[82] CD19$^+$CD27$^+$memory B cells that produce IL-10 are significantly reduced in RA patients and are defective in suppressing IFN-γ production.[83] It was also shown that B10 cells from patients with RA can polarize naïve T cells into Th1 cells, while this was not the case for B10 cells from healthy controls.[84]

In RA patients, CD19$^+$CD24^{hi}CD38^{hi} Breg cells had reduced capacity to convert naïve Tcells into Treg cells or prevent Th17 differentiation. Additionally, the frequency and number of these Breg cells were reduced in patients with RA.[85] A similar finding was reported for PD-L1 expressing B cells. Untreated RA patients had reduced numbers of PD-L1 B cells, but successful treatment of RA with methotrexate, TNF inhibitors or Tofacitinib (JAK inhibitor) was able to restore PD-L1 expression.[86]

Besides medical treatment, a natural way to induce Breg cells in RA patients has also been described. Butyrate supplementation was able to induce aryl hydrocarbon receptor (AhR), in Breg cells and support Breg function and thereby suppress RA.[62]

5.3 | SYSTEMIC LUPUS ERYTHEMATOSUS

In SLE patients, Breg cell numbers were reduced or had impaired inhibitory effects.[87] CD19$^+$CD24^{hi}CD38^{hi}Breg cells in SLE patients were unable to suppress pro-inflammatory cytokine secretion of T cells, due to dampened IL-10 secretion and impaired CD40 signaling.[28] Also, the percentage of IL-35$^+$and IL-10$^+$ B cells was reduced in SLE patients compared to healthy controls and there was an inverse correlation between SLE disease activity and IL-35$^+$ B cells.[88] And it was shown that CD1d$^+$ B cells from SLE patients are unable to aid expansion of iNKT cells, which can contribute to maintaining tolerance in autoimmunity.[89] CD38 seems to have an inhibitory effect on Breg cells in a murine model of SLE since CD38$^{-/-}$ mice develop a milder disease and increase the frequency of IL-10-producing B cells.[90]

5.4 | SJÖGREN'S SYNDROME

Breg cells have also been reported to be defective in Sjögren's syndrome. CD19$^+$CD24$^+$CD38^{hi}Breg cells from Sjögren's syndrome patients had reduced IL-10 production and were less able to suppress autologous follicular helper T(Tfh) cell expansion.[91]

Taken together, Breg cells appear to play an important role in preventing autoimmune diseases. Therapies aimed at inducing Bregs or restoring Breg functions could ameliorate autoimmune disorders and benefit patients.

6 | BREG CELLS IN ALLERGY

The first studies that hinted at the existence of immunosuppressive B cells were performed in animal hypersensitivity models. In 1974, a reduced suppression of delayed-type hypersensitivity reaction in the skin of B cell–depleted animals was reported.[92] More recent work involving high-dose allergen-induced tolerance induction revealed more about the immunoregulating function of Bregs in allergy (Table 3).

