Journal of Neuroscience Research 94:693–701 (2016)

Review

Role of Regulatory B Cells in Neuroimmunologic Disorders

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B lymphocytes augment the immune response by producing antibodies and activating T cells by antigen presentation. Recent studies have highlighted a specific and functionally significant B-cell subset that could downregulate excessive immune and inflammatory responses through a vast array of inhibitory cytokines, such as interleukin (IL)-10 and transforming growth factor-β (TGF-β). This subset of B cells is generally referred to as *regulatory B cells* (Bregs). In addition, recent studies have shown that IL-35-producing Bregs also play a role in downregulation of immunity. Diverse phenotypes of Bregs have been proposed to underlie human disorders and their animal models. Most studies have focused on the role of different subsets of Bregs and Bregs-associated molecules such as IL-10, TGF-β, and IL-35 in the pathogenesis of neuroimmunologic disorders. Furthermore, Bregs exert regulatory function mainly through suppressing the differentiation of Th1/Th17 cells and promoting regulatory T-cell expansion. Reduced presence of Bregs is reportedly associated with progression of several neuroimmunologic disorders. This Review summarizes the current knowledge on the role of Bregs in neuroimmunologic disorders, including multiple sclerosis, neuromyelitis optica, and myasthenia gravis. © 2016 The Authors. Journal of Neuroscience Research Published by Wiley Periodicals, Inc.

Key words: regulatory B cells; IL-10; TGF-β; IL-35; neuroimmunologic disorders

B cells, as precursors of plasmablasts and plasma cells, are thought to upregulate humoral immune response by producing antibodies and activating T cells by antigen presentation. Recent work has revealed a specific protective role of B cells in modulating the immune response under pathogenic conditions (Tedder, 2015). These specific B-cell subsets can downmodulate the immune response through production of anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor-β (TGF-β; Mizoguchi and Bhan, 2006; DiLillo et al., 2010; Kalampokis et al., 2013; Yang et al., 2013; Candando et al., 2014; Goode et al., 2014). These subsets of B cells are generally referred to as *regulatory B cells* (Bregs). Recent studies also suggest that Bregs are related to the pathogenesis in several immune-related disorders (Blair et al., 2010; Noh et al., 2010; Olkhanud et al.,

SIGNIFICANCE

B cells are thought to upregulate humoral immune response by producing antibodies and activating T cells by antigen presentation. This Review provides a succinct synopsis of the current literature and highlights a specific and functionally significant subset of B cells that can downregulate immune response through inhibitory cytokines such as interleukin (IL)-10, IL-35, and transforming growth factor-β. This subset of B cells is generally referred to as *regulatory B cells* (Bregs). Additional research is required for understanding how to expand Bregs efficiently *in vitro* to achieve maximal regulatory function of B cells. This crucial knowledge will open the gates for a promising, novel approach to treatment of human neuroimmunologic disorders.

J. Han and L. Sun contributed equally to this work.

Contract grant sponsor: Young Scholars Program of the National Natural Science Foundation of China; Contract grant number: 81301021; Contract grant sponsor: General Program of the National Natural Science Foundation of China; Contract grant number: 81471216; Contract grant sponsor: Young Scholars Program of Jilin Provincial Science and Technology Development of China; Contract grant number: 20130522025JH; Contract grant sponsor: International Science and Technology Cooperation Program of Jilin Provincial Science and Technology Development of China; Contract grant number: 20150414011GH; Contract grant sponsor: Norman Bethune Cultivation Plan of Jilin University; Contract grant sponsor: Swedish Research Council; Contract grant numbers: K2013-66X-22337-01-3; 2015-03005; Contract grant sponsor: The First Hospital of Jilin University

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Received 9 January 2016; Revised 29 March 2016; Accepted 29 March 2016

Published online 26 April 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.23749

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TABLE I. Phenotypic Characterization of Regulatory B Cells in Mice and Humans

