Immunology Letters 215 (2019) 48–59

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Potential role of regulatory B cells in immunological diseases

Amir Valizadeh[a], Roozbeh Sanaei[b,c], Nima Rezaei[a,c], Gholamreza Azizi[d], Saba Fekrvand[a], Asghar Aghamohammadi[a], Reza Yazdani[a,*]

[a] Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran
[b] Immunology Research Center (IRC), Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran
[c] Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran
[d] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

ARTICLE INFO

Keywords:
Regulatory B cells
Autoimmunity
Chronic infectious disease
Malignancies
Allergies
Primary immunodeficiencies

ABSTRACT

Regulatory B cells (Bregs) are immune-modulating cells that affect the immune system by producing cytokines or cellular interactions. These cells have immunomodulatory effects on the immune system by cytokine production. The abnormalities in Bregs could be involved in various disorders such as autoimmunity, chronic infectious disease, malignancies, allergies, and primary immunodeficiencies are immune-related scenarios. Ongoing investigation could disclose the biology and the exact phenotype of these cells and also the assigned mechanisms of action of each subset, as a result, potential therapeutic strategies for treating immune-related anomalies. In this review, we collect the findings of human and mouse Bregs and the therapeutic efforts to change the pathogenicity of these cells in diverse disease.

1. Introduction

B cells have an important role in the mediation of the humoral immune response by differentiating into antibody-secreting cells. A new subset of B cells entitled 'regulatory B cells (Bregs)' have been found with immunomodulatory effects via interleukin (IL)-10, transforming growth factor-β (TGF-β), and IL-35 secretion. There is no specific transcription factor or surface marker to distinguish Bregs from other B cell subsets [1]. To date, IL-10 production has been considered as a defining trait of Bregs [2]. IL-10 is mainly produced by T helper 2 (Th2) cells and accompanies with secretion of-type cytokines such as IL-4, IL-5, and IL-13. However, other immune cells such as Th1 [3–5], Th17 [6–9], $CD8^+$ T [10–12], mast cells [13,14], dendritic cells (DCs), macrophages, natural killer (NK) cells, eosinophils, and neutrophils could produce IL-10 [15]. Different B cell subsets including $CD19^+CD24^{hi}CD38^{hi}$ and $CD19^+CD24^{hi}CD27^+$ B cells have been indicated to produce IL-10 and exhibit regulatory functions in various diseases, however, the phenotypes of human Bregs remain controversial yet [16,17]. B regulatory lymphocytes play an important role in the pathogenesis and progression of multiple diseases through secretion of IL-10.

In this review, we focused on the role of Breg cells in different diseases, including autoimmune diseases, allergy, intestinal inflammatory diseases, infectious diseases, primary immunodeficiency disorders, and malignancies. Furthermore, we have a look at the therapeutic potential of manipulating these cells.

2. Breg features

Bregs are derived from subsets of B cells, however, it is unclear yet whether Breg cells are uniquely derived by a specific progenitor or conventional B cell subsets [18] (Fig. 1a). Since plasmablasts can also suppress inflammatory responses, the hypothesis of B cells differentiation into a Breg cell is strengthened [19]. However, according to the pathogenic role of antibody-producing B cells in deriving inflammatory responses in autoimmunity or allergy, the idea of the regulatory feature of these cells is controversial. This could suggest a subset of plasmablasts with features of regulating inflammatory responses produce antibody [1]. In this regard, the Toll-like receptor (TLR) and/or CD40 activation are the most well-characterized stimuli to induce Breg differentiation [2]. It has been revealed that pro-inflammatory cytokines can also induce IL-10-producing Breg cells [1].

Breg cells physiologically are at low levels, while, the rate of cells increases in response to inflammation and develops the ability to regulate the immunity [20,21]. In this way, one pathway for Breg cells to find an inflammatory signal is B cell antigen receptor (BCR) signal transduction [22]. Several studies have reported antigen-specific and non-specific immunoregulatory mechanisms of Breg cells in various

* Corresponding author at: Children's Medical Center Hospital, 62 Qarib St., Keshavarz Blvd., Tehran, 14194, Iran.
E-mail addresses: reza_yazdani86@yahoo.com, r_yazdani@sina.tums.ac.ir (R. Yazdani).

https://doi.org/10.1016/j.imlet.2019.08.004
Received 20 March 2019; Received in revised form 4 August 2019; Accepted 20 August 2019
Available online 20 August 2019

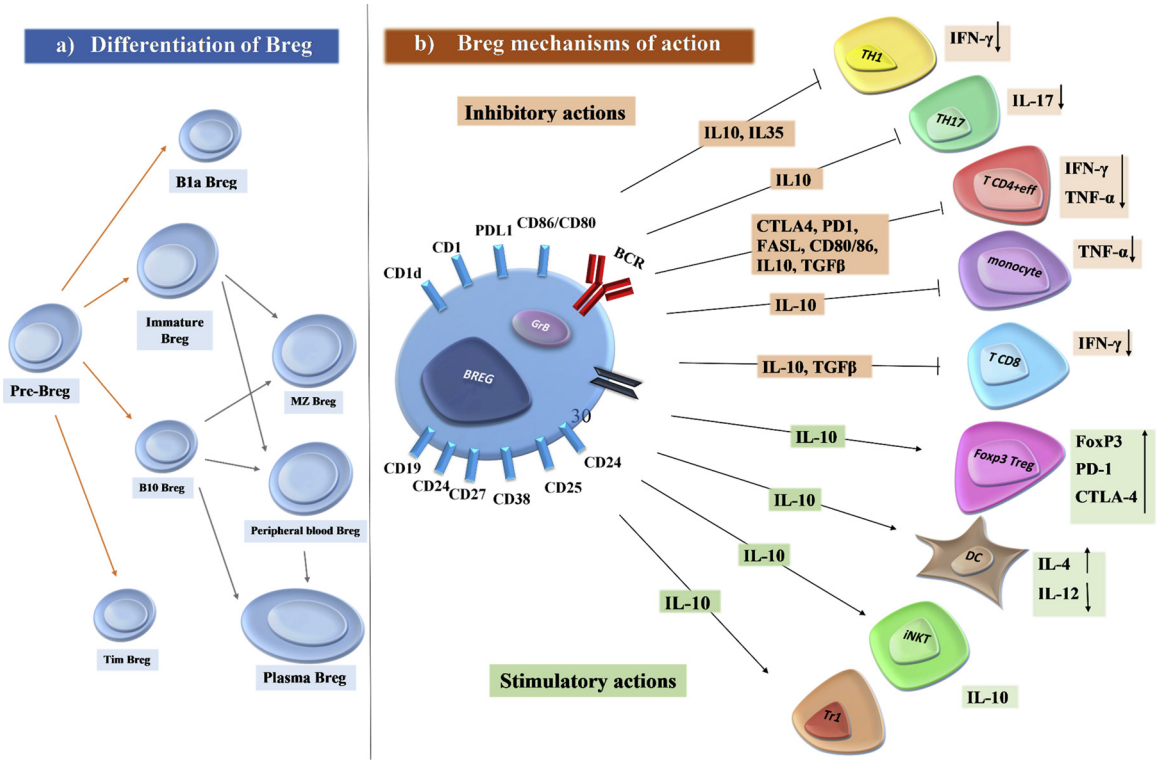

Fig. 1. a) Differentiated subsets of B cells with B regulatory traits can either be emerged from one common precursor Breg cell (Pre-Breg) or be derived after a series of developmental events. Accordingly, orange arrows show differentiation of an individual Pre-Breg into different Breg subsets (like B1a, immature Breg, B10, and Tim Breg), potentially by using distinct transcription factors; and, gray arrows exhibit additional steps taken to form other Breg subsets (Marginal Zone, Peripheral blood, and Plasma blast Bregs). Activation through BCR, TLR, and CD40, in addition to other practical elements of the milieu like IL10, IL23, TGF-beta, can decide Bregs' developing phenotype. Yet, there is no assigned transcription factor or elaborated phenotypes for them. b) In this section, identifying markers of various Breg subsets are collected. Their mechanisms of action on cells of the immune system and the effect on them are also summarized; the regulatory action of Breg has been indicated to be either stimulatory or inhibitory. Evidence regarding the consequences in disease is discussed through the text.

disorders such as autoimmune diseases, allergic disease, graft-*versus*-host diseases, and cancer.

Breg cells decrease chronic inflammation by producing anti-inflammatory cytokines like IL-10 and transforming growth factor-B (TGF-B) [23,24]. The negative regulation of the immune system is the main role of Bregs. Primary inhibitory mechanism of B cells is related to IL-10 production, however Bregs exhibit their immunomodulatory effects by multiple IL-10-independent mechanisms such as production of IL-35, indoleamine-2,3-dioxygenase (IDO), adenosine or IgG4, as well as programmed cell death-1 molecule (PD-1)-mediated or Fas ligand (FasL)-mediated manner. Breg cells act by skewing T cell differentiation, induction of regulatory T cells (Tregs), maintenance of Tregs, and suppression of pro-inflammatory cells. On the other hand, the naive $CD4^+$ T cell convert to Treg cells by TGF-β to develop immune tolerance [25]. TGF-β is also involved in several processes such as tissue reconstruction and immune regulation (Fig. 1b).

Various Breg subsets with multiple mechanisms of suppression have been identified in mice and humans. The identified murine Breg subsets include transitional 2-marginal zone precursor (T2-MZP) B cells, MZ B cells, GIFT-15 B cells, B10 cells, plasmablasts, plasma cells, T cell Ig and mucin domain (Tim)-1^+ B cells, B-1a cells, killer B cells and PD-$L1^{hi}$ B cells. In humans, plasmablasts, immature B cells, B10 cells, B regulatory 1 (Br1) cells, and Granzyme B $(GrB)^+$ B cells comprise the identified Breg subsets. T2-MZP B cells play their suppressive function via IL-10-induced increase in Treg and decrease in Th1/Th17 frequencies in autoimmune diseases and allergic airway inflammation [26–28]. MZ B cells produce IL-10 in autoimmune diseases and suppress the antigen-specific $CD8^+$ T cell responses during infection [29,30]. GIFT-15 B cells share many surface markers with T2-MZP Bregs. GIFT-15 is made by fusion of granulocyte macrophage-colony stimulating factor (GM-CSF) and IL-15. GIFT-15 induced Bregs are found to play their suppressive role in autoimmunity via the production of IL-10 and by upregulation of signal transducer and activator of transcription 6 (STAT-6) [31]. B10 cells are known to exclusively produce IL-10 [32]. They are found to be involved in limiting inflammatory responses in human autoimmune diseases as well as multiple mouse models of autoimmune diseases in an IL-10-mediated manner by skewing $CD4^+$ Th cell responses towards a Th2 and away from Th1 and Th17 phenotypes, regulation of macrophage function by decreasing their activation, phagocytosis and cytokine (including TNF-α) and nitric oxide (NO) production, and limiting T cell activation by negatively regulation of antigen presentation, expression of co-stimulatory molecules (such as CD86) and proinflammatory cytokine production in antigen-presenting cells (APCs) [17,27,33,34]. Murine plasmablasts are found in draining lymph nodes and inhibit function of DCs in autoimmune inflammation, while plasma cells reside in spleen and exhibit their suppressive effect in autoimmunity and infection through IL-10 and IL-35-mediated Treg promotion as well as Th1 and Th17 inhibition. Human regulatory plasmablasts are suggested to drive from immature B cells and act through IL-10 production [19,35]. Tim-1^+ B cells play their immunomodulatory function by IL-10-mediated increasing Th1 and Th17, and reducing Tregs frequencies [36]. B1-a cells act in an IL-10-dependent manner [37] while killer B cells that are the splenic $FasL^+$ B1-a cells mediate $CD4^+$ effector T cell apoptosis during parasitic infections via FasL-mediated manner [38,39]. PD-$L1^{hi}$ B cells act via PD-1/PD-L1 pathway and subsequent decrease in follicular helper T cells (T_{FH}) frequencies [40]. Another Breg IL-10-independent mechanism of action observed both in mice and humans is the generation of adenosine by $CD39^+CD73^+$ B cells that suppresses effector $CD4^+$ and $CD8^+$ T cell functions through binding to several adenosine receptors [41,42].

Table 1
Characteristic and features of different subsets of Bregs.