TABLE 3 Breg cells in different disease models

		Human	Mouse	
Disease		**Role of Bregs**	**Model**	**Role of Bregs**
Autoimmune disorders	MS	Decreased amount of Breg cells in MS patients.[72,73]	EAE	Adoptive transfer of B10 cells was able to reduce EAE initiation.[67]
		Breg cells from MS patients show decreased IL–10 production after ex vivo stimulation.[74,75]		Depletion of B10 cells resulted in increased T-cell infiltration and EAE symptom severity.[6]
		Successful treatment of MS leads to an increased amount/functioning of Bregs.[72,73,76,77,78]		Absence of IL–10-producing B cells hampered disease recovery.[68,69]
				Breg cells can polarize M2 macrophages, promote oligodendrocytes, and increase remyelination.[70]
			EAU	Bregs inhibiting pathogenic Th17 and Th1 cells by IL–35[52]
	RA	RA patients have reduced amounts of IL–10-producing B cells.[82,83]		
		RA patients have reduced numbers of PD-L1 B cells.[86]		
		B10 cells from patients with RA can polarize naïve T cells into Th1 cells.[84]		
		Aryl hydrocarbon receptor (AhR) in Breg cells and support Breg function and thereby suppress RA.[62]		
	SLE	Breg cells have impaired inhibitory effects in SLE patients.[28,87]	Murine lupus model	$CD38^{-/-}$ mice develop a milder disease and increase the frequency of IL–10-producing B cells. [90]
		Percentage of IL–35+ and IL–10 + B cells was reduced in SLE patients.[88]		
	Sjörgen's syndrome	Bregs have reduced IL–10 production and have impaired autologous Tfh cell suppression.[90]		
Allergy	Asthma	$CD19^+CD24^{hi}$ $CD27^+$ circulating Breg cells was decreased. [93]	Helminth parasite-infected OVA-induced mice model	$IL–10^+$ Bregs have a protective role for allergic airway inflammation.[110]
		IL–10 producing capacity of these cells in response to LPS[94] but not CpG[95] stimulation was decreased.	HDM induced allergic inflammatory BALB/c mice	$CD9^+$ B cells subset could reverse airway inflammation by inhibiting Th2 and Th17 responses through IL–10 production.[111]
		Frequencies of $CD5^+$ and $CD1d^+CD5^+$ B cells were decreased.[96]		
	Allergic Rhinitis	$CD19^+CD24^{hi}$ $CD27^+$ Breg cells frequencies were increased, while $CD19^+CD24^{hi}$ $CD38^{hi}$, $CD19^+CD25^+$ $CD71^+CD73^-$, and $CD19^+CD5^{hi}CD1d^+$ Bregs were decreased.[97,98]		
	Food allergy	$CD19^+CD5^+$ Bregs were decreased in the milk allergic patients compared to the milk-tolerant group.[99]	Whey or partially hydrolyzed whey sensitized mice	An extensively hydrolyzed allergen could induce immunotolerance, while partially hydrolyzed allergens promoted CD5+ Bregs and suppressed clinical allergic symptoms.[112]
		$CD19^+CD25^+CD71^+CD73^-$ Breg cells had lower IL–10 secretion capacity and increased $CD4^+CD25^+$ T-cell proliferation for ulcerative colitis (UC) patients.[100]		

(Continues)

Table 3 (Continued)