Species	Phenotypes/markers	Relevance to disorders/models*	References
Mice	$CD19^+CD5^+CD1d^{hi}$	CHS, EAE	Matsushita et al., 2008; Yanaba et al., 2008
	$CD1d^{hi}CD21^{hi}CD23^-CD24^{hi}IgM^{hi}IgD^{lo}$	IBD	Wei et al., 2005
	$TIM\text{-}1^+B$	EAE	Ding et al., 2011
	$CD1d^{hi}CD21^{hi}CD23^+CD24^{hi}lgM^{hi}IgD^+$	Experimental arthritis	Evans et al., 2007
	$CD19^+CD25^+B220^+$	Breast cancer	Olkhanud et al., 2011
Human	$CD19^+CD5^+CD1d^{hi}$	NMO, CHB, CHC	Wang et al., 2014a; Yang et al., 2015
	$CD19^+CD5^+Foxp3^+$	Normal subjects	Noh et al., 2010
	$CD19^+CD24^{hi}CD27^+$	cGVHD, RA, SS, SLE	Iwata et al., 2011; Daien et al., 2014; de Masson et al., 2015
	$CD19^+CD25^+$	MS	de Andres et al., 2014
	$CD19^+CD38^+CD1d^+IgM^+CD147^+$	Solid tumors	Lindner et al., 2013
	$CD5^+CD24^{hi}CD38^{hi}$	AAV	Aybar et al., 2015
	$CD19^+CD24^{hi}CD38^{hi}$	MS, NMO, SLE, RA, SS, pemphigus, ITP, AAV	Blair et al., 2010; Furuzawa-Carballeda et al., 2013; Wilde et al., 2013; Daien et al., 2014; Hua et al., 2014; Zhu et al., 2015

*CHS, contact hypersensitivity; IBD, inflammatory bowel disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; cGVHD, chronic graft versus host disease; RA, rheumatoid arthritis; SS, primary Sjogren's syndrome; AAV, ANCA-associated vasculitis; ITP, immune thrombocytopenia.

2011; Furuzawa-Carballeda et al., 2013, 2014; Wilde et al., 2013; Daien et al., 2014; He et al., 2014; Hua et al., 2014; L. Wang et al., 2014; Aybar et al., 2015; de Masson et al., 2015; Zhu et al., 2015). Bregs are known mainly for suppressing the pathogenic Th1/Th17 cells and promoting regulatory T-cell (Treg) expansion, thereby allowing Bregs to exert their regulatory function. The lack or loss of Bregs has been shown to be associated with progression of several neuroimmunologic diseases, such as multiple sclerosis (MS; Knippenberg et al., 2011; de Andres et al., 2014), neuromyelitis optica (NMO; Quan et al., 2013), and myasthenia gravis (MG; Sun et al., 2014). More importantly, recent articles have described a new IL-35-producing B-cell (i35-Breg) subset that appears to downregulate the immune response through production of IL-35 (Shen et al., 2014; R.X. Wang et al., 2014; Egwuagu and Yu, 2015). Bregs comprise several immunophenotypically distinct B-cell lineages identifiable by the production of the immunomodulatory cytokines IL-10, TGF-β, and IL-35. However, the precise phenotypic characterization and signaling molecules of Bregs remain unclear. Additional insights into the role and characteristics of Bregs may well provide new therapeutic targets in patients with neuroimmunologic disorders. This Review provides a summary of the current state of knowledge on the role of Bregs in neuroimmunologic disorders.

PHENOTYPIC CHARACTERIZATION OF BREGS

Phenotypic Characterization of Mice Bregs

Because no precise phenotypic characteristics or signaling molecules of Bregs exist, the best strategy for identifying Bregs would be by intracellular staining for IL-10. However, this process involves fixing and permeabilizing cells, which may affect the functional characterization of Bregs. So exact cell surface phenotypes and markers are key to the identification of Bregs. Some of the cell surface phenotypes that are reportedly specific to Bregs in mice, related to their capacity to produce IL-10, are summarized in Table I.