Breg Subsets	Mouse CD markers	Human CD marker	Functions of Breg	Ref.
T2-MZP cells	$CD19^{+}CD21^{hi}C$ $D23^{hi}CD24^{hi}IgM^{hi}IgD^{hi}CD1d^{hi}$		found in spleen, produce IL-10, induce Treg cells, and suppress effector $CD4^{+}$ and $CD8^{+}$ T cells	[26–28,193]
MZ cells	$CD19^{+}CD21^{hi}CD23^{-}CD24^{hi}IgM^{hi}IgD^{lo}CD1d^{hi}$		found in spleen, produce IL-10, induce Treg cells, and suppress effector $CD4^{+}$ and $CD8^{+}$ T cells	[29,30,194]
B10 cells	$CD1d^{hi}$ $CD5^{+}$	$CD19^{+}CD1d^{hi}CD5^{+}$ $CD24^{hi}CD27^{+}$	found in spleen (mice) and blood (humans), produce IL- 10, and suppress effector $CD4^{+}$T cells, monocytes, and DCs	[17,20,93,195]
B-1 a cells	$CD19^{+}CD5^{+}$		neutralize invading pathogens via producing natural antibodies particularly IgM, suppress inflammatory responses through production of IL-10	[37,196]
Killer B cells	$FasL^{+}CD5^{+}CD178^{+}$		found in spleen, induced by IL-10 and IL-4, FasL-mediated apoptosis of $CD4^{+}$ effector T cell	[38,39]
Transitional B cells (Immature cells)		$CD19^{+}CD24^{hi}$ $CD38^{hi}$	Found in blood and inflammation site, produce IL-10, induce Treg, suppress Th1, Th17 and $CD8^{+}$ T cells, are defective in patients with SLE, ITP, and RA, and support iNKT cell homeostasis	[16,43,145,197,198]
Memory B cells		$CD19^{+}CD27^{+}IgM^{+}$	Found in blood, suppress $CD4^{+}$ T cell proliferation and effector function via IL-10 production	[197]
Plasma cells	$CD138^{hi}IgM^{+}TACI^{+}CXCR4^{+}CD1d^{hi}Tim1^{int}MHC\text{-}11^{lo}B220^{+}$		found in spleen, produce IL-10 and IL-35, and suppress NK cells, neutrophils, and effector $CD4^{+}$ T cells	[35,199]
LAG-3^{+} plasma cells	$LAG\text{-}3^{+}CD138^{hi}$		produce IL-10, reduce memory Th1 frequency	[200]
Tim-1^{+} B cells	$Tim\text{-}1^{+}CD19^{+}$		found in spleen (mice), produce IL-10, and suppress effector $CD4^{+}$T cells	[201,202]
Plasmablasts	$CD138^{+}CD44^{hi}$	$CD19^{+}CD24^{hi}$ $CD27^{int}CD38^{hi}$	found in draining lymph nodes (mice) and blood (humans), produce IL-10, and suppress DCs and effector $CD4^{+}$ T cells	[19]
GrB-expressing B cells		$CD19^{+}CD38^{+}CD1d^{+}IgM^{+}CD147^{+}$	induced by IL-21, infiltrate tumors and regulate T cells	[45]
Br1 cells		$CD19^{+}CD25^{hi}$ $CD71^{hi}$ $CD73^{lo}$	found in blood and produce IL-10 and IgG4	[44]
GIFT-15 B cells	$B220^{+}CD21^{+}CD$ $22^{+}CD23^{+}CD24^{+}CD1d^{+}CD138^{+}IgD^{+}IgM^{+}$		found in spleen, produce IL-10, suppress IFN responses, induced by GM-CSF and IL-15	[31]
PD-$L1^{hi}$ B cells	PD-$L1^{hi}$ $CD19^{+}B220^{+}$		restriction of T_{FH} cell expansion in spleen and lymph nodes, suppress memory B cell development and plasma cell differentiation (attenuation in immunoglobulin's level)	[40]
–	$B220^{+}CD39^{+}CD73^{+}$	$CD39^{+}CD73^{+}$	suppress effector $CD4^{+}$ and $CD8^{+}$ T cell function through catalyzing the dephosphorylation of adenine nucleotides to adenosine	[41,42]
Unclassified (in order to the reported markers in previous studies)		$CD19^{+}$ $CD24^{+}$ $FOXP3^{+}$		[49]

Table 2
Role of Bregs in immunological diseases.

Type of diseases	Alterations of Breg in diseases			Ref.
	Diseases	Breg	investigated subsets	
Autoimmune diseases	Immune thrombocytopenia	Decrease	$CD19^+$ $CD24^{hi}$ $CD38^{hi}$	[46]
	Myasthenia gravis	Decrease	$CD19^+$ $CD1d^{hi}$ $CD5^+$ $CD19^+$ $CD24^{hi}$ $CD38^{hi}$	[57]
	Multiple sclerosis and Experimental Autoimmune Encephalomyelitis	Decrease	$CD19^+$ IL-10^+ $CD19^+$ IL-10^+ TGF-β^+	[65]
	Psoriasis	Decrease	$CD19^+CD24$-$^{hi}CD38^{hi}IL10^+$	[90]
	Rheumatoid arthritis	Decrease	$CD19^+$ $TIM1^+$ $IL10^+$ $CD19^+$ $CD5^+$ $CD1d^+IL10^+CD19^+$ $CD24^+FOXP3^+$ $CD19^+$ $CD27^+$ IL-10^+	[97]
	Systemic lupus erythematosus	Increase	$CD19^+$ $CD24^{hi}$ $CD38^{hi}$ $CD25^{hi}$ $FoxP3^{hi}$	[55]
	Dermatomyositis	Decrease	$CD19^+CD24^{hi}CD38^{hi}$	[203]
	Systemic sclerosis	Decrease	$CD19^+$ $CD24^{hi}$ $CD38^{hi}$ $CD19^+$ $CD27^+$ $CD24^{hi}$	[120]
Allergy	Allergic asthma	Increase	$CD19^+IL10^+CD1d^{hi}IgD^+IgM^{hi}CD5^+CD21^{hi}$	[130]
Inflammatory disease	Inflammatory bowel disease	Decrease	$CD19^{hi}CD1d^{hi}$ $CD24^{hi}CD38^{hi}$ $CD5^+$ Bregs	[138,139]
	Acute respiratory distress syndrome	Increase		[204]
Primary Immunodeficiency	Selective IgM deficiency disease	Increase	$CD19^+CD24^+CD38^+$	[163,205]
	Selective IgA deficiency disease	Decrease	$CD19^+CD24^{hi}CD38^{hi}$	[160]
	Common variable immunodeficiency disease	Increase	$CD19^+CD24^{hi}CD38^{hi}$ IL-10^+	[164]
Infectious diseases	Chronic hepatitis B virus infection	Increase	$CD19^+CD24^{hi}CD38^{hi}$	[145]
	Tuberculosis infection	Increase	$CD19^+CD5^+CD1d^+$	[149]
	Leshmaniosis	Increase	$CD19^+CD24^+CD27^-IL10^+$ $CD19^+CD21^+CD5^+CD1d^+CD23^{hi}$	[206]
	Leprosy	Increase	IL10, FOXP3, PDL-1	[207]
Malignancies	Breast cancer	Increase	$CD19^+CD25^{hi}CD69^{hi}$ $B7\text{-}H1^{hi}CD81^{hi}CD86^{hi}$ $CD62L^{low}IgM^{Int}$ $CD19^+CD24^+CD38^+$PD-L1	[165]
	Esophageal cancer	Increase	$CD5^+CD19^+Foxp3^+$	[174]
	Hepatocellular carcinoma	Increase		[181]

Human immature B cells exhibit their immunomodulatory function in autoimmune diseases through IL-10-mediated induction of Tregs and inhibition of Th1 and Th17 [16,43]. Br1 cells are another human subset of Bregs associated with allergen tolerance by both IL-10-dependent suppression of antigen-specific $CD4^+$ T cell proliferation as well as IL-10-independent mechanism of production of anti-inflammatory allergen-specific IgG4 antibodies [44]. GrB^+ B cells are found in patients with solid tumors and regulate T cell responses by infiltrating tumors and producing IL-10, along with production of IDO and CD25 [45]. Detailed phenotypic characteristics, features and function of different subsets of Bregs in mice and humans are provided in Table 1.

3. Role of Breg in immunologic disorders

We describe the role of Breg cells in different immunologic diseases such as autoimmune diseases, allergy, intestinal inflammatory diseases, primary immunodeficiency, infectious diseases, and malignancies. Table 2 summarize these explanations.

3.1. Autoimmune diseases

3.1.1. Immune thrombocytopenia (ITP)

ITP is an autoimmune disorder that is characterized by immune-mediated destruction of platelets and insufficient platelet production. The pathogenesis of ITP remains enigmatic. ITP in children often represents the cross-reacting phenomena of 'molecular mimicry' with an anti-viral antibody specific to human platelet epitopes. Chronic ITP in children and almost all adults involves functional aberrations of APCs, decreased Tregs, increased Th17 cells, and decreased number of Bregs [46].

A cohort of chronic ITP patients with low platelet count, consisted of patients without treatment [thrombopoietic (TPO) agents] and splenectomy, showed decreased Breg $CD19^+CD24^{hi}CD38^{hi}$ cells and incapable activated B cells to inhibit monocytes [47]. Interestingly, patients with elevated platelet count after treatment with thrombopoietic agents increased Breg $CD19^+CD24^{hi}CD38^{hi}$ cells compared to those without treatment. In contrast to this, the frequency of $CD19^+CD24^{int}CD38^{int}$ (mostly mature B cells) and $CD19^+CD24^+CD38$- (primarily memory B cells) Breg subsets were not statistically different compared to healthy controls and did not affect by platelet counts [47]. Another study has investigated the lymphocyte subtypes of the splenectomized patients following refractory chronic ITP in comparison with the splenectomized patients following a traumatic injury. In this survey, the $CD19^+CD24^+CD38^+$ Bregs did not significantly differ, but $CD19^+CD24^+FOXP3^+$ Bregs markedly increased in the ITP patient's spleens [48]. It has been indicated that this $CD19^+CD24^+FOXP3^+$ Breg population were in human blood [49], and diminished in the blood of rheumatoid arthritis (RA) patients [50]. CD40L is expressed on the platelets [51] and B-cell regulatory activity *in vitro* requires CD40 engagement [16], thus low platelet count may directly contribute to the impaired Breg activity *in vivo* in ITP patients. Therefore, platelets could be involved in the stimulation of Breg activity, although up-regulation of CD40L is normally associated with activation of the platelets [52].

These data indicate that decreased $CD19^+CD24^{hi}CD38^{hi}$ circulating Breg cells of chronic ITP patients could be responsible for the pathogenesis of the disease, revealing Bregs importance in downregulation of the immune responses, however, these findings also suggest the insufficient treatment of ITP disease by increasing Breg activity.

3.1.2. Myasthenia gravis (MG)

MG is a relatively rare autoimmune disorder in which autoantibodies are produced against acetylcholine receptors (AChRs), muscle-specific tyrosine kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4), or Agrin [53,54].

A study has indicated that twosubsetsofIL-10-producing Bcells such as the $CD19^+CD24^+CD38^+$ and $CD1d^{hi}CD5^+$ B cells were decreased in MG that were correlated with the disease severity and responsiveness to rituximab therapy [38]. In this study, Sun et al. proposed that the B10 cells proliferation is related to the responsiveness to rituximab by showing the rapid repopulation of B10 cells in MG patients who had a good response to B cell depletion therapy by rituximab [55]. In another study, Sheng et al. focused on the $CD19^+CD1d^{hi}CD5^+$ and $CD19^+CD24^{hi}CD38^{hi}$ subsets of 18 MG patients, of which 14 patients did not take any immunosuppressants (IS-naive) [56]. As expected, the frequency of Breg subsets was meaningfully decreased and IL-10

producing B cells, which correlated with disease severity. There was no correlation between serum AChR Ab levels and the Breg cells quantity. This study has also revealed suppressed $CD4^+$T cell differentiation into IFN-γ^+- and TNF-α^+-cells via $CD19^+CD24^{hi}$ $CD38^{hi}$ Bregs in healthy subjects without any effect on $CD4^+$T cell proliferation. They suggested that the decrease in the frequency of Breg subsets of MG patients may be involved in impaired suppression of $CD4^+$T cell differentiation into Th1 cells, which also could be due to MG patient's T cells resistance to Breg-mediated suppression. Another study has indicated Bregs from Experimental autoimmune myasthenia gravis (EAMG) mice to alter T cell cytokine profile but not $CD4^+$T cell proliferation *in vitro* [57]. Moreover, Karim et al. demonstrated the significant reduction of $CD19^+CD5^+CD1d^+$ expression in B cells of MG patients, besides the significant reduction of IL-10 and TGF-β1 secretion compared to healthy controls [58]. As they collected all samples in a proper condition, they suggest that medications did not affect the reduced subset. The reduction was harder in severe patients as per Myasthenia Gravis Foundation of America (MGFA) clinical classification, as measured by Quantitative Myasthenia Gravis (QMG) scores.

Considering the above-mentioned studies, it seems that the reduction in Bregs, especially the $CD19^+CD5^+CD1d^+$ subset, is highly correlated with the pathogenesis and severity of MG, indicating the potential role of Bregs in downregulating immune responses. Thus, manipulation of Bregs proliferation might be a good therapeutic approach for these patients.

3.1.3. Multiple sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE)

MS is an autoimmune disorder with unknown etiology in which T and B lymphocytes are involved in the demyelination and axonal damage of the central nervous system (CNS). Myelin-specific antibodies are present in the cerebrospinal fluid, serum, and demyelinating plaques of MS patients [59–61].

According to recent studies, $CD19^+$ B cells of MS patients have low ability to produce IL-10 [62–64]. In 2016, Piancone et al. also showed reduced $CD19^+$IL-10^+ and $CD19^+$IL-10^+TGF-β^+ Bregs in MS patients compared with healthy controls [65]. In addition, the analyses performed on relapsing-remitting MS (RRMS) showed fingolimod-induced disease remission to associate with a significant increase in the $CD19^+$ $BTLA^+$, and $CD19^+$ $BTLA^+$IL-10^+ B lymphocytes. Fingolimod is an FDA approved oral treatment agent for patients with relapsing-remitting MS [66,67]. In another study, fingolimod therapy highly increased transitional B cells proportion as well as additional regulatory subsets, including $IL10^+$, $CD25^+$, and $CD5^+$ B cells [68], other previous researches have supported this observation by increased $IL10^+$ B cells and transitional cells in fingolimod-treated patients in comparison with other MS patients [69,70].

Various studies on EAE (as the most widely investigated animal model of MS) indicated the immunomodulatory role of IL-10 producing B cells [71]. Kala et al. reported that treatment of EAE mice with Glatiramer acetate (an FDA-approved-drug for treating the relapsing-remitting MS) could enhance the IL-10 production compared with the level before the therapy [72]. In another study on EAE, IL-10-producing B cells were found to exploit the CD40-stimulation to produce IL-10 for their regulatory action [73,74]. Although based on EAE models, Rituximab positively controls the disease by depleting B cells, they promote both pathogenic and protective mechanisms in MS [75–79].

These findings could suggest that Breg depletion associated with more severe relapsing-remitting MS or EAE. Also, fingolimod and Glatiramer acetate, as the FDA approved agents for MS treatment, might work through increasing Breg cells, and subsequently suppressing autoimmune processes.