Disease		Human	Mouse	
		Role of Bregs	Model	Role of Bregs
	Allergic dermatitis	Frequency of $CD24^{hi}CD38^{hi}$ Bregs was reduced in AD patients, and the disease severity was inversely correlated with this Breg subset. IL–10 producing capacity was lower in response to IL–6 stimulation.[101]		
	Allergen tolerance	Patients responding to HDM AIT therapy were characterized by increased numbers of $IL–10^+$ and/or $IL–1RA^+$ Breg cells.[104]	Cat allergic mouse	Fel d 1 peptide immunotherapy increased Breg cells and markedly found a bystander effect of immunosuppression toward an unrelated allergen.[113]
		Immunotherapy induced $IL–35^+$ and $IL–10^+$ Treg cells and promoted Breg cell induction.[107]		
		$IL–10^+$ Breg cell frequencies were increased during the season in the active group.[108]		
		$CD73^-CD25^+CD71^+IL–10^+$ BR1 cells were increased in beekeepers and in patients receiving VIT after venom exposure.[109]		
		The proportion of $IL–10^+$ B cells was higher in bee venom allergen-specific than non-specific B cells, and IL–10-producing CD27-naïve B cells showed a selective upregulation of IgG4 production compared with non-IL–10-producing B cells.[29]		
Infections	Viral infections	Chronic hepatitis B increases the percentage of IL–10-producing B cells.[115]	RSV model	Breg cells produced IL–10 and reduce the expression of type-I interferon.[117]
		HIV patients have higher Breg frequencies.[116]		
	Bacterial Infections	*Helicobacter pylori* induces IL–10 + B cells.[118]	EAE	Cholera toxin B treated B cells can induce Tregs.[121]
		Mycobacterium tuberculosis increases $CD19^+CD1d^+CD5^+$ Breg that suppress Th17 cells.[119]	Apolipoprotein E deficient mice	B cells treated with Cholera toxin B develop a regulator phenotype [122]
	Helminth infections	*Schistosoma haematobium* increases numbers of IL10-producing Breg cells[124]	*S mansoni* infection	*S. mansoni* induces IL–10-producing B cells.[125]
		MS patients with helminth parasites showed increased IL–10 production by B cells and reduced disease severity.[123]		*S. mansoni* eggs induce IL–10 production in B cells.[127]
				S. mansoni eggs reduce lung eosinophilia.[128]
Cancer		Breg antibody-mediated cytotoxicity of tumor cells.[132–134]		B cells can promote tumor growth via IgG4.[140–142]
		$IgA^+CD138^+PD\text{-}L1^+IL–10^+$ plasma cells was found to suppress cytotoxic T cell responses.[38,147]	B cell–deficient mice	CD1dhiCD5+ B cells increase tumor growth via IL–35.[143]
		Frequency of $IL–10^+$ B cells was increased, among $CD19^+CD24^{hi}$ $CD27^+$ B cells in gastric cancer.[148]		B cell–deficient mice also showed reduced tumor growth compared to wild-type (WT) mice.[144,145]
			Melanoma model	Increased tumor infiltration of $CD19^+CD5^+$ $CD43^+$ B1a Bregs. Adoptive transfer exacerbated melanoma growth.[149]
Allograft rejection		Patients treated with rituximab showed higher incidence of graft rejection.[152]		Bregs increased the duration of allograft survival. Adoptive transfer of $CD19^+CD21^{hi}$ $CD23^{hi}CD24^{hi}$ B cells led to prolonged skin allograft survival.[16,150]

6.1 | HUMAN BREG CELLS IN ALLERGY

Among the main chronic allergic diseases such as asthma, allergic rhinitis, food allergy, atopic dermatitis, and insect venom allergy, the frequencies of different Breg subsets varies compared with healthy individuals.

For asthmatic patients, decreased frequencies and absolute numbers of $CD19^+CD24^{hi}CD27^+$ circulating Breg cells were reported.[93] Moreover, the IL-10 producing capacity of these cells in response to LPS[94] but not CpG[95] stimulation was decreased. A recent study compared different Breg cell subsets using markers CD5, CD27, CD10, and CD1d. They reported decreased frequencies of $CD5^+$ and $CD1d^+CD5^+$B cells in asthma patients, and the proportions of these two subsets also decreased after oral corticosteroid treatment, while $CD27^+$ transitional B cells and $CD10^+CD24^{hi}CD27^+$ Bregs increased after the treatment. Furthermore, the IL-10 expression by three subsets of $CD24^{hi}CD27^+$ B cells ($CD1d^+$, $CD10^+$, and $CD5^+$), as well as Br1 cells was decreased after oral corticosteroid treatment.[96]

For allergic rhinitis, $CD19^+CD24^{hi}CD27^+$ Breg cells showed increased frequencies, while $CD19^+CD24^{hi}CD38^{hi}$ and $CD19^+CD25^+CD71^+CD73^-$Bregs were decreased.[97,98]

In the context of food allergy, decreased frequencies of $CD19^+CD5^+$ Bregs were observed in the milk allergic patients compared with the milk-tolerant group.[99]$CD19^+CD25^+CD71^+CD73^-$ Breg cells from ulcerative colitis (UC) patients, an inflammatory bowel disease related to food allergy, had lower IL-10 secretion capacity and increased $CD4^+CD25^+$ T-cell proliferation.[100] A reduced frequency of $CD24^{hi}CD38^{hi}$ Bregs was found in AD patients, and the disease severity was inversely correlated with this Breg subset. IL-10 producing capacity was also lower for AD patients in response to IL-6 stimulation.[101]