IL-10-producing spleen B cells were restricted to a unique $CD1d^{hi}CD5^+$ Breg subset that was absent in $Cd19^{-/-}$ mice. This relatively rare $CD19^+CD5^+CD1d^{hi}$ Breg subset has been named *B10 cells* because it is attributable to IL-10 production (Yanaba et al., 2008). In earlier studies, splenic marginal zone (MZ) B cells ($CD1d^{hi}CD21^{hi}CD23^-CD24^{hi}IgM^{hi}IgD^{lo}$) were shown to produce IL-10 and inhibit the development of inflammatory bowel disease in animal models (Wei et al., 2005; Mauri and Bosma, 2012). Moreover, transitional 2-MZ precursor (T2-MZP) B cells ($CD1d^{hi}CD21^{hi}CD23^+CD24^{hi}lgM^{hi}IgD^+$) are known to inhibit the progression of arthritis. The negative regulation of T2-MZP cells apparently depends on IL-10 secretion, given that T2-MZP cells from $IL\text{-}10^{-/-}$ mice failed to protect against the development of arthritis (Evans et al., 2007; Mauri and Bosma, 2012). T-cell immunoglobulin domain and mucin domain-1 (TIM-1) have been shown to identify more than 70% of spleen IL-10-producing B cells. TIM-1 was expressed by a large number of IL-10-producing regulatory B cells in all major B-cell subsets (Ding et al., 2011). TIM-1-deficient B cells have been shown to enhance Th1/Th17 responses and to aggravate experimental autoimmune encephalomyelitis (EAE; Xiao et al., 2015). Bregs are thought to exert their suppressive effect through the production of inhibitory cytokines. Much progress has been made in the identification of Bregs through studies in mice.

Phenotypic Characterization of Human Bregs

The current state of knowledge on the phenotypes and markers of human Bregs (Blair et al., 2010; Iwata et al., 2011; Furuzawa-Carballeda et al., 2013; Daien et al., 2014; L. Wang et al., 2014) is presented in Table I. Human Bregs have been shown to share some of the phenotypic characteristics with previously defined markers in mice (Correale et al., 2008; Yanaba et al., 2008). Human

IL-10-expressing Bregs were shown to be normally present in low but readily identifiable numbers in the peripheral blood and spleen, a finding similar to that observed in mice (Iwata et al., 2011; Kalampokis et al., 2013). After *ex vivo* stimulation with phorbol myristate acetate and ionomycin plus brefeldin-A, human Bregs were shown to block protein production (Candando et al., 2014). This method provides an indirect assessment of the active Bregs associated with human autoimmune disorders because Bregs could not be observed directly *ex vivo* (Candando et al., 2014).

Bregs from peripheral blood were shown to produce more IL-10 after stimulation by CD40 compared with that after stimulation by both B-cell receptor (BCR) and CD40. Furthermore, Bregs were shown to secrete markedly less IL-10 in MS patients compared with healthy controls under both conditions (Duddy et al., 2007).

Iwata et al. (2011) described a subset of human Bregs with $CD19^{+}CD24^{hi}CD27^{+}$ that played an immune regulatory role and appeared to impair functionally patients with systemic lupus erythematosus (SLE). Furthermore, this subset of Bregs showed a reduced capacity for secreting IL-10 after CD40 engagement in SLE patients compared with healthy controls (Iwata et al., 2011). B cells that express granzyme B revealed a $CD19^{+}CD38^{+}CD1d^{+}IgM^{+}CD147^{+}$ phenotype in the microenvironment of various solid tumors. The establishment of this regulatory phenotype in solid tumor infiltrates was shown to suppress antitumor immune responses (Lindner et al., 2013). Human Bregs are known to have a high expression level of CD48 and CD148 markers. CD48 is a marker for B-cell activation, and CD148 is considered a marker for human memory B cells (Kalampokis et al., 2013). Phenotypes that are unique to Bregs have not yet been identified; nonetheless, Bregs are thought to modulate immunity negatively through complex mechanisms in human autoimmune disorders.