3.1.4. Psoriasis

Psoriasis is a cutaneous disorder characterized by widespread erythematous plaques with adherent scales that affect 2% of the general population [80]. Histologically, psoriasis is characterized by marked thickening of the epidermis with an inflammatory infiltrate predominantly composed of Th1, Th17 and Th22 cells [81]. These infiltrated cells stimulate keratinocytes to produce cytokines, which further amplify the inflammatory response [82]. A study on psoriasis patients showed increased $CD19^+CD24^{hi}CD38^{hi}$ cells compared with the healthy controls, while there was a significant decrease in IL-10 producing regulatory B10 cells [83]. One interesting finding was that the therapeutic intervention with immunosuppressants substantially increased the frequency of B10 cells, but decreased the frequency of $CD24^{hi}CD38^{hi}$ B cells. In addition, their results showed no difference in the frequencies of $CD19^+$ B cells, $CD19^+IgD^+$ CD27- naive B cells, and $CD19^+$IgD-$CD27^+$ memory B cells between patients and controls. This observation may support the hypothesis that there are potential abnormalities in the process of B10 cell development from $CD19^+CD24^{hi}CD38^{hi}$ cells in patients with psoriasis. Despite the decreased B10 cells in their patients, the serum IL-10 levels were comparable with those of healthy controls, and no correlation was found with disease severity as measured by PSORIASIS AREA AND SEVERITY INDEX (PASI) scores. However, evidence found by other studies has shown significantly decreased plasma IL-10 levels in psoriasis patients compared with healthy individuals. This reduction negatively correlated with the skin lesions severity [84,85]. Considering the fact that IL-10 plays a protective role in psoriasis development [86], a larger, randomized, double-blind, placebo-controlled study has evaluated the systemic administration of human rIL-10 which resulted in only a temporary improvement [87]. One possible explanation for the disappointing results of rIL-10 treatment against psoriasis could be due to the serum half-life of rIL-10 which is only 2.6 H in humans [88]. The B cell depletion using rituximab developed psoriasis in patients with no previous history of psoriasis or psoriatic arthritis [89,90], however, it has also been reported that rituximab administration in a psoriatic arthritis patient could increase the disease severity [91]. Therefore, it is possible that the balance between opposing positive and negative regulatory B cell functions shapes the course of disease in psoriasis [92].

Topical application of imiquimod induces inflamed skin lesions and models an experimental animal for human psoriasis. Yanaba et al. found that imiquimod-induced skin psoriasis were more severe in $CD19^{-/-}$ mice than the wild-type [92]. The inflammatory responses were negatively regulated by a unique IL-10 producing $CD1d^{hi}$ $CD5^+$ Breg subset (B10 cells) that was absent in $CD19^{-/-}$ mice and represented only 1–2% of splenic $B220^+$ cells in wild-type mice. In this study, the splenic B10 cells disappeared during imiquimod-induced skin inflammation, whereas IL-10-producing B cells with a B10 phenotype were present in the blood and draining lymph nodes. This suggests that during imiquimod-induced skin inflammation splenic B10 cells enter the circulation and migrate to the draining LNs, thereby inhibiting Th1, Th17, and Th22 immune responses. The current findings demonstrate that B10 cells play a regulatory role in imiquimod-induced skin inflammation and the adoptive transfer of B10 cells before the induction could ameliorate the severity rather than transferring after the induction. In this regard, recent evidence suggests that B10 cells predominantly regulate disease initiation, while Tregs suppress late-phase disease [20,70,93].

The above findings indicate that the reduced IL-10-producing B cells are probably one of the main pathogenic factors in the course of psoriasis disease. This hypothesis becomes more reliable considering the successful improvement of the disease after systemic human rIL-10 administration, however, the low half-life of it could be a drawback. Further, according to the paradoxical results of Rituximab therapy in different psoriasis patients, the balance between opposing positive and negative regulatory B cell functions can shape the course of psoriasis disease.

3.1.5. Rheumatoid arthritis (RA)

RA is a chronic autoimmune disease characterized by persistent

inflammation in the synovium, which eventually leads to joint destruction and deformity. RA prevalence is approximately 0.5–1% in the adult population [94–96]. In a study, Kim et al. reported no significant difference in IL-10$^+$ B cells proportion between RA patients and healthy controls. However, the proportion of induced IL-10$^+$ B of course with a negative correlation with disease activity [97]. In another study, RA patients were found with significantly less number of circulating CD19$^+$TIM1$^+$IL10$^+$ and CD19$^+$CD5$^+$CD1d$^+$ IL10$^+$ B cells compared with healthy controls [98]. Drug therapy for 12 weeks (containing 10 mg methotrexate weekly, 20 mg leflunomide, and 60 mg common three- wingnut root daily without any steroid therapy) modulated different subsets of Breg and Treg cells balance [98]. In this sense, one study indicated a decreased proportion of CD19$^+$CD5$^+$CD1d^{hi} B cells along with reduced IL-10 and IL-21 in RA patients compared with healthy controls [99]. Another study by Banko et al. showed similar results with significantly fewer CD19$^+$CD27$^+$IL-10$^+$ cells in RA patients, while these cells were also functionally defective in suppressing IFN-γ production by CD4$^+$ T cells in the co-culture [100].

Taken together, the immunomodulatory role of Bregs could be understood by all of these studies, which show decrement of IL-10 producing cells in RA patients, while the remaining cells are functionally defective in suppressing IFN-γ production. Targeting these cells might be considered as a potential therapeutic method for RA in the future.

3.1.6. Systemic lupus erythematosus (SLE)

SLE is an autoimmune disease that involves multiple organ systems [101]. The pathogenesis of this disorder is unclear yet; however, the potential disturbed immune balance between regulatory and effector T or B lymphocytes may contribute to the autoimmune injuries in SLE [102–105]. A study by Yang et al. reported an elevated percentage of circulating Breg cells their ability to produce IL-10 in SLE patients [106]. They found a relation between Tfh cell expansion, autoantibody production and the increased percentage of Breg cells. A recent finding in this regard has also shown expanded circulating Tfh cells with CD4$^+$CXCR5$^+$ICOS^{hi}PD-1^{hi} phenotype in SLE patients [107]. In addition, Yang et al. found an increased percentage of Breg cells during SLE flares and a decreased percentage following the disease remission. This suggests that SLE flares may link to Tfh cells expansion and increase Breg cells as a regulatory feedback manner. However, in another study by Gao et al., induced Breg cells (iBregs) from SLE patients were less effective in controlling T helper cell's proliferation [108]. They believed that the malfunctioning SLE iBreg cells might allow immune responses overstimulation and initiation and/or perpetuation of disease. According to their findings, malfunctioned iBreg cells seem specific to SLE and cannot be explained by the intricate *in vivo* inflammation. The SLE B cells possess well-described features distinguishing them from healthy donor B cells with respect to B cell homeostasis [109–112], phenotype, or function [112–117]. In another study, SLE patients had a higher expansion of CD25^{hi} FoxP3^{hi} Bregs compared with healthy individuals [118], correlating with SLE disease activity. They assumed that these cells expansion is an attempt of regulatory immune responses to maintain self-tolerance and to suppress the activity of SLE disease as much as possible.

According to mentioned studies, it seems that Breg cells might not have the main role in the pathogenesis of SLE, (based on SLE flares correlation with Tfh cells expansion), however, increased Breg cell production is an attempt by the immune system to suppress autoimmunity.

However, these Bregs thought to be malfunction due to unknown causes, which need further investigations.

3.1.7. Systemic sclerosis (SSc)

SSc is a chronic disease characterized by microvasculopathy, production of autoantibodies, and excessive collagen deposition in the skin and internal organs. The pathogenesis of SSc is incompletely understood and there is a potential interference of the immune system [119]. Matsushita T et al. found a significantly lower frequency of blood Breg cells in SSc patients than healthy controls, as the frequency of CD24^{hi} CD27$^+$ B cells was significantly lower in SSc patients [120]. Furthermore, Breg cells inversely correlate with SSc activity. Consistently, Mavropoulos et al. showed that total and memory Breg cells have decreased in SSc patients [121]. Moreover, Breg cells are functionally impaired in SSc patients, as they exhibit a markedly decreased expression of IL-10 upon stimulation with TLR-9, which provides a potential new treatment strategy for SSc. Another potential therapeutic approach was suggested by Wang et al. who showed IL-35 protection against autoimmune and inflammatory disease via expanding the autologous Breg cells and IL10$^+$IL35$^+$ Breg cells, leading the pathogenic TH1 and TH17 cells reduction [122].

Based on Breg cell reduction in SSc and their inverse correlation with the disease severity, the above studies once again emphasize Breg cells as an immunomodulatory agent for therapeutic strategies.

3.1.8. Hashimoto's thyroiditis (HT)

HT is a subtype of autoimmune thyroid disease, which affects 1%–4% of the total world population. Regardless of the appropriate response of HT individuals to treatment, they present an elevated risk of autoimmune conditions, such as rheumatic arthritis, type 1 diabetes, and celiac disease [123,124]. Evaluating the IL10 production by Bregs has shown a significant increased IL10 expression in healthy controls after CpG stimulation of B cells compared with HT patients. Yu et al. found an increased circulating CD24$^+$CD38$^+$ B cells in HT individuals; a lower percentage of IL10$^+$ cells among the increased B cells was also observed. They also showed CD24$^+$CD38$^+$ B cells ability to suppress T cell proliferation as well as TNF and IFN-γ production in cell cultures containing CD24$^+$CD38$^+$ B cells [125]. Thus, the increased Breg cells could deteriorate IL10 production and play a role in the pathogenesis of HT.

3.2. Allergy

3.2.1. Allergic asthma

Allergic asthma is a chronic inflammatory disease of the airways associated with airway hyper-responsiveness to inhaled allergens and dysregulated type 2 immunity [126]. Mangan et al. indicated that IL-10 producing B cells downregulate the inflammation in airway hyper-responsiveness [127]. In another report, Bregs had a protective role against allergic airway inflammation [128]. CD19$^+$IL-10$^+$CD1d^{hi}IgD$^+$IgM^{hi}CD5$^+$CD21^{hi} Breg cells decrease allergic airway inflammation [129] by inducing natural Treg (CD4$^+$CD25$^+$FoxP3$^+$) cells recruitment to the lungs in a TGF-β-independent manner [130]. Regarding a recent evidence, adoptive transfer of Breg cells into allergen-sensitized mice suppresses the allergen-induced airway hyperresponsiveness through IL-10 dependent mechanisms [131]. The parasitic infections such as Schistosoma mansoni contribute to both B cell and B10 cell expansion in mice [131]. Interestingly, transferring the spleen CD1d^{hi}CD5$^+$CD19^{hi} B cells from parasite-infected mice into allergen-challenged recipients could inhibit both acute and established airway inflammation [132].

Based on the above studies, IL-10 producing Bregs have an undeniable role in immunity suppression. Furthermore, induced IL-10 production improves airway inflammation, while deteriorated Breg induction is associated with airway hyper-responsiveness and asthma. Knowing this feature could open a path to reduce or even cure allergic diseases, (especially asthma) in the future.

3.3. Intestinal inflammation

3.3.1. Inflammatory bowel disease (IBD)

IBD is a term to define a couple of diseases, including Crohn's disease (CD) and ulcerative colitis (UC). CD is a chronic intestinal immune-mediated disorder characterized by a relapsing-remitting course [133],

and a dysfunction in innate and adaptive host immune systems [134,135]. UC is characterized by continuous ascending inflammation from the rectum to the colon and periods of relapse and remittance [136,137]. In 2014, a study by Oka et al. showed a decreased frequency of IL-10-producing $CD19^{hi}CD1d^{hi}$ and $CD24^{hi}CD38^{hi}$ B cells in CD patients that were in the inactive phase [138]. In this study, the intestinal inflammation severity was substantially increased in the Breg-depleted mice. More interestingly, a lack of IL-10–producing $CD19^{hi}CD1d^{hi}$ B cells exacerbated the intestinal inflammation in an adaptive transferred colitis model mice regardless of the presence or absence of Tregs. In 2016, Wang et al. found similar results in UC patients [139]. In their study, the UC patients indicated significantly reduced frequencies of $CD24^{hi}CD38^{hi}$ and $CD5^{+}$ Bregs and IL-10 levels, both in peripheral blood and intestinal tissue. The stimulated B cells of their UC patients also produced significantly reduced IL-10. Incidentally, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were negatively correlated with the frequency of Bregs and IL-10 concentration. The failure of rituximab therapy in UC patients might be another sign to make us believe the Bregs' importance in the physiopathology of UC [139–141]. Overall, the IL-10 level increases in active IBD patients while there is no significant increase in healthy individuals having inactive IBD. This could suggest the IL-10 as a naturally occurring damper in the acute inflammatory process of IBD [142,143]. The failure of Rituximab therapy in these diseases could also be due to the suppression of other B lymphocytes rather than the Bregs merely.

3.4. Infectious diseases

3.4.1. Chronic hepatitis B virus (HBV) infection

HBV infection affects more than 200 million people worldwide and is a major risk factor for cirrhosis and hepatocellular carcinoma [144]. For the first time, Das et al. reported elevated $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs and IL-10 levels in chronic HBV infected patients [145]. Furthermore, there was a correlation between the frequency of B10 cells with hepatic flares. Interestingly, the *in vitro* blockade of IL-10 rescued poly-functional virus-specific $CD8^{+}$ T cell responses, indicating that $CD19^{+}CD24^{hi}CD38^{hi}$ cells suppress HBV-specific $CD8^{+}$ T cell responses in an IL-10–dependent manner. In another study, Gong et al. confirmed the increased Bregs count in patients with chronic HBV infection [146]. They also observed a strikingly decreased proportion of Th1 cells in patients with a negative correlation with Bregs prevalence. Consistently, Liu et al. reported a higher level of $CD19^{+}CD24^{hi}CD38^{hi}$ in chronic HBV infected patients with a negative correlation with ALT levels and histological inflammation grades, while a positive association with the advanced histological fibrosis stages and enhanced HBV replication [147]. In addition, a therapeutic attempt by Bregs depletion from samples led to a dramatically reduction of Treg counts and cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), IL-10 and TGF-β expression.