6.2 | HUMAN MODELS OF ALLERGEN TOLERANCE

Allergen immunotherapy (AIT), the only curative treatment for allergic diseases that is currently used in clinical practice, was used to study the mechanisms of allergen tolerance.[102] IgG antibodies, especially IgG4, play a crucial role in AIT, since IgG4 has anti-inflammatory properties.[32] After AIT, a 10- to a 100-fold increase of IgG1 and IgG4 was observed.[29,103] A recent study on AIT to human dust mite (HDM) found that patients responding to therapy were characterized by increased numbers of $IL\text{-}10^+$ and/or $IL\text{-}1RA^+$ Breg cells.[104] The efficacy of AIT for the treatment of food allergies is also improved by using IFN-γ as an adjuvant, in both IgE- and non–IgE-mediated food allergies,[105] as it increases the percentage of Bregs after in vitro and *in vivo* re-stimulation with the allergen.[106] In a study in patients with allergic rhinitis, immunotherapy induced $IL\text{-}35^+$, and $IL\text{-}10^+$ Treg cells and promoted Breg cell induction.[107] Another study indicated that local nasal and serum IgG4 levels as well as inhibitory activity correlated with the clinical response to AIT. Moreover, $IL\text{-}10^+$ Breg cell frequencies were increased during the season in the active group.[108]

Beekeeper and venom immunotherapy (VIT) models are useful for the characterization of Breg cells. Boonpiyathad et al. showed that $CD73^-CD25^+CD71^+IL\text{-}10^+$ B_R1 cells were increased in beekeepers and in patients receiving VIT after venom exposure.[109] Moreover, we found that the proportion of $IL\text{-}10^+$ B cells was higher in bee venom allergen-specific than non-specific B cells and that IL-10-producing $CD27^-$ B cells showed a selective upregulation of IgG4 production compared with non-IL-10-producing B cells.[29]

Although there are strong indications that Breg cells are involved in the induction and maintenance of allergen tolerance, there are currently no therapeutic strategies under development that selectively enhance Breg function to modify immune responses in allergy.

6.3 | BREGS IN MOUSE MODELS OF ALLERGIC INFLAMMATION

Studies on the role of Bregs in murine models of allergic inflammation mainly use allergen-induced type-2 inflammatory models. Consistent with studies in human, Bregs had an immunoregulating function in these models. A study about allergic airway inflammation on a helminth parasite-infected OVA-induced mouse model supported the protective role of $IL\text{-}10^+$ Bregs.[110] A $CD9^+$ B cell subset could reverse airway inflammation in a mouse model by inhibiting Th2 and Th17 responses through IL-10 production.[111] In food allergies, the functions of hydrolyzed allergen proteins have been studied. An extensively hydrolyzed allergen could induce immunotolerance, while partially hydrolyzed allergen promoted $CD5^+$ Bregs and suppressed clinical allergic symptoms.[112] One recent study found an increased percentage of $IL\text{-}10^+$ B cells after Fel d 1 peptide immunotherapy and markedly found a bystander effect of immunosuppression toward an unrelated allergen.[113]

7 | BREG CELL RESPONSES DURING INFECTIONS

Although Breg cells can provide benefits in chronic inflammatory conditions and autoimmune diseases, potentially they can also impair immune responses during infections and be associated with increased disease severity.[114] There is a delicate balance in having a strong enough immune response to ward of pathogens, but prevent excessive inflammation. Breg cells may influence the response to viral and bacterial infections (Table 3).