FUNCTIONS OF BREGS

Bregs Exercise Function Through IL-10

There are several mechanisms by which Bregs exert their regulatory function during immune response (Fig. 1). IL-10 is an immunoregulatory cytokine that plays a pivotal role in controlling excessive inflammation and downregulating the immune response (Lemoine et al., 2009; Yao et al., 2013). IL-10-producing Bregs are known to regulate macrophage and dendritic cell activation negatively (Kalampokis et al., 2013). According to Flores-Borja et al. (2013), $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs were shown to downregulate Th1/Th17 response. Carter et al. (2011) showed that mice specifically lacking IL-10-producing B cells developed a progressive arthritis and exhibited an increased frequency in inflammatory Th1/Th17 cells compared with wild-type (WT) mice. Furthermore, adoptive transfer of Bregs to $IL\text{-}10^{-/-}$ mice was shown to reduce the frequencies of Th1/Th17 pathogenic cells and suppress autoreactive inflammation. Overall, Bregs appear to suppress the differentiation of Th1/Th17 cells and enhance Th2 polarization, resulting in decreased T-cell activation (Lampropoulou et al., 2008; Kalampokis et al., 2013).

In an experimental study, mice with IL-10-deficient B cells did not fully recover from EAE, which prompted the notion that IL-10-producing Bregs could suppress inflammation in autoimmune disorders (Wolf et al., 1996). The transfer of WT IL-10-producing Bregs ameliorated the inflammation and severity of EAE, whereas the transfer of Bregs from $IL\text{-}10^{-/-}$ mice had no such effect. Consequently, disease recovery is attributed predominantly to autoantigen-reactive IL-10-producing Bregs (Wolf et al., 1996). These specific IL-10-producing Bregs are also referred to as *B10 cells* (Kalampokis et al., 2013). Several studies have shown a significant decrease in B10 cells in human neuroimmunologic disorders (Knippenberg et al., 2011; Quan et al., 2013; Sun et al., 2014).

BCR-induced signals appear to be essential for B10 cells to function effectively. Early studies of CD19 transgenic mice showed that $Cd19^{-/-}$ mice had impaired BCR signaling and decreased B10 cells, whereas overexpression of CD19 in mice resulted in an increased number of B10 cells (Yanaba et al., 2008). B-cell-mediated immune inhibition was shown to involve antigen-specific B-cell activation through both BCR and CD40 signaling (Hilgenberg et al., 2014). Nonetheless, these signals were inadequate to stimulate the production of IL-10, given that the naïve B cells did not produce inhibitory cytokine IL-10, suggesting that they were not responsible for the suppression of disease after stimulation by BCR and CD40 (Lampropoulou et al., 2008, 2010).

Several studies showed marked increases in secretion of IL-10 by naïve B cells after stimulation with agonists of Toll-like receptor (TLR) signaling, which is also known to trigger the inhibitory response (Lampropoulou et al., 2008, 2010). Mice carrying B-cell-restricted deficiency in the MyD88 signaling pathway, an essential signaling adaptor protein for most TLR-developed chronic relapses of EAE, were clinically indistinguishable from mice lacking IL-10 production by B cells. TLR signaling in B cells appears to be a requirement for B-cell-mediated suppressive function in the pathogenesis of diseases (Lampropoulou et al., 2008). The suppressive function of B cells is thought to be initiated by a two-step process, TLR signaling and subsequent amplification through BCR and CD40 signaling (Yao et al., 2013). In another crucial recent discovery, Yoshizaki et al. (2012) showed that CD40 signals could induce Breg expansion into functional IL-10-producing effector-cell generation through IL-21-dependent cognate interactions.