It seems that the increased Bregs of chronic HBV patients could be a risk factor for HBV infection to become chronic. Bregs might have an essential role in the chronicity process by an IL-10-dependent manner. Moreover, the higher Breg induction is positively correlated with HBV-infection-induced fibrosis and cirrhosis. Thus, targeting Bregs might be a potential therapeutic goal in the future to prevent the HBV infection to become chronic and cause cirrhosis.

3.4.2. Tuberculosis (TB) infection

TB is an infectious disease caused by the *Mycobacterium tuberculosis* (MTB) [148] that generally affect the lungs, but can also affect other parts of the body. Zhang et al. found that the $CD19^{+}CD5^{+}CD1d^{+}$ Bregs suppress IL-22 production [149]. Th22, an important subset of $CD4^{+}$ T cells, plays an important role in the immune response against TB infection by producing IL-22 [150–157]. According to a previous report a successful anti-TB treatment could restore MTB antigen-specific IL-22 response by reducing the frequencies of $CD19^{+}CD5^{+}CD1d^{+}$ regulatory B cells [149]. Thus, the Bregs suppression might be considered as an option to control the deadly TB infections by enhancing IL-22 secretion and TH22 proliferation. However, further studies need to confirm this point.

3.5. Primary immunodeficiency disorders

Selective IgA deficiency (SIgAD) disease is the most common primary immune deficiency [158], however, most of these patients are clinically asymptomatic [159]. In 2018, Lemarquis et al. studied the phenotype and function of peripheral blood B and T lymphocytes in 15 IgAD patients, besides the TLR9 induced B cell maturation and induction of IgA. The frequencies of transitional B cells ($CD19^{+}CD24^{hi}CD38^{hi}$) were decreased in SIgAD compared with controls, specifically IL10 producing cells [160]. As previously reported, these cells play a role in the pathogenesis of IgA nephropathy [161], and autoimmunity [162]. Moreover, after CpG stimulation of TLR9, they found B cell defects especially within its IL-10 producing B regulatory subset [160]. Another selective immunoglobulin deficiency entitled primary selective IgM deficiency (SIGMD) was evaluated by their Breg cells. SIGMD individuals are susceptible to infections, autoimmunity and allergies who have decreased IgM levels below two standard deviations (SD) of mean with normal serum IgG and IgA. In an effort to elucidate the pathogenesis of SIGMD, Louis et al. evaluated the different subsets of B and T cells in twenty patients [163]. They observed a significant increase in $CD21^{low}$, IgM memory B cells, $CD19^{+}CD24^{+}CD38^{+}$ Breg and $CD8^{+}$Treg. They proposed that these increased levels are a compensatory mechanism of the immune system against autoimmunity development. Although it remains undiscovered, Breg was suggested to suppress the B cells differentiation to antibody-producing plasma cells either directly or by regulating $CD8^{+}$Treg.

In addition, Breg assay has been done in patients with common variable immunodeficiency (CVID); CVID is clinically the most frequent primary immunodeficiency disease. A clinical study on 26 CVID patients has shown the increased frequency of $CD19^{+}CD24^{hi}CD38^{hi}$ $IL\text{-}10^{+}$ peripheral blood B cells in response to T cell stimulation. The $CD19^{+}CD24^{hi}CD38^{hi}IL\text{-}10^{+}$ regulatory B suppress $IFN\text{-}\gamma^{+}TNF\text{-}\alpha^{+}$ producing $CD4^{+}$ T cells, however, Vlkova et al. reported impairment in this process among CVID patients [164]. This finding explains the excessive T cell activation regarded as an immune-regulatory abnormality that is common in CVID patients.

3.6. Malignancies

3.6.1. Breast cancer

Based on studies, Breg cells are increased in the blood of breast cancer patients [165,166]. Olkhanud et al. recognized a type of Bregs [named tumor-evoked Bregs (tBreg)] which was phenotypically similar to activated but poorly proliferative mature B2 cells ($CD19^{+}CD25^{hi}CD69^{hi}$) and expressed constitutively active Stat3 and $B7\text{-}H1^{hi}CD81^{hi}CD86^{hi}$ $CD62L^{low}IgM^{Int}$ [167]. Moreover, they investigated the 4T1 mouse-model of breast cancer and indicated the primary role of tBregs in lung metastases by inducing TGF-β–dependent conversion of $FoxP3^{+}$ Tregs from resting $CD4^{+}$ T cells [167]. Therefore, in the tBregs absence, 4T1 tumors could not metastasize into the lungs efficiently due to poor Treg conversion. They concluded that interruption of the initiating key cancer-induced immunosuppressive event via tBregs manipulation is critical for inhibiting the cancer metastasis progression. In another study, it has been shown that resveratrol (RSV), a plant-derived polyphenol, can efficiently inhibit lung metastasis in mice at low and non-cytotoxic doses for immune cells [168]. The mechanism of this process is the Stat3 inactivation followed by the tBregs generation and function prevention and consequent blocked TGF-β expression [169,170]. As the result, disabled conversion of $Foxp3^{+}$ Tregs releases the antitumor effector immune responses. In 2016, Guan et al. found elevated $CD19^{+}CD24^{+}CD38^{+}$Bregs in the

PBMCs of invasive breast carcinoma patients compared with fibro-adenoma or healthy individuals. Interestingly, a positive correlation was also observed between Bregs and $CD4^+CD25^+CD127$- Tregs [171]. In their study, Bregs of invasive breast carcinoma patients had higher expression of PD-L1 compared with fibro-adenoma or healthy individuals, and there was a tight correlation between $CD19^+CD24^+CD38^+PD\text{-}L1^+$ and $CD19^+CD24^+CD38^+$ Bregs. Moreover, PD-1 expression on $CD4^+CD25^+CD127^+$ effector T cells was high. Notably, PD-L1 on Bregs had a positive correlation with Tregs but negative correlation with $PD\text{-}1^{hi}$ effector T cells.

Based on these studies, invasive breast carcinoma sufferers showed a higher number of Bregs, which through the production of IL-10 could have a principal role in helping malignant cells to escape the immune system. Therefore, dampening IL-10 via Bregs suppression beside the blockage of TGF-β-mediated Treg induction could be a potential therapeutic approach in preventing metastasis of breast cancer.

3.6.2. Esophageal cancer (EC)

EC is globally the eighth leading cause of cancer-related mortality with a poor prognosis among digestive tract malignancies and an annual diagnosis of 482,000 individuals worldwide [172,173]. In the study that was performed in 2014 by Shi et al., the functions of $CD5^+CD19^+$B cell-derived IL-10, TGF-β, and FOXP3 were investigated in EC patients. They found a higher percentage of peripheral $CD5^+CD19^+Foxp3^+$ Bregs in EC patients compared with healthy controls [174]. In addition, a decrement in the percentage of $CD5^+CD19^+Foxp3^+$ Bregs and an elevation in peripheral B10 cells percentage were observed. These findings suggest that Bregs have a negative immunoregulatory role in the development and progression of EC. In 2015, Qian et al. reported a higher level of B10 cells in the peripheral blood of EC patients compared with healthy controls [175]. In addition, they observed a higher B10 level among patients in stage III-IV than those in stage I-II with a higher level of B10 cell in comparison to the controls. Increased B10 level along with the clinical progression of EC suggest B10 cells influence in the pathogenesis of the EC. In another research, Li et al. showed an interesting adapted pathway by cancerous cells to escape the immunity. They found EC-derived micro-vesicles carrying LAMP1 (Lysosomal Associated Membrane Protein 1) and MMP9 (Matrix Metalloproteinase 9) [176]. Previously, it has also been found that MMP9, by using its proteolytic properties to convert LTGFβ (Latent Transforming Growth factor-beta) to TGF-β in B cells, develops $TGF\text{-}\beta^+$ Bregs with the capacity to suppress $CD8^+$ T-cell activities. As $CD8^+$ T cells are one of the major anti-tumor cells [177], this study implies that the induced Bregs in this circle may help the tumor cells to escape from the immune surveillance and facilitate the tumor growth. Thus, micro-vesicles full of MMP9 could present a new therapeutic target in EC treatment.

Based on EC-derived micro-vesicles ability in helping the malignant EC cells to escape from $CD8^+$ T-cells, (besides the significant reduction of Bregs following the surgical removal of the tumor) it is safe to conclude that almost all of these cells are induced mainly by malignant cells. This could show the way to investigate the future therapeutic methods.

3.6.3. Hepatocellular carcinoma (HCC)

HCC is one of the most common malignancies worldwide characterized by altered expression of many genes, proteins, and other diverse molecules of cellular processes [178–180]. Shao et al. found a significantly increased percentage of circulating Bregs associated with the advanced tumor staging, tumor multiplicity, and venous infiltration in HCC patients [181]. In this regard, the human Bregs induce HCC cell proliferation and invasion in both *in vivo* and *in vitro* models via the CD40/CD40L signaling pathway. In the co-culture of Bregs and HCC cells, the CD40/CD40L inhibited interaction could cause reduced levels of TGF-β1 and IL-10, but increased secretion of TNF-α. Regarding another study, an association was found between HCC development with a dominant increase of IL-10 and a decrease of TNF-α [182]. Therefore, new strategies such as depleting Bregs or breaking the tumor-Breg interactions via the anti-CD40 antibody could represent potential therapeutic approaches for HCC.

In an animal study of HCC progression, the frequency of IL-10-producing Bregs was significantly increased in the model group compared with the normal group [183]. They demonstrated that total glucoside of paeony (TGP) (an effective composition extracted from the root of the *Paeonia Lactiflora*) decreased IL-10-producing Bregs proportion that led to an improvement of the N-nitrosodiethylamine (DEN)-induced pathological hepatic lesions of mice. In addition, the increased enzymes of alanine aminotransferase (ALT), glutamic oxalacetic transaminase (AST), and alpha-fetoprotein (ALP), besides the number of tumor nodes were significantly decreased after TGP treatment. The DEN is a well-known potent activator of HCC, and due to the similarity of the DEN-induced HCC in the animal model to human HCC, it represents a good tool to study human HCC [184]. B cell-activating factor (BAFF) induces MZB cell differentiation into the B10 cells with the regulatory functions both *in vitro* and *in vivo*. TGP has bi-directional regulatory action on immune cells [185,186]. In this context, there were a decreased level of BAFF and a marked decrement of IL-10-producing Bregs proportion after TGP treatment, in addition to a significant correlation between Bregs and TGP [187,188].

In summary, Bregs have a unique role in contributing to HCC cells to escape from the immune system via the CD40/CD40L signaling pathway. Moreover, inhibition of CD40/CD40L interaction could be therapeutic through reduction of IL-10 secretion and augmentation of TNF-α secretion as a critical antitumor element. Interestingly, the TGP can lead to decreased Breg production by decreasing the BAFF levels.

3.7. Therapeutic potentials

Based on all the mentioned findings, Breg cells play an undeniable and important role in the pathogenesis of immune-related disorders. Therefore, targeting subsets of B cells might be a new potential cure for a variety of diseases. The specific potential future therapeutic methods based on the involved Breg subsets and their diverse immunomodulatory role in the mentioned immune-related pathologies has been discussed above. Based on the mentioned findings, novel therapies targeting Breg activity and depletion of them could be therapeutic in a variety of malignancies, including breast cancer, esophageal cancer, and hepatocellular carcinoma. It could also be beneficial in the treatment of some chronic infectious diseases, including chronic hepatitis B virus infection and Tuberculosis. Above finding also indicate a probable benefit of Breg depletion in the therapeutic path of systemic lupus erythematosus. Bregs depletion can be achieved using drugs like Rituximab [188–191]. However, depletion of all B cells in this way is disadvantageous due to concomitant elimination of inflammation-suppressive Bregs. Thus, selective depletion of Bregs or effector B cell subsets (Beffs) depending on the disease setting is advantageous. In this regards, further studies for identification of Breg-specific markers are required in order to develop depletion therapies specifically targeting Bregs or effector B cells. Also, Breg cells expansion could be beneficial in a variety of autoimmune disorders, including ITP, myasthenia gravis, multiple sclerosis, psoriasis, dermatomyositis, and systemic sclerosis. Induction of Breg cells could be achieved by exposing them to inflammatory cytokines, such as IL-1β, IL-6, IL-21, IL-35, IFN-β, IFN-α, and B cell activating factor (BAFF) [31,122,162,188,190,191]. Also, in mouse models, anti-inflammatory cytokines such as IL-35 [122] and commensal bacteria [192] are found to contribute to Breg differentiation. Thus, better understanding of the stimuli that induce Breg differentiation and expansion could lead to novel strategies for the *in vivo* expansion of Bregs. Intracellular pathogens clearance beside the enhanced efficacy of the vaccines could be achieved via inhibition or depletion of the Breg. Furthermore, future cell therapies to treat allergic and autoimmune disease by *in vitro* parasite-antigen-activated Bregs

could be successful, if the phenotypes of Breg will have elucidated.

Altogether, further studies are required to comprehensively understand the characteristics, activation mechanism and function of Bregs in order to exploit their therapeutic potential in treatment of various immune-mediated disorders.