In patients with chronic hepatitis B, an increased percentage of IL-10-producing cells was observed. These Breg cells were able to suppress hepatitis B virus-specific $CD8^+$ T cells and the frequency of IL-10-producing B cells correlated with hepatic flares.[115] A similar principle was shown in HIV infection, where HIV-infected individuals showed a higher Breg percentage that reduced $CD8^+$T-cell

effector functions.[116] In respiratory syncytial virus (RSV) infection, Breg cells also might have potential pathogenic effects. After RSV infection, Breg cells produced IL-10 that can reduce the expression of type-I interferon secretion and thereby possibly reduce antiviral responses.[117]

Besides viruses, bacterial infections can also trigger the induction of Breg cells. *Helicobacter pylori* infection is associated with an increased number of IL-10$^+$ B cells. However, the number of IL-10-producing B cells was not associated with *H. pylori* density, and therefore, Breg cells do not appear to impair the anti-bacterial immune response.[118] In patients infected with *Mycobacterium tuberculosis*, CD19$^+$CD1d$^+$CD5$^+$B cells suppressed IL-22 production and were observed in higher frequencies in severe tuberculosis, which might indicate that CD19$^+$CD1d$^+$CD5$^+$B cells impair protective immunity against tuberculosis.[119]

However, the effect that bacteria have on Breg cells can be useful in the context of other diseases. Cholera toxin B, produced by the bacteria *Vibrio cholerae*, is able to induce Breg cells that can promote the expansion of Tregs. It was shown that Cholera toxin B can be used to reduce inflammation and could be used in therapies for asthma and autoimmune diseases.[120–122]

Similarly, helminth infections can also provide beneficial effects in the context of immune-related diseases by inducing Breg cells. MS patients with helminth parasites showed increased IL-10 and IL-35 production by B cells and less clinical progression of the disease after the 4-year follow-up, compared with uninfected patients, suggesting helminth infections can reduce disease severity.[123] It was shown that children infected with *Schistosoma (S) haematobium* have increased numbers of IL-10-producing CD1d^{hi} B cells.[124] And in a mouse model, *S. mansoni* is able to induce IL-10-producing B cells.[125] Especially the soluble egg antigens (SEA) are important for the induction of Breg cells. SEA from *S. japonicum* promoted expression of PD-L1 and TGF-β in splenic B cells, which suppressed Th1 and Th2 cells.[126] Also, SEA from *S. mansoni* induced Breg cells and IL-10 production. Exposure to IPSE/alpha-1, a major antigen in SEA, was sufficient to induce IL-10 production in B cells.[127] Despite the strong Th2 responses that are induced upon *S. mansoni* infections, *S. mansoni* eggs can reduce lung eosinophilia and thereby protect against allergic airway inflammation.[128]

Another helminth, *Wuchereria Bancrofti*, also induced Breg cells. Individuals with an active infection had increased numbers of CD19+CD24^{hi}CD38^{hi}, CD19$^+$CD24^{hi}CD5+CD1d^{hi}, and CD19$^+$CD5$^+$CD1d^{hi}IL-10$^+$B cells. This induction of regulatory cell populations might contribute to the survival and fertility of the parasite.[129]

Other parasitic infections have also been associated with Breg cell development. During Leishmania infection, B cells adopt a regulatory phenotype and produce higher amounts of IL-10.[114] IL-10 downregulates IL-12 production in DCs and contributes to hampered immune responses and Th2 cell development.[130] In infections with *Plasmodium chabaudi*, Breg cells were responsible for increased susceptibility to infection and increased parasitemia by producing high amounts of IL-10.[131] To conclude, Breg cells are often induced after infections. And although Breg cells can prevent excessive inflammation in certain situations, it can impair protective responses to infections and thereby worsen the disease in others.