Bregs Exercise Function Through IL-35

IL-35, a recently identified cytokine that belongs to the IL-12 family, is a potent anti-inflammatory cytokine produced by Tregs and Bregs (Collison et al., 2010; Mauri and Nistala, 2014; Xiang and Xie, 2015). A novel i35-Breg subpopulation was shown to downregulate the immune response by inhibiting Th1/Th17 cells (Choi

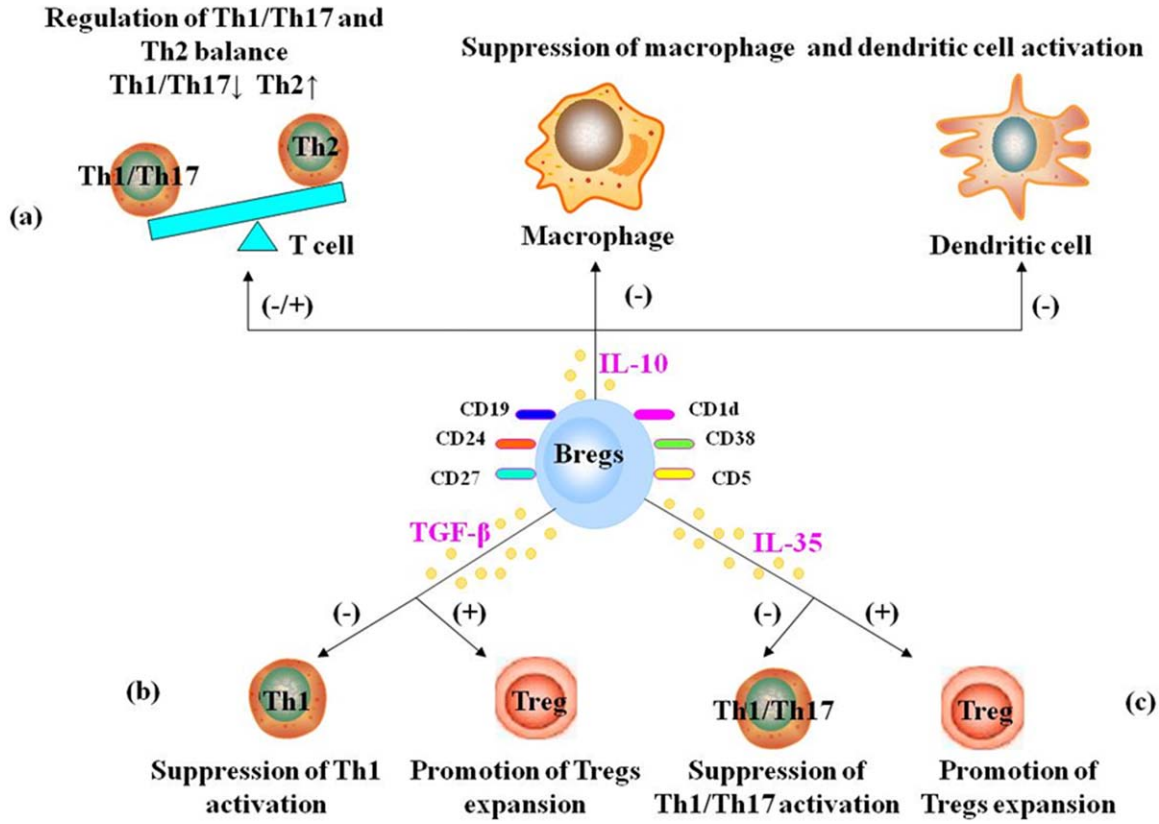

Fig. 1. Bregs play their roles in immune response through IL-10, TGF-β, and/or IL-35. **a:** IL-10-producing Bregs appear to suppress the differentiation of Th1/Th17 cells and enhance Th2 polarization. IL-10-producing Bregs also suppress macrophage and dendritic cells activation. **b:** TGF-β-producing Bregs appear to suppress Th1 activation and promote Tregs expansion. **c:** i35-Bregs appear to suppress Th1/ Th17 activation and promote Tregs expansion. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

et al., 2015). This new key player appears promising and could open new horizons for treating human autoimmune disorders in the future (Shen et al., 2014; R.X. Wang et al., 2014; Egwuagu and Yu, 2015).