4. Conclusion

The pathogenic role of Bregs in different immunological disorders are clarified in this review. In autoimmunity, decreased quantity and function of these cells are involved in the development of them. Regarding the infection, it could be concluded that the increased Breg cells correlate with the viral and bacterial load, which facilitates pathogen survival, especially in the early stage. Furthermore, regarding the evidence about both protective action against solid tumors and improvement of tumor survival, it suggests Bregs' dual action based on different environment and stimulus elements. Taken together, comprehensive picture of the regulatory mechanisms of Bregs need to unravel the exact characteristics of these cells, resulting in successful development in therapeutic approaches.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

References

[1] E.C. Rosser, C. Mauri, Regulatory B cells: origin, phenotype, and function, Immunity 42 (4) (2015) 607–612.
[2] C. Mauri, A. Bosma, Immune regulatory function of B cells, Annu. Rev. Immunol. 30 (2012) 221–241.
[3] C.L. Maynard, C.T. Weaver, Diversity in the contribution of interleukin-10 to T-cell-mediated immune regulation, Immunol. Rev. 226 (1) (2008) 219–233.
[4] A. O'Garra, P. Vieira, T H 1 cells control themselves by producing interleukin-10, Nat. Rev. Immunol. 7 (6) (2007) 425.
[5] G. Trinchieri, Interleukin-10 production by effector T cells: Th1 cells show self control, J. Exp. Med. 204 (2) (2007) 239–243.
[6] D.C. Fitzgerald, G.-X. Zhang, M. El-Behi, Z. Fonseca-Kelly, H. Li, S. Yu, C.J. Saris, B. Gran, B. Ciric, A. Rostami, Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27–stimulated T cells, Nat. Immunol. 8 (12) (2007) 1372.
[7] M.J. McGeachy, K.S. Bak-Jensen, Y. Chen, C.M. Tato, W. Blumenschein, T. McClanahan, D.J. Cua, TGF-β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T H-17 cell–mediated pathology, Nat. Immunol. 8 (12) (2007) 1390.
[8] M. Saraiva, J.R. Christensen, M. Veldhoen, T.L. Murphy, K.M. Murphy, A. O'Garra, Interleukin-10 production by Th1 cells requires interleukin-12-induced STAT4 transcription factor and ERK MAP kinase activation by high antigen dose, Immunity 31 (2) (2009) 209–219.
[9] J.S. Stumhofer, J.S. Silver, A. Laurence, P.M. Porrett, T.H. Harris, L.A. Turka, M. Ernst, C.J. Saris, J.J. O'Shea, C.A. Hunter, Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10, Nat. Immunol. 8 (12) (2007) 1363.
[10] M. Gilliet, Y.-J. Liu, Generation of human CD8 T regulatory cells by CD40 ligand–activated plasmacytoid dendritic cells, J. Exp. Med. 195 (6) (2002) 695–704.
[11] P. Salgame, J.S. Abrams, C. Clayberger, H. Goldstein, J. Convit, R.L. Modlin, B.R. Bloom, Differing lymphokine profiles of functional subsets of human CD4 and CD8 T cell clones, Science 254 (5029) (1991) 279–282.
[12] C. Tanchot, S. Guillaume, J. Delon, C. Bourgeois, A. Franzke, A. Sarukhan, A. Trautmann, B. Rocha, Modifications of CD8+ T cell function during in vivo memory or tolerance induction, Immunity 8 (5) (1998) 581–590.
[13] M.A. Grimbaldeston, S. Nakae, J. Kalesnikoff, M. Tsai, S.J. Galli, Mast cell–derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B, Nat. Immunol. 8 (10) (2007) 1095.
[14] A. Masuda, Y. Yoshikai, K. Aiba, T. Matsuguchi, Th2 cytokine production from mast cells is directly induced by lipopolysaccharide and distinctly regulated by c-Jun N-terminal kinase and p38 pathways, J. Immunol. 169 (7) (2002) 3801–3810.
[15] K.W. Moore, R. de Waal Malefyt, R.L. Coffman, A. O'Garra, Interleukin-10 and the interleukin-10 receptor, Annu. Rev. Immunol. 19 (1) (2001) 683–765.
[16] P.A. Blair, L.Y. Noreña, F. Flores-Borja, D.J. Rawlings, D.A. Isenberg, M.R. Ehrenstein, C. Mauri, CD19+ CD24hiCD38hi B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients, Immunity 32 (1) (2010) 129–140.
[17] Y. Iwata, T. Matsushita, M. Horikawa, D.J. DiLillo, K. Yanaba, G.M. Venturi, P.M. Szabolcs, S.H. Bernstein, C.M. Magro, A.D. Williams, Characterization of a rare IL-10–competent B-cell subset in humans that parallels mouse regulatory B10 cells, Blood 117 (2) (2011) 530–541.
[18] G. Vitale, F. Mion, C. Pucillo, Regulatory B cells: evidence, developmental origin and population diversity, Mol. Immunol. 48 (1–3) (2010) 1–8.
[19] M. Matsumoto, A. Baba, T. Yokota, H. Nishikawa, Y. Ohkawa, H. Kayama, A. Kallies, S.L. Nutt, S. Sakaguchi, K. Takeda, Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation, Immunity 41 (6) (2014) 1040–1051.
[20] K. Yanaba, J.-D. Bouaziz, K.M. Haas, J.C. Poe, M. Fujimoto, T.F. Tedder, A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses, Immunity 28 (5) (2008) 639–650.
[21] K. Yanaba, J.-D. Bouaziz, T. Matsushita, T. Tsubata, T.F. Tedder, The development and function of regulatory B cells expressing IL-10 (B10 cells) requires antigen receptor diversity and TLR signals, J. Immunol. 182 (12) (2009) 7459–7472.
[22] B. Peng, Y. Ming, C. Yang, Regulatory B cells: the cutting edge of immune tolerance in kidney transplantation, Cell Death Dis. 9 (2) (2018) 109.
[23] J. Tian, D. Zekzer, L. Hanssen, Y. Lu, A. Olcott, D.L. Kaufman, Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice, J. Immunol. 167 (2) (2001) 1081–1089.
[24] V.V. Parekh, D.V. Prasad, P.P. Banerjee, B.N. Joshi, A. Kumar, G.C. Mishra, B cells activated by lipopolysaccharide, but not by anti-Ig and anti-CD40 antibody, induce anergy in CD8+ T cells: role of TGF-β1, J. Immunol. 170 (12) (2003) 5897–5911.
[25] M. Akdis, A. Aab, C. Altunbulakli, K. Azkur, R.A. Costa, R. Crameri, S. Duan, T. Eiwegger, A. Eljaszewicz, R. Ferstl, Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: receptors, functions, and roles in diseases, J. Allergy Clin. Immunol. 138 (4) (2016) 984–1010.
[26] P.A. Blair, K.A. Chavez-Rueda, J.G. Evans, M.J. Shlomchik, A. Eddaoudi, D.A. Isenberg, M.R. Ehrenstein, C. Mauri, 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) (2009) 3492–3502.
[27] N.A. Carter, R. Vasconcellos, E.C. Rosser, C. Tulone, A. Muñoz-Suano, M. Kamanaka, M.R. Ehrenstein, R.A. Flavell, C. Mauri, Mice lacking endogenous IL-10–producing regulatory B cells develop exacerbated disease and present with an increased frequency of Th1/Th17 but a decrease in regulatory T cells, J. Immunol. 186 (10) (2011) 5569–5579.
[28] J.G. Evans, K.A. Chavez-Rueda, A. Eddaoudi, A. Meyer-Bahlburg, D.J. Rawlings, M.R. Ehrenstein, C. Mauri, Novel suppressive function of transitional 2 B cells in experimental arthritis, J. Immunol. 178 (12) (2007) 7868–7878.
[29] R. Bankoti, K. Gupta, A. Levchenko, S. Stäger, Marginal zone B cells regulate antigen-specific T cell responses during infection, J. Immunol. 188 (8) (2012) 3961–3971.
[30] M. Gray, K. Miles, D. Salter, D. Gray, J. Savill, Apoptotic cells protect mice from autoimmune inflammation by the induction of regulatory B cells, Proc. Natl. Acad. Sci. U. S. A. 104 (35) (2007) 14080–14085.
[31] M. Rafei, J. Hsieh, S. Zehntner, M. Li, K. Forner, E. Birman, M.-N. Boivin, Y.K. Young, C. Perreault, J. Galipeau, A granulocyte-macrophage colony–stimulating factor and interleukin-15 fusokine induces a regulatory B cell population with immune suppressive properties, Nat. Med. 15 (9) (2009) 1038.
[32] I. Kalampokis, A. Yoshizaki, T.F. Tedder, IL-10-producing regulatory B cells (B10 cells) in autoimmune disease, Arthritis Res. Ther. 15 (1) (2013) S1.
[33] A. Mizoguchi, E. Mizoguchi, R.N. Smith, F.I. Preffer, A.K. Bhan, Suppressive role of B cells in chronic colitis of T cell receptor α mutant mice, J. Exp. Med. 186 (10) (1997) 1749–1756.
[34] M. Yang, J. Deng, Y. Liu, K.-H. Ko, X. Wang, Z. Jiao, S. Wang, Z. Hua, L. Sun, G. Srivastava, IL-10–producing regulatory B10 cells ameliorate collagen-induced arthritis via suppressing Th17 cell generation, Am. J. Pathol. 180 (6) (2012) 2375–2385.
[35] P. Shen, T. Roch, V. Lampropoulou, R.A. O'Connor, U. Stervbo, E. Hilgenberg, S. Ries, Y. Jaimes, C. Daridon, R. Li, IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases, Nature 507 (7492) (2014) 366.
[36] S. Xiao, C.R. Brooks, R.A. Sobel, V.K. Kuchroo, Tim-1 is essential for induction and maintenance of IL-10 in regulatory B cells and their regulation of tissue inflammation, J. Immunol. 194 (4) (2015) 1602–1608.
[37] X. Zhang, E. Deriaud, X. Jiao, D. Braun, C. Leclerc, R. Lo-Man, Type I interferons protect neonates from acute inflammation through interleukin 10–producing B cells, J. Exp. Med. 204 (5) (2007) 1107–1118.
[38] S.K. Lundy, D.L. Boros, Fas ligand-expressing B-1a lymphocytes mediate CD4+-T-cell apoptosis during schistosomal infection: induction by interleukin 4 (IL-4) and IL-10, Infect. Immun. 70 (2) (2002) 812–819.
[39] S.K. Lundy, D.A. Fox, Reduced Fas ligand-expressing splenic CD5+ B lymphocytes in severe collagen-induced arthritis, Arthritis Res. Ther. 11 (4) (2009) R128.
[40] A.R. Khan, E. Hams, A. Floudas, T. Sparwasser, C.T. Weaver, P.G. Fallon, PD-L1 hi B cells are critical regulators of humoral immunity, Nat. Commun. 6 (2015) 5997.
[41] H. Kaku, K.F. Cheng, Y. Al-Abed, T.L. Rothstein, A novel mechanism of B cell–mediated immune suppression through CD73 expression and adenosine production, J. Immunol. 193 (12) (2014) 5904–5913.
[42] Z. Saze, P.J. Schuler, C.-S. Hong, D. Cheng, E.K. Jackson, T.L. Whiteside, Adenosine production by human B cells and B cell–mediated suppression of activated T cells, Blood 122 (1) (2013) 9–18.
[43] F. Flores-Borja, A. Bosma, D. Ng, V. Reddy, M.R. Ehrenstein, D.A. Isenberg, C. Mauri, CD19+ CD24hiCD38hi B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation, Sci. Transl. Med. 5 (173) (2013) 173ra23.
[44] W. van de Veen, B. Stanic, G. Yaman, M. Wawrzyniak, S. Söllner, D.G. Akdis, B. Rückert, C.A. Akdis, M. Akdis, IgG4 production is confined to human IL-10–producing regulatory B cells that suppress antigen-specific immune responses, J. Allergy Clin. Immunol. 131 (4) (2013) 1204–1212.
[45] S. Lindner, K. Dahlke, K. Sontheimer, M. Hagn, C. Kaltenmeier, T.F. Barth, T. Beyer, F. Reister, D. Fabricius, R. Lotfi, Interleukin 21–induced granzyme B–expressing B cells infiltrate tumors and regulate T cells, Cancer Res. 73 (8) (2013) 2468–2479.