8 | BREG CELLS IN CANCER

B cells can contribute to tumor-promoting and tumor-suppressing immune responses (Table 3). Tumor-suppressing effects of B cells were mostly reported in murine models of melanoma. Different mechanisms appear to be at play with respect to B cell–mediated tumor suppression. These include augmented T- and NK-cell–mediated tumoricidal responses, as well as antibody-mediated cytotoxicity of tumor cells.[132–134] More recently, it was reported that B cell–related gene expression signatures in tumor tissue were predictive for a response to checkpoint inhibitor therapy in melanoma patients, indicating that B cells contribute to anti-tumor responses.[135] The role of B cells in anti-tumor immunity is reviewed elsewhere in more detail.[136,137]

B cells can also promote tumor growth. This may occur through mechanisms involving suppressing anti-tumor immune responses, through angiokine production[138,139] or the production of IgG4 antibodies.[140–142] B cells were found in human pancreatic intraepithelial neoplasia and ductal adenocarcinoma lesions as well as in murine Kras-driven pancreatic neoplasms. B cell–deficient mice showed reduced pancreatic neoplasms, while tumor growth was restored upon adoptive transfer of CD1d^{hi}CD5$^+$ B cells. Although CD1d^{hi}CD5$^+$ B cells have been reported to produce elevated levels of IL-10, this pro-tumorigenic effect was mediated by IL-35 and not by IL-10.[143] In different murine cancer models, B cell–deficient mice also showed reduced tumor growth compared with wild type (WT) mice.[144,145] This was associated with enhanced T- and NK-cell responses, and tumor growth could be restored upon adoptive transfer of WT as well as IL-10$^{-/-}$ B cells, indicating that suppression of tumor growth was not dependent on IL-10.[146]

A subset of IgA$^+$CD138$^+$PD-L1$^+$IL-10$^+$ plasma cells was found to suppress cytotoxic T-cell responses and promoted tumor progression in prostate cancer and hepatocellular carcinoma.[38,147] The Immunosuppressive function of plasma cells required TGFβR expression and IgA class switch recombination.[38] Therefore, elimination of tumor-infiltrating IgA$^+$ plasma cells may improve the response to cancer chemotherapy.

In gastric cancer patients, the frequency of IL-10$^+$ B cells was increased, among CD19$^+$CD24^{hi}CD27$^+$ B cells. Moreover, the ratio of tumor-infiltrating IL-10$^+$B cells over total B cells was proposed as a possible independent prognostic indicator of gastric cancer survival. Five-year survival rates differed significantly between the patients with a low or a high Breg over total B cell ratio, where the patients with a ratio <19.35% showed a 65.4% survival rate, patients with a ratio >19.35% had a 13.3% survival rate.[148]

In a mouse model of melanoma, increased tumor growth and decreased IFN-γ- and TNF-α-producing CD8$^+$ T cells were observed when B cells were selectively deficient of PTEN. These mice also showed increased tumor infiltration of CD19$^+$CD5$^+$CD43$^+$ B1a