[46] C.G. McKenzie, L. Guo, J. Freedman, J.W. Semple, Cellular immune dysfunction in immune thrombocytopenia (ITP), Br. J. Haematol. 163 (1) (2013) 10–23.
[47] X. Li, H. Zhong, W. Bao, N. Boulad, J. Evangelista, M.A. Haider, J. Bussel, K. Yazdanbakhsh, Defective regulatory B-cell compartment in patients with immune thrombocytopenia, Blood 120 (16) (2012) 3318–3325.
[48] R. Aslam, G.B. Segel, R. Burack, S.A. Spence, E.R. Speck, L. Guo, J.W. Semple, Splenic lymphocyte subtypes in immune thrombocytopenia: increased presence of a subtype of B-regulatory cells, Br. J. Haematol. 173 (1) (2016) 159–160.
[49] J. Noh, W.S. Choi, G. Noh, J.H. Lee, Presence of Foxp3-expressing CD19 (+) CD5 (+) B cells in human peripheral blood mononuclear cells: human CD19 (+) CD5 (+) Foxp3 (+) regulatory B cell (Breg), Immune Netw. 10 (6) (2010) 247–249.
[50] Y. Guo, X. Zhang, M. Qin, X. Wang, Changes in peripheral CD19+ Foxp3+ and CD19+ TGFβ+ regulatory B cell populations in rheumatoid arthritis patients with interstitial lung disease, J. Thorac. Dis. 7 (3) (2015) 471.
[51] A. Solanilla, J.-M. Pasquet, J.-F. Viallard, C. Contin, C. Grosset, J. Déchanet-Merville, M. Dupouy, M. Landry, F. Belloc, P. Nurden, Platelet-associated CD154 in immune thrombocytopenic purpura, Blood 105 (1) (2005) 215–218.
[52] A.E. May, T. Kälsch, S. Massberg, Y. Herouy, R. Schmidt, M. Gawaz, Engagement of glycoprotein IIb/IIIa (αIIbβ3) on platelets upregulates CD40L and triggers CD40L-dependent matrix degradation by endothelial cells, Circulation 106 (16) (2002) 2111–2117.
[53] C. Gasperi, A. Melms, B. Schoser, Y. Zhang, J. Meltoranta, V. Risson, L. Schaeffer, B. Schalke, S. Kröger, Anti-agrin autoantibodies in myasthenia gravis, Neurology 82 (22) (2014) 1976–1983.
[54] A. Pevzner, B. Schoser, K. Peters, N.-C. Cosma, A. Karakatsani, B. Schalke, A. Melms, S. Kröger, Anti-LRP4 autoantibodies in AChR-and MuSK-antibody-negative myasthenia gravis, J. Neurol. 259 (3) (2012) 427–435.
[55] F. Sun, S.S. Ladha, L. Yang, Q. Liu, S.X.Y. Shi, N. Su, R. Bomprezzi, F.D. Shi, Interleukin-10 producing-B cells and their association with responsiveness to rituximab in myasthenia gravis, Muscle Nerve 49 (4) (2014) 487–494.
[56] J.R. Sheng, K. Rezania, B. Soliven, Impaired regulatory B cells in myasthenia gravis, J. Neuroimmunol. 297 (2016) 38–45.
[57] J.R. Sheng, S. Quan, B. Soliven, CD1dhiCD5+ B cells expanded by GM-CSF in vivo suppress experimental autoimmune myasthenia gravis, J. Immunol. 193 (6) (2014) 2669–2677.
[58] M.R. Karim, H.-Y. Zhang, J. Yuan, Q. Sun, Y.-F. Wang, Regulatory B cells in seropositive myasthenia gravis versus healthy controls, Front. Neurol. 8 (2017) 43.
[59] L.M. Villar, M.C. Sádaba, E. Roldán, J. Masjuan, P. González-Porqué, N. Villarrubia, M. Espiño, J.A. García-Trujillo, A. Bootello, J.C. Álvarez-Cermeño, Intrathecal synthesis of oligoclonal IgM against myelin lipids predicts an aggressive disease course in MS, J. Clin. Invest. 115 (1) (2005) 187–194.
[60] T. Berger, P. Rubner, F. Schautzer, R. Egg, H. Ulmer, I. Mayringer, E. Dilitz, F. Deisenhammer, M. Reindl, Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event, N. Engl. J. Med. 349 (2) (2003) 139–145.
[61] C.P. Genain, B. Cannella, S.L. Hauser, C.S. Raine, Identification of autoantibodies associated with myelin damage in multiple sclerosis, Nat. Med. 5 (2) (1999) 170.
[62] M. Duddy, M. Niino, F. Adatia, S. Hebert, M. Freedman, H. Atkins, H.J. Kim, A. Bar-Or, Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis, J. Immunol. 178 (10) (2007) 6092–6099.
[63] M. Saresella, P. Tortorella, I. Marventano, N. Al-Daghri, F. Piancone, A. Gatti, M. Gironi, D. Caputo, M. Rovaris, M. Clerici, TH17-driven inflammation is present in all clinical forms of multiple sclerosis; disease quiescence is associated with GATA3-expressing cells, Eur. J. Inflamm. 11 (1) (2013) 223–235.
[64] D. Trabattoni, M. Saresella, M. Pacei, I. Marventano, L. Mendozzi, M. Rovaris, D. Caputo, M. Borelli, M. Clerici, Costimulatory pathways in multiple sclerosis: distinctive expression of PD-1 and PD-L1 in patients with different patterns of disease, J. Immunol. 183 (8) (2009) 4984–4993.
[65] F. Piancone, M. Saresella, I. Marventano, F. La Rosa, M. Zoppis, S. Agostini, R. Longhi, D. Caputo, L. Mendozzi, M. Rovaris, B lymphocytes in multiple sclerosis: bregs and BTLA/CD272 expressing-CD19+ lymphocytes modulate disease severity, Sci. Rep. 6 (2016) 29699.
[66] A. Horga, X. Montalban, FTY720 (fingolimod) for relapsing multiple sclerosis, Expert Rev. Neurother. 8 (5) (2008) 699–714.
[67] V. Brinkmann, A. Billich, T. Baumruker, P. Heining, R. Schmouder, G. Francis, S. Aradhye, P. Burtin, Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis, Nat. Rev. Drug Discov. 9 (11) (2010) 883.
[68] S. Blumenfeld, E. Staun-Ram, A. Miller, Fingolimod therapy modulates circulating B cell composition, increases B regulatory subsets and production of IL-10 and TGFβ in patients with Multiple Sclerosis, J. Autoimmun. 70 (2016) 40–51.
[69] B. Grützke, S. Hucke, C.C. Gross, M.V. Herold, A. Posevitz-Fejfar, B.T. Wildemann, B.C. Kieseier, T. Dehmel, H. Wiendl, L. Klotz, Fingolimod treatment promotes regulatory phenotype and function of B cells, Ann. Clin. Transl. Neurol. 2 (2) (2015) 119–130.
[70] T. Matsushita, K. Yanaba, J.-D. Bouaziz, M. Fujimoto, T.F. Tedder, Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression, J. Clin. Invest. 118 (10) (2008) 3420–3430.
[71] M.K. Mann, K. Maresz, L.P. Shriver, Y. Tan, B.N. Dittel, B cell regulation of CD4+ CD25+ T regulatory cells and IL-10 via B7 is essential for recovery from experimental autoimmune encephalomyelitis, J. Immunol. 178 (6) (2007) 3447–3456.
[72] M. Kala, S.N. Rhodes, W.-H. Piao, F.-D. Shi, D.I. Campagnolo, T.L. Vollmer, B cells from glatiramer acetate-treated mice suppress experimental autoimmune encephalomyelitis, Exp. Neurol. 221 (1) (2010) 136–145.
[73] S. Fillatreau, C.H. Sweenie, M.J. McGeachy, D. Gray, S.M. Anderton, B cells regulate autoimmunity by provision of IL-10, Nat. Immunol. 3 (10) (2002) 944.
[74] M.E. Duddy, A. Alter, A. Bar-Or, Distinct profiles of human B cell effector cytokines: a role in immune regulation? J. Immunol. 172 (6) (2004) 3422–3427.
[75] A. Bar-Or, P.A. Calabresi, D. Arnold, C. Markowitz, S. Shafer, L.H. Kasper, E. Waubant, S. Gazda, R.J. Fox, M. Panzara, Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial, Ann. Neurol. 63 (3) (2008) 395–400.
[76] S.L. Hauser, E. Waubant, D.L. Arnold, T. Vollmer, J. Antel, R.J. Fox, A. Bar-Or, M. Panzara, N. Sarkar, S. Agarwal, B-cell depletion with rituximab in relapsing–remitting multiple sclerosis, N. Engl. J. Med. 358 (7) (2008) 676–688.
[77] A.H. Cross, J.L. Stark, J. Lauber, M.J. Ramsbottom, J.-A. Lyons, Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients, J. Neuroimmunol. 180 (1–2) (2006) 63–70.
[78] K. Hawker, P. O'Connor, M.S. Freedman, P.A. Calabresi, J. Antel, J. Simon, S. Hauser, E. Waubant, T. Vollmer, H. Panitch, Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial, Ann. Neurol. 66 (4) (2009) 460–471.
[79] R. Naismith, L. Piccio, J. Lyons, J. Lauber, N. Tutlam, B. Parks, K. Trinkaus, S.-K. Song, A. Cross, Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial, Neurology 74 (23) (2010) 1860–1867.
[80] F.O. Nestle, D.H. Kaplan, J. Barker, Psoriasis, N. Engl. J. Med. 361 (5) (2009) 496–509.
[81] A. Mirshafiey, A. Simhag, N.M. El Rouby, G. Azizi, T-helper 22 cells as a new player in chronic inflammatory skin disorders, Int. J. Dermatol. 54 (8) (2015) 880–888.
[82] M.P. Schön, T. Ruzicka, Psoriasis: the plot thickens, Nat. Immunol. 2 (2) (2001) 91.
[83] M. Hayashi, K. Yanaba, Y. Umezawa, Y. Yoshihara, S. Kikuchi, Y. Ishiuji, H. Saeki, H. Nakagawa, IL-10-producing regulatory B cells are decreased in patients with psoriasis, J. Dermatol. Sci. 81 (2) (2016) 93–100.
[84] A. Borghi, E. Fogli, M. Stignani, L. Melchiorri, E. Altieri, O. Baricordi, R. Rizzo, A. Virgili, Soluble human leukocyte antigen-G and interleukin-10 levels in plasma of psoriatic patients: preliminary study on a possible correlation between generalized immune status, treatments and disease, Arch. Dermatol. Res. 300 (10) (2008) 551–559.
[85] H. Takahashi, H. Tsuji, Y. Hashimoto, A. Ishida-Yamamoto, H. Iizuka, Serum cytokines and growth factor levels in Japanese patients with psoriasis, Clin. Exp. Dermatol.: Exp. Dermatol. 35 (6) (2010) 645–649.
[86] E. Weiss, A.J. Mamelak, S. La Morgia, B. Wang, C. Feliciani, A. Tulli, D.N. Sauder, The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases, J. Am. Acad. Dermatol. 50 (5) (2004) 657–675.
[87] A.B. Kimball, T. Kawamura, K. Tejura, C. Boss, A.R. Hancox, J.C. Vogel, S.M. Steinberg, M.L. Turner, A. Blauvelt, Clinical and immunologic assessment of patients with psoriasis in a randomized, double-blind, placebo-controlled trial using recombinant human interleukin 10, Arch. Dermatol. 138 (10) (2002) 1341–1346.
[88] S. Van Deventer, C. Elson, R. Fedorak, Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group, Gastroenterology 113 (2) (1997) 383–389.
[89] S. Dass, E.M. Vital, P. Emery, Development of psoriasis after B cell depletion with rituximab, Arthritis Rheum. 56 (8) (2007) 2715–2718.
[90] F. Mielke, J. Schneider-Obermeyer, T. Dörner, Onset of psoriasis with psoriatic arthropathy during rituximab treatment of non-Hodgkin lymphoma, Ann. Rheum. Dis. 67 (7) (2008) 1056–1057.
[91] J. Cohen, Successful treatment of psoriatic arthritis with rituximab, Ann. Rheum. Dis. 67 (11) (2008) 1647–1648.
[92] K. Yanaba, M. Kamata, N. Ishiura, S. Shibata, Y. Asano, Y. Tada, M. Sugaya, T. Kadono, T.F. Tedder, S. Sato, Regulatory B cells suppress imiquimod-induced, psoriasis-like skin inflammation, J. Leukoc. Biol. 94 (4) (2013) 563–573.
[93] T. Matsushita, M. Horikawa, Y. Iwata, T.F. Tedder, Regulatory B cells (B10 cells) and regulatory T cells have independent roles in controlling experimental autoimmune encephalomyelitis initiation and late-phase immunopathogenesis, J. Immunol. 185 (4) (2010) 2240–2252.
[94] M. Feldmann, F.M. Brennan, R.N. Maini, Rheumatoid arthritis, Cell 85 (3) (1996) 307–310.
[95] G.S. Firestein, Evolving concepts of rheumatoid arthritis, Nature 423 (6937) (2003) 356.
[96] D.L. Scott, F. Wolfe, T.W. Huizinga, Rheumatoid arthritis, Lancet 376 (9746) (2010) 1094–1108.
[97] J. Kim, H.J. Lee, I.S. Yoo, S.W. Kang, J.H. Lee, Regulatory B cells are inversely associated with disease activity in rheumatoid arthritis, Yonsei Med. J. 55 (5) (2014) 1354–1358.
[98] L. Ma, B. Liu, Z. Jiang, Y. Jiang, Reduced numbers of regulatory B cells are negatively correlated with disease activity in patients with new-onset rheumatoid arthritis, Clin. Rheumatol. 33 (2) (2014) 187–195.
[99] D. Cui, L. Zhang, J. Chen, M. Zhu, L. Hou, B. Chen, B. Shen, Changes in regulatory B cells and their relationship with rheumatoid arthritis disease activity, Clin. Exp. Med. 15 (3) (2015) 285–292.
[100] Z. Bankó, J. Pozsgay, D. Szili, M. Tóth, T. Gáti, G. Nagy, B. Rojkovich, G. Sármay, Induction and differentiation of IL-10–producing regulatory B cells from healthy blood donors and rheumatoid arthritis patients, J. Immunol. 198 (4) (2017) 1512–1520.
[101] M.R. Arbuckle, M.T. McClain, M.V. Rubertone, R.H. Scofield, G.J. Dennis, J.A. James, J.B. Harley, Development of autoantibodies before the clinical onset of systemic lupus erythematosus, N. Engl. J. Med. 349 (16) (2003) 1526–1533.
[102] J. Yang, Y. Chu, X. Yang, D. Gao, L. Zhu, X. Yang, L. Wan, M. Li, Th17 and natural Treg cell population dynamics in systemic lupus erythematosus, Arthritis Rheum. 60 (5) (2009) 1472–1483.
[103] D.J. DiLillo, T. Matsushita, T.F. Tedder, B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer, Ann. N. Y. Acad. Sci. 1183 (1) (2010) 38–57.
[104] R.A. Herlands, S.R. Christensen, R.A. Sweet, U. Hershberg, M.J. Shlomchik, T cell-independent and toll-like receptor-dependent antigen-driven activation of autoreactive B cells, Immunity 29 (2) (2008) 249–260.
[105] J. Yang, X. Yang, H. Zou, Y. Chu, M. Li, Recovery of the immune balance between

Th17 and regulatory T cells as a treatment for systemic lupus erythematosus, Rheumatology 50 (8) (2011) 1366–1372.
[106] X. Yang, J. Yang, Y. Chu, Y. Xue, D. Xuan, S. Zheng, H. Zou, T follicular helper cells and regulatory B cells dynamics in systemic lupus erythematosus, PLoS One 9 (2) (2014) e88441.
[107] N. Simpson, P.A. Gatenby, A. Wilson, S. Malik, D.A. Fulcher, S.G. Tangye, H. Manku, T.J. Vyse, G. Roncador, G.A. Huttley, Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus, Arthritis Rheum. 62 (1) (2010) 234–244.
[108] N. Gao, J. Dresel, V. Eckstein, R. Gellert, H. Störch, R.K. Venigalla, V. Schwenger, R. Max, N. Blank, H.M. Lorenz, Impaired suppressive capacity of activation-induced regulatory B cells in systemic lupus erythematosus, Arthritis Rheumatol. 66 (10) (2014) 2849–2861.
[109] M. Odendahl, A. Jacobi, A. Hansen, E. Feist, F. Hiepe, G.R. Burmester, P.E. Lipsky, A. Radbruch, T. Dörner, Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus, J. Immunol. 165 (10) (2000) 5970–5979.
[110] C. Wei, J. Anolik, A. Cappione, B. Zheng, A. Pugh-Bernard, J. Brooks, E.-H. Lee, E.C. Milner, I. Sanz, A new population of cells lacking expression of CD27 represents a notable component of the B cell memory compartment in systemic lupus erythematosus, J. Immunol. 178 (10) (2007) 6624–6633.
[111] A.M. Jacobi, M. Odendahl, K. Reiter, A. Bruns, G.R. Burmester, A. Radbruch, G. Valet, P.E. Lipsky, T. Dörner, Correlation between circulating CD27high plasma cells and disease activity in patients with systemic lupus erythematosus, Arthritis Rheum. 48 (5) (2003) 1332–1342.
[112] A.M. Jacobi, K. Reiter, M. Mackay, C. Aranow, F. Hiepe, A. Radbruch, A. Hansen, G.R. Burmester, B. Diamond, P.E. Lipsky, Activated memory B cell subsets correlate with disease activity in systemic lupus erythematosus: delineation by expression of CD27, IgD, and CD95, Arthritis Rheum. 58 (6) (2008) 1762–1773.
[113] M. Bijl, G. Horst, P.C. Limburg, C.G. Kallenberg, Expression of costimulatory molecules on peripheral blood lymphocytes of patients with systemic lupus erythematosus, Ann. Rheum. Dis. 60 (5) (2001) 523–526.
[114] N.-H. Chang, T. McKenzie, G. Bonventi, C. Landolt-Marticorena, P.R. Fortin, D. Gladman, M. Urowitz, J.E. Wither, Expanded population of activated antigen-engaged cells within the naive B cell compartment of patients with systemic lupus erythematosus, J. Immunol. 180 (2) (2008) 1276–1284.
[115] P.E. Lipsky, Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity, Nat. Immunol. 2 (9) (2001) 764.
[116] S.A. Jenks, I. Sanz, Altered B cell receptor signaling in human systemic lupus erythematosus, Autoimmun. Rev. 8 (3) (2009) 209–213.
[117] V.T. Chu, P. Enghard, S. Schürer, G. Steinhauser, B. Rudolph, G. Riemekasten, C. Berek, Systemic activation of the immune system induces aberrant BAFF and APRIL expression in B cells in patients with systemic lupus erythematosus, Arthritis Rheum. 60 (7) (2009) 2083–2093.
[118] Z. Vadasz, R. Peri, N. Eiza, G. Slobodin, A. Balbir-Gurman, E. Toubi, The expansion of CD25highIL-10highFoxP3high B regulatory cells is in association with SLE disease activity, J. Immunol. Res. 2015 (2015).
[119] L.I. Sakkas, I.C. Chikanza, C.D. Platsoucas, Mechanisms of disease: the role of immune cells in the pathogenesis of systemic sclerosis, Nat. Rev. Rheumatol. 2 (12) (2006) 679.
[120] T. Matsushita, Y. Hamaguchi, M. Hasegawa, K. Takehara, M. Fujimoto, Decreased levels of regulatory B cells in patients with systemic sclerosis: association with autoantibody production and disease activity, Rheumatology 55 (2) (2015) 263–267.
[121] A. Mavropoulos, T. Simopoulou, A. Varna, C. Liaskos, C.G. Katsiari, D.P. Bogdanos, L.I. Sakkas, Breg cells are numerically decreased and functionally impaired in patients with systemic sclerosis, Arthritis Rheumatol. 68 (2) (2016) 494–504.
[122] R.-X. Wang, C.-R. Yu, I.M. Dambuza, R.M. Mahdi, M.B. Dolinska, Y.V. Sergeev, P.T. Wingfield, S.-H. Kim, C.E. Egwuagu, Interleukin-35 induces regulatory B cells that suppress autoimmune disease, Nat. Med. 20 (6) (2014) 633.
[123] K. Boelaert, P.R. Newby, M.J. Simmonds, R.L. Holder, J.D. Carr-Smith, J.M. Heward, N. Manji, A. Allahabadia, M. Armitage, K.V. Chatterjee, Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease, Am. J. Med. 123 (2) (2010) 183 e1–183. e9.
[124] R.C. Jenkins, A.P. Weetman, Disease associations with autoimmune thyroid disease, Thyroid 12 (11) (2002) 977–988.
[125] S. Yu, Y. Qi, H. Wang, J. Jiang, L. Sun, Q. Zhou, Dysfunction of CD24+ CD38+ B cells in patients with Hashimoto's thyroiditis is associated with a lack of interleukin 10, Int. J. Biochem. Cell Biol. 90 (2017) 114–120.
[126] Y. Matsumura, S.N. Byrne, D.X. Nghiem, Y. Miyahara, S.E. Ullrich, A role for inflammatory mediators in the induction of immunoregulatory B cells, J. Immunol. 177 (7) (2006) 4810–4817.
[127] N.E. Mangan, N. van Rooijen, A.N. McKenzie, P.G. Fallon, Helminth-modified pulmonary immune response protects mice from allergen-induced airway hyperresponsiveness, J. Immunol. 176 (1) (2006) 138–147.
[128] S. Lundy, A. Berlin, T. Martens, N.W. Lukacs, Deficiency of regulatory B cells increases allergic airway inflammation, Inflamm. Res. 54 (12) (2005) 514–521.
[129] N.E. Mangan, R.E. Fallon, P. Smith, N. van Rooijen, A.N. McKenzie, P.G. Fallon, Helminth infection protects mice from anaphylaxis via IL-10-producing B cells, J. Immunol. 173 (10) (2004) 6346–6356.
[130] G. Noh, J.H. Lee, Regulatory B cells and allergic diseases, Allergy Asthma Immunol. Res. 3 (3) (2011) 168–177.
[131] S. Amu, S.P. Saunders, M. Kronenberg, N.E. Mangan, A. Atzberger, P.G. Fallon, Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model, J. Allergy Clin. Immunol. 125 (5) (2010) 1114–1124 e8.
[132] T.F. Tedder, T. Matsushita, Regulatory B cells that produce IL-10: a breath of fresh air in allergic airway disease, J. Allergy Clin. Immunol. 125 (5) (2010) 1125–1127.
[133] S. Ishihara, M. Aziz, T. Yuki, H. Kazumori, Y. Kinoshita, Inflammatory bowel disease: review from the aspect of genetics, J. Gastroenterol. 44 (11) (2009) 1097–1108.
[134] Y. Ogura, D.K. Bonen, N. Inohara, D.L. Nicolae, F.F. Chen, R. Ramos, H. Britton, T. Moran, R. Karaliuskas, R.H. Duerr, A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease, Nature 411 (6837) (2001) 603.
[135] T. Saitoh, N. Fujita, M.H. Jang, S. Uematsu, B.-G. Yang, T. Satoh, H. Omori, T. Noda, N. Yamamoto, M. Komatsu, Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1β production, Nature 456 (7219) (2008) 264.
[136] C. Schmidt, A. Stallmach, Etiology and pathogenesis of inflammatory bowel disease, Minerva Gastroenterol. Dietol. 51 (2) (2005) 127–145.
[137] A. Dignass, J.O. Lindsay, A. Sturm, A. Windsor, J.-F. Colombel, M. Allez, G. D'Haens, A. D'Hoore, G. Mantzaris, G. Novacek, Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management, J. Crohn's Colitis 6 (10) (2012) 991–1030.
[138] A. Oka, S. Ishihara, Y. Mishima, Y. Tada, R. Kusunoki, N. Fukuba, T. Yuki, K. Kawashima, S. Matsumoto, Y. Kinoshita, Role of regulatory B cells in chronic intestinal inflammation: association with pathogenesis of Crohn's disease, Inflamm. Bowel Dis. 20 (2) (2014) 315–328.
[139] X. Wang, Y. Zhu, M. Zhang, H. Wang, Y. Jiang, P. Gao, Ulcerative colitis is characterized by a decrease in regulatory B cells, J. Crohn's Colitis 10 (10) (2016) 1212–1223.
[140] K. Leiper, K. Martin, A. Ellis, S. Subramanian, A.J. Watson, S.E. Christmas, D. Howarth, F. Campbell, J.M. Rhodes, Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis, Gut 60 (11) (2011) 1520–1526.
[141] M. Goetz, R. Atreya, M. Ghalibafian, P.R. Galle, M.F. Neurath, Exacerbation of ulcerative colitis after rituximab salvage therapy, Inflamm. Bowel Dis. 13 (11) (2007) 1365–1368.
[142] T. Kucharzik, R. Stoll, N. Lügering, W. Domschke, Circulating antiinflammatory cytokine IL-10 in patients with inflammatory bowel disease (IBD), Clin. Exp. Immunol. 100 (3) (1995) 452–456.
[143] I. Ciećko-Michalska, I. Wierzbicka-Tutka, M. Szczepanek, D. Fedak, T. Mach, Could the cytokines concentration be a marker of IBD activity and be useful in evaluation of IBD differentiation? Prz. Lek. 73 (5) (2016) 301–304.
[144] J.J. Ott, G.A. Stevens, J. Groeger, S.T. Wiersma, Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity, Vaccine 30 (12) (2012) 2212–2219.
[145] A. Das, G. Ellis, C. Pallant, A.R. Lopes, P. Khanna, D. Peppa, A. Chen, P. Blair, G. Dusheiko, U. Gill, IL-10–producing regulatory B cells in the pathogenesis of chronic hepatitis B virus infection, J. Immunol. 189 (8) (2012) 3925–3935.
[146] Y. Gong, C. Zhao, P. Zhao, M. Wang, G. Zhou, F. Han, Y. Cui, J. Qian, H. Zhang, H. Xiong, Role of IL-10-producing regulatory B cells in chronic hepatitis B virus infection, Dig. Dis. Sci. 60 (5) (2015) 1308–1314.
[147] Y. Liu, L.-s. Cheng, S.-q. Wang, L. Li, W.-m. She, J. Li, J.-y. Wang, W. Jiang, IL-10-producing regulatory B-cells suppressed effector T-cells but enhanced regulatory T-cells in chronic HBV infection, Clin. Sci. 130 (11) (2016) 907–919.
[148] W.H. Organization, Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2008, World Health Organization, 2008.
[149] M. Zhang, G. Zeng, Q. Yang, J. Zhang, X. Zhu, Q. Chen, P. Suthakaran, Y. Zhang, Q. Deng, H. Liu, Anti-tuberculosis treatment enhances the production of IL-22 through reducing the frequencies of regulatory B cell, Tuberculosis 94 (3) (2014) 238–244.
[150] R. Basu, D.B. O'Quinn, D.J. Silberger, T.R. Schoeb, L. Fouser, W. Ouyang, R.D. Hatton, C.T. Weaver, Th22 cells are an important source of IL-22 for host protection against enteropathogenic bacteria, Immunity 37 (6) (2012) 1061–1075.
[151] M. Muñoz, M.M. Heimesaat, K. Danker, D. Struck, U. Lohmann, R. Plickert, S. Bereswill, A. Fischer, I.R. Dunay, K. Wolk, Interleukin (IL)-23 mediates Toxoplasma gondii–induced immunopathology in the gut via matrixmetalloproteinase-2 and IL-22 but independent of IL-17, J. Exp. Med. 206 (13) (2009) 3047–3059.
[152] N. Ota, K. Wong, P.A. Valdez, Y. Zheng, N.K. Crellin, L. Diehl, W. Ouyang, IL-22 bridges the lymphotoxin pathway with the maintenance of colonic lymphoid structures during infection with Citrobacter rodentium, Nat. Immunol. 12 (10) (2011) 941.
[153] G. Pickert, C. Neufert, M. Leppkes, Y. Zheng, N. Wittkopf, M. Warntjen, H.-A. Lehr, S. Hirth, B. Weigmann, S. Wirtz, STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing, J. Exp. Med. 206 (7) (2009) 1465–1472.
[154] R. Dhiman, M. Indramohan, P.F. Barnes, R.C. Nayak, P. Paidipally, L.V.M. Rao, R. Vankayalapati, IL-22 produced by human NK cells inhibits growth of Mycobacterium tuberculosis by enhancing phagolysosomal fusion, J. Immunol. 183 (10) (2009) 6639–6645.
[155] T.J. Scriba, B. Kalsdorf, D.-A. Abrahams, F. Isaacs, J. Hofmeister, G. Black, H.Y. Hassan, R.J. Wilkinson, G. Walzl, S.J. Gelderbloem, Distinct, specific IL-17- and IL-22-producing CD4+ T cell subsets contribute to the human anti-mycobacterial immune response, J. Immunol. 180 (3) (2008) 1962–1970.
[156] G. Zeng, C.Y. Chen, D. Huang, S. Yao, R.C. Wang, Z.W. Chen, Membrane-bound IL-22 after de novo production in tuberculosis and anti-Mycobacterium tuberculosis effector function of IL-22+ CD4+ T cells, J. Immunol. 187 (1) (2011) 190–199.
[157] R. Dhiman, S. Periasamy, P.F. Barnes, A.G. Jaiswal, P. Paidipally, A.B. Barnes, A. Tvinnereim, R. Vankayalapati, NK1. 1+ cells and IL-22 regulate vaccine-induced protective immunity against challenge with Mycobacterium tuberculosis, J. Immunol. 189 (2) (2012) 897–905.
[158] A. Bousfiha, L. Jeddane, C. Picard, F. Ailal, H.B. Gaspar, W. Al-Herz, T. Chatila, Y.J. Crow, C. Cunningham-Rundles, A. Etzioni, The 2017 IUIS phenotypic classification for primary immunodeficiencies, J. Clin. Immunol. 38 (1) (2018) 129–143.
[159] R. Yazdani, G. Azizi, H. Abolhassani, A. Aghamohammadi, Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management, Scand. J. Immunol. 85 (1) (2017) 3–12.
[160] A.L. Lemarquis, H.K. Einarsdottir, R.N. Kristjansdottir, I. Jonsdottir, B.R. Ludviksson, Transitional B cells and TLR9 responses are defective in selective