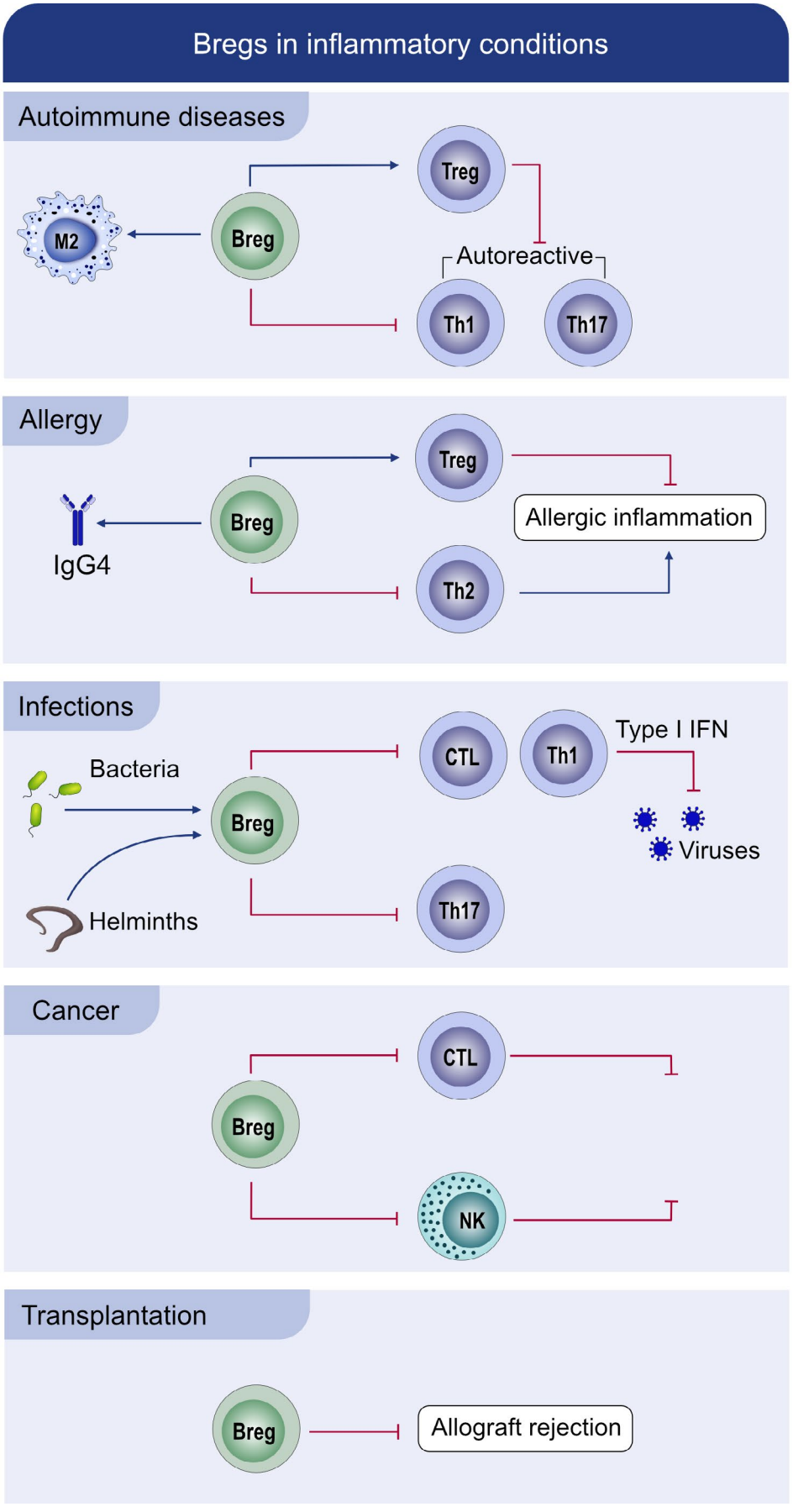

FIGURE 3 Breg cells in inflammatory conditions. Bregs have been implicated in different diseases such as autoimmune diseases (A), allergies (B), infections (C), cancer (D), and transplantation pathology. (A) Breg cells can reduce auto-reactive Th1 and Th17 cell responses and can polarize M2 macrophages and thereby limit damaging responses to the host. (B) Allergic individuals often have reduced numbers of Bregs. Immunotherapy induces the development of IL-10-producing B cells, which have a potent suppressive capacity on T-cell responses, produce anti-inflammatory IgG4, can activate Treg cells, and thereby reduce allergic inflammation. (C) Numerous pathogens can induce Breg cells, most notably helminths (Schistosomas and *Wuchereria Bancfoti*), but also different bacteria (*Helicobacter pylori*, *Mycobacterium tuberculosis* and *Vibrio cholerea*), and viruses (Hepatitis B, HIV, RSV). Breg cells can restore homeostasis after pathogen clearance, but also impair cytotoxic T-cell responses and the production of antiviral factors like type 1 interferons. (D). Breg cells can reduce T cell and NK cell responses to tumor cells and thereby promote progression of cancer. (E) Bregs can increase the duration of allograft survival, and reduced B cells can increase the chance of graft rejection

Bregs. Adoptive transfer of these B1a cells from WT but not from IL-10$^{-/-}$ mice exacerbated melanoma growth. These findings indicate that B1a Bregs may be a target for melanoma immunotherapy.[149] It should be noted that the use of CD5 and the existence of B1a cells in humans is controversial. Therefore, the translation of these findings to the human system requires further research.