IgA deficiency, Front. Immunol. 9 (2018) 909.
[161] Y.Y. Wang, L. Zhang, P.W. Zhao, L. Ma, C. Li, H.B. Zou, Y.F. Jiang, Functional implications of regulatory B cells in human IgA nephropathy, Scand. J. Immunol. 79 (1) (2014) 51–60.
[162] A. Yoshizaki, T. Miyagaki, D.J. DiLillo, T. Matsushita, M. Horikawa, E.I. Kountikov, R. Spolski, J.C. Poe, W.J. Leonard, T.F. Tedder, Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions, Nature 491 (7423) (2012) 264.
[163] A.G. Louis, S. Agrawal, S. Gupta, Analysis of subsets of B cells, Breg, CD4Treg and CD8Treg cells in adult patients with primary selective IgM deficiency, Am. J. Clin. Exp. Immunol. 5 (1) (2016) 21.
[164] M. Vlkova, O. Ticha, J. Nechvatalova, T. Kalina, J. Litzman, C. Mauri, P.A. Blair, Regulatory B cells in CVID patients fail to suppress multifunctional IFN-γ+ TNF-α+ CD4+ T cells differentiation, Clin. Immunol. 160 (2) (2015) 292–300.
[165] F. Mehdipour, M. Razmkhah, A. Hosseini, M. Bagheri, A. Safaei, A.R. Talei, A. Ghaderi, Increased B regulatory phenotype in non-metastatic lymph nodes of node-positive breast cancer patients, Scand. J. Immunol. 83 (3) (2016) 195–202.
[166] J. Zhou, Z. Min, D. Zhang, W. Wang, F. Marincola, X. Wang, Enhanced frequency and potential mechanism of B regulatory cells in patients with lung cancer, J. Transl. Med. 12 (1) (2014) 304.
[167] P.B. Olkhanud, B. Damdinsuren, M. Bodogai, R.E. Gress, R. Sen, K. Wejksza, E. Malchinkhuu, R.P. Wersto, A. Biragyn, Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4+ T cells to T-regulatory cells, Cancer Res. 71 (10) (2011) 3505–3515.
[168] C. Lee-Chang, M. Bodogai, A. Martin-Montalvo, K. Wejksza, M. Sanghvi, R. Moaddel, R. De Cabo, A. Biragyn, Inhibition of breast cancer metastasis by resveratrol-mediated inactivation of tumor-evoked regulatory B cells, J. Immunol. 191 (8) (2013) 4141–4151.
[169] A. Bhardwaj, G. Sethi, S. Vadhan-Raj, C. Bueso-Ramos, Y. Takada, U. Gaur, A.S. Nair, S. Shishodia, B.B. Aggarwal, Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-κB–regulated antiapoptotic and cell survival gene products in human multiple myeloma cells, Blood 109 (6) (2007) 2293–2302.
[170] H. Lee, P. Zhang, A. Herrmann, C. Yang, H. Xin, Z. Wang, D.S. Hoon, S.J. Forman, R. Jove, A.D. Riggs, Acetylated STAT3 is crucial for methylation of tumor-suppressor gene promoters and inhibition by resveratrol results in demethylation, Proc. Natl. Acad. Sci. U. S. A. 109 (20) (2012) 7765–7769.
[171] H. Guan, Y. Wan, J. Lan, Q. Wang, Z. Wang, Y. Li, J. Zheng, X. Zhang, Z. Wang, Y. Shen, PD-L1 is a critical mediator of regulatory B cells and T cells in invasive breast cancer, Sci. Rep. 6 (2016) 35651.
[172] F. Kamangar, G.M. Dores, W.F. Anderson, Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world, J. Clin. Oncol. 24 (14) (2006) 2137–2150.
[173] J. Ferlay, H.R. Shin, F. Bray, D. Forman, C. Mathers, D.M. Parkin, Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008, Int. J. Cancer 127 (12) (2010) 2893–2917.
[174] J. Shi, S. Li, Y. Zhou, L. Wang, J. Wen, Y. Wang, Z. Kang, Perioperative changes in peripheral regulatory B cells of patients with esophageal cancer, Mol. Med. Rep. 10 (3) (2014) 1525–1530.
[175] L. Qian, G.-R. Bian, Y. Zhou, Y. Wang, J. Hu, X. Liu, Y. Xu, Clinical significance of regulatory B cells in the peripheral blood of patients with oesophageal cancer, Cent. J. Immunol. 40 (2) (2015) 263.
[176] Y. Li, J. An, S. Huang, J. He, J. Zhang, Esophageal cancer-derived microvesicles induce regulatory B cells, Cell Biochem. Funct. 33 (5) (2015) 308–313.
[177] T.R. Mempel, C.A. Bauer, Intravital imaging of CD8+ T cell function in cancer, Clin. Exp. Metastasis 26 (4) (2009) 311.
[178] R.N. Aravalli, E.N. Cressman, C.J. Steer, Cellular and molecular mechanisms of hepatocellular carcinoma: an update, Arch. Toxicol. 87 (2) (2013) 227–247.
[179] M. Casper, S.N. Weber, M. Kloor, R. Müllenbach, R. Grobholz, F. Lammert, V. Zimmer, Hepatocellular carcinoma as extracolonic manifestation of Lynch syndrome indicates SEC63 as potential target gene in hepatocarcinogenesis, Scand. J. Gastroenterol. 48 (3) (2013) 344–351.
[180] H.C. Spangenberg, R. Thimme, H.E. Blum, Targeted therapy for hepatocellular carcinoma, Nat. Rev. Gastroenterol. Hepatol. 6 (7) (2009) 423.
[181] Y. Shao, C.M. Lo, C.C. Ling, X.B. Liu, K.T.-P. Ng, A.C.Y. Chu, Y.Y. Ma, C.X. Li, S.T. Fan, K. Man, Regulatory B cells accelerate hepatocellular carcinoma progression via CD40/CD154 signaling pathway, Cancer Lett. 355 (2) (2014) 264–272.
[182] A. Budhu, X.W. Wang, The role of cytokines in hepatocellular carcinoma, J. Leukoc. Biol. 80 (6) (2006) 1197–1213.
[183] S. Song, P. Yuan, P. Li, H. Wu, W. Ni, J. Lu, W. Wei, Protective effects of total glucosides of paeony on N-nitrosodiethylamine-induced hepatocellular carcinoma in rats via down-regulation of regulatory B cells, Immunol. Invest. 44 (6) (2015) 521–535.
[184] J. Iwasa, M. Shimizu, M. Shiraki, Y. Shirakami, H. Sakai, Y. Terakura, K. Takai, H. Tsurumi, T. Tanaka, H. Moriwaki, Dietary supplementation with branched-chain amino acids suppresses diethylnitrosamine-induced liver tumorigenesis in obese and diabetic C57BL/KsJ-db/db mice, Cancer Sci. 101 (2) (2010) 460–467.
[185] X. Wang, M. Chen, S. Xu, The effects of total glucosides' of paeony (TGP) on T lymphocyte subsets, Zhongguo Yao Li Xue Tong Bao 8 (1992) 340–343.
[186] D.-Y. He, S.-M. Dai, Anti-inflammatory and immunomodulatory effects of Paeonia lactiflora Pall., a traditional Chinese herbal medicine, Front. Pharmacol. 2 (2011) 10.
[187] C. Mauri, M.R. Ehrenstein, The 'short' history of regulatory B cells, Trends Immunol. 29 (1) (2008) 34–40.
[188] M. Yang, L. Sun, S. Wang, K.-H. Ko, H. Xu, B.-J. Zheng, X. Cao, L. Lu, Cutting edge: novel function of B cell-activating factor in the induction of IL-10–producing regulatory B cells, J. Immunol. 184 (7) (2010) 3321–3325.
[189] M. Ramos-Casals, M. Soto, M. Cuadrado, M. Khamashta, Rituximab in systemic lupus erythematosusA systematic review of off-label use in 188 cases, Lupus 18 (9) (2009) 767–776.
[190] C. Mauri, M. Menon, Human regulatory B cells in health and disease: therapeutic potential, J. Clin. Invest. 127 (3) (2017) 772–779.
[191] M. Menon, P.A. Blair, D.A. Isenberg, C. Mauri, A regulatory feedback between plasmacytoid dendritic cells and regulatory B cells is aberrant in systemic lupus erythematosus, Immunity 44 (3) (2016) 683–697.
[192] E.C. Rosser, K. Oleinika, S. Tonon, R. Doyle, A. Bosma, N.A. Carter, K.A. Harris, S.A. Jones, N. Klein, C. Mauri, Regulatory B cells are induced by gut microbiota–driven interleukin-1β and interleukin-6 production, Nat. Med. 20 (11) (2014) 1334.
[193] T. Schioppa, R. Moore, R.G. Thompson, E.C. Rosser, H. Kulbe, S. Nedospasov, C. Mauri, L.M. Coussens, F.R. Balkwill, B regulatory cells and the tumor-promoting actions of TNF-α during squamous carcinogenesis, Proc. Natl. Acad. Sci. U. S. A. 108 (26) (2011) 10662–10667.
[194] K. Miles, J. Heaney, Z. Sibinska, D. Salter, J. Savill, D. Gray, M. Gray, A tolerogenic role for Toll-like receptor 9 is revealed by B-cell interaction with DNA complexes expressed on apoptotic cells, Proc. Natl. Acad. Sci. U. S. A. 109 (3) (2012) 887–892.
[195] M. Horikawa, E.T. Weimer, D.J. DiLillo, G.M. Venturi, R. Spolski, W.J. Leonard, M.T. Heise, T.F. Tedder, Regulatory B cell (B10 Cell) expansion during Listeria infection governs innate and cellular immune responses in mice, J. Immunol. 190 (3) (2013) 1158–1168.
[196] A. O'garra, R. Chang, N. Go, R. Hastings, G. Haughton, M. Howard, Ly-1 B (B-1) cells are the main source of B cell-derived interleukin 10, Eur. J. Immunol. 22 (3) (1992) 711–717.
[197] A. Khoder, A. Sarvaria, A. Alsuliman, C. Chew, T. Sekine, N. Cooper, S. Mielke, H. De Lavallade, M. Muftuoglu, I.F. Curbelo, Regulatory B cells are enriched within the IgM memory and transitional subsets in healthy donors but are deficient in chronic GVHD, Blood 124 (13) (2014) 2034–2045.
[198] A. Bosma, A. Abdel-Gadir, D.A. Isenberg, E.C. Jury, C. Mauri, Lipid-antigen presentation by CD1d+ B cells is essential for the maintenance of invariant natural killer T cells, Immunity 36 (3) (2012) 477–490.
[199] P. Neves, V. Lampropoulou, E. Calderon-Gomez, T. Roch, U. Stervbo, P. Shen, A.A. Kühl, C. Loddenkemper, M. Haury, S.A. Nedospasov, Signaling via the MyD88 adaptor protein in B cells suppresses protective immunity during Salmonella typhimurium infection, Immunity 33 (5) (2010) 777–790.
[200] A.C. Lino, V. Lampropoulou, A. Welle, J. Joedicke, J. Pohar, Q. Simon, J. Thalmensi, A. Baures, V. Flühler, I. Sakwa, LAG-3 inhibitory receptor expression identifies immunosuppressive natural regulatory plasma cells, Immunity 49 (1) (2018) 120–133 e9.
[201] Q. Ding, M. Yeung, G. Camirand, Q. Zeng, H. Akiba, H. Yagita, G. Chalasani, M.H. Sayegh, N. Najafian, D.M. Rothstein, 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) (2011).
[202] S. Xiao, C.R. Brooks, C. Zhu, C. Wu, J.M. Sweere, S. Petecka, A. Yeste, F.J. Quintana, T. Ichimura, R.A. Sobel, Defect in regulatory B-cell function and development of systemic autoimmunity in T-cell Ig mucin 1 (Tim-1) mucin domain-mutant mice, Proc. Natl. Acad. Sci. U. S. A. 109 (30) (2012) 12105–12110.
[203] W. Li, X. Tian, X. Lu, Q. Peng, X. Shu, H. Yang, Y. Li, Y. Wang, X. Zhang, Q.J.S.r. Liu, Significant decrease in peripheral regulatory B cells is an immunopathogenic feature of dermatomyositis, Sci. Rep. 6 (2016) 27479.
[204] H. Li, R. Zhou, C. Wang, Y. Li, G. Zheng, S. Jiang, T. Dong, J. Bai, S.J.Ir. Xu, T follicular regulatory cells infiltrate the human airways during the onset of acute respiratory distress syndrome and regulate the development of B regulatory cells, Immunol. Res. 66 (4) (2018) 548–554.
[205] S. Gupta, A.J.F. Gupta, Selective IgM deficiency—an underestimated primary immunodeficiency, Front. Immunol. 8 (2017) 1056.
[206] R.R. Soares, L.M.R. Antinarelli, C. Abramo, G.C. Macedo, E.S. Coimbra, K.K.G. Scopel, What do we know about the role of regulatory B cells (Breg) during the course of infection of two major parasitic diseases, malaria and leishmaniasis? Pathog. Glob. Health 111 (3) (2017) 107–115.
[207] M. Tarique, H. Naz, S.V. Kurra, R.A. Naqvi, C. Saini, R. Rai, M. Suhail, N. Khanna, D.N. Rao, A.J.F. Sharma, IL-10-producing regulatory B cells transformed CD4+ CD25-into Tregs and enhanced regulatory T cells function in human leprosy, Front. Immunol. 9 (2018) 1636.