Because B cells can both promote and suppress anti-tumor immunity, certain patients may benefit from B-cell activation while B-cell depletion may be beneficial in other patients. In order to make informed decisions about which approach is suitable for which patient, identification of the type of B cells that are present in the tumor microenvironment will be of great importance.

9 | BREG CELLS IN TRANSPLANTATION

Given the importance of immune suppression in allograft survival, Bregs were expected to have beneficial effects on this process (Table 3). Indeed, Bregs increased the duration of allograft survival in several murine transplantation models. Adoptive transfer of CD19^{+}CD21^{hi}CD23^{hi}CD24^{hi} B cells led to prolonged skin allograft survival.[16,150] Another study reported that marginal zone precursor B cell–derived IL-10 was required for acceptance of cardiac allografts through controlling Th17, Tfh, and follicular regulatory T-cell differentiation.[16] Conversely, the depletion of B cells using anti-CD20 in a murine islet transplantation model reduced allograft survival.[151]

Patients undergoing kidney transplantation who were subjected to B-cell depletion therapy using rituximab showed higher incidence of graft rejection than a group that was treated with the anti-CD25 antibody daclizumab. This supports the existence of Bregs that prevent acute graft rejection.[152] Another study compared the characteristics of peripheral B cells from patients who had stable graft function but were under pharmacologic immunosuppression, to patients with chronic rejection and healthy volunteers, their result has a significant increase in both absolute cell number and frequency of total B cells, especially activated, memory and early memory B cells in patients with drug-free long-term graft function. Their findings suggest B cells play a role in the maintenance of long-term graft function.[153] Moreover, patients with chronic rejection seem to have a lower number of CD25^{hi}CD4^{+}T cells and FOXP3transcripts compared with drug-free clinically tolerant patients.[154]

10 | DISCUSSION

During the past two decades, significant progress has been made in understanding the role of Breg cells in the regulation of inflammatory conditions (Figure 3). Thus far, several surface markers have been described to identify immunosuppressive B cell populations. However, no Breg cell-specific lineage marker has been identified in human or animal models. Breg cells can exert immunosuppressive functions through a variety of mechanisms. Most studies on chronic inflammatory conditions found a reduction in circulating Breg cell frequencies. Reduced frequencies and/or suppressive capacity of Breg cells were reported in autoimmune disease as well as in asthma patients and food-allergic patients. The limited data that are currently available from AIT studies indicate that Breg cell frequencies increase during AIT. In contrast to what was found in autoimmune and allergic conditions, bacterial and helminth infections are typically associated with elevated Breg cell frequencies. Similarly, Breg frequencies were increased in cancer patients. Considering these suppressive functions, Breg cells could be exploited for the treatment of immune disorders and allergic diseases and others. However, overactivation of Breg cells could hamper immune responses in infection and cancer, thereby contributing to the worsening of the disease. So far, no Breg cell-targeting therapies are being tested in clinical trials. Therefore, it is important to continue exploring the underlying mechanisms of Breg cell induction, expansion, and differentiation, to be able to develop Breg-based therapies.

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AUTHOR CONTRIBUTIONS

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ORCID

Kirstin Jansen https://orcid.org/0000-0002-9176-8562
Mübeccel Akdis https://orcid.org/0000-0003-0554-9943
Willem van de Veen https://orcid.org/0000-0001-9951-6688

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