B-cell-derived IL-35 is thought to be an important regulator of T-cell-mediated autoimmunity. In one study, mice lacking expression of IL-35 in B cells lost their ability to recover completely from EAE in contrast to the WT mice (Shen et al., 2014). This study also demonstrated secretion of IL-35 by B cells after TLR4 and CD40 stimulation. Although TLR4 triggered the formation of IL-10-producing Bregs, such an effect was not observable after costimulation by TLR4 and CD40 (Shen et al., 2014).

Treatment of mice with IL-35 has been shown to restrain harmful immune responses in an animal model of uveitis. Furthermore, mice that were lacking IL-35 or had dysfunctional IL-35 signaling (comprising IL-12Rβ2/IL-27Rα subunits) showed a poor expansion of Bregs and manifested progression of uveitis. After adoptive transfer of recombinant IL-35, however, Bregs induced by IL-35 suppressed uveitis, inhibiting the pathogenic Th1/Th17 cells and promoting Tregs expansion. Furthermore, IL-35 induced the conversion of human B cells into Bregs, suggesting that IL-35 could be one possible molecule for treating autoimmune disorders by virtue of its effect in enhancing Bregs function (R.X. Wang et al., 2014).

Bregs Exercise Function Through TGF-β

Bregs have been shown to regulate negatively the immune response through the production of the anti-inflammatory cytokine TGF-β (Holan et al., 2014; Vadasz and Toubi, 2014). Bregs were shown to downregulate pathogenic Th1 immunity effectively through anti-inflammatory TGF-β (Tian et al., 2001). Furthermore, Bregs were also shown to promote graft survival by enhancing Tregs expansion, possibly through TGF-β production (Lee et al., 2014). TGF-β can inhibit T-cell immunity by directly suppressing cytokine production by effector T cells or indirectly downregulating the activity of antigen-presenting cells (Tian et al., 2001; Holan et al., 2014; Lee et al., 2014). It is interesting to note that the adoptive transfer of TGF-β-producing Bregs, generated in vitro by lipopolysaccharide stimulation, appeared to inhibit the development of diabetes in mice by inducing apoptosis of the effector T cells (Tian et al., 2001).

TABLE II. Phenotypic Characterization of Bregs in Human Neuroimmunologic Disorders

Neuroimmunologic disorders	Changes in various phenotype Bregs	References
MS	↑$CD19^+CD25^+$ Bregs in relapsing MS vs. remitting MS	Knippenberg et al., 2011;
	↑$CD19^+CD25^+$ Bregs in remitting MS vs. HC	de Andres et al., 2014; Michel et al., 2014
	–$CD19^+CD24^{hi}CD38^{hi}$ Bregs in MS vs. HC	
	↓$CD19^+IL10^+$ Bregs in MS vs. HC	
NMO	↓$CD19^+CD24^{hi}CD38^{hi}$ Bregs in NMO vs. MS	Quan et al., 2013; Yang et al., 2015
	↓$CD19^+CD24^{hi}CD38^{hi}$ Bregs in NMO vs. HC	
	↓$CD19^+CD5^+CD1d^{hi}$ Bregs in NMO vs. MS	
	↓$CD19^+CD5^+CD1d^{hi}$ Bregs in NMO vs. MS	
MG	↓$CD19^+CD24^{hi}CD38^{hi}$ Bregs in MG vs. HC	Sun et al., 2014
	↓$CD19^+CD5^+CD1d^{hi}$ Bregs in MG vs. HC	

BREGS IN NEUROIMMUNOLOGIC DISORDERS

EAE and MS

The established MS animal model EAE is a Th1-mediated demyelinating autoimmune disease of the central nervous system (CNS). B cells are known to be involved in the pathogenesis of EAE. EAE can typically be induced in mice either by immunization with myelin antigens such as myelin oligodendrocyte glycoprotein (MOG) or by adoptive transfer of autoantigen-specific $CD4^+$ T cells (Ray et al., 2011; Robinson et al., 2014). In this regard, EAE has been widely used to study the pathogenesis and potential treatments for MS (Ray et al., 2011; Duffy et al., 2014; Pierson et al., 2014; Robinson et al., 2014). The regulatory effects of B cells on EAE were demonstrated almost 20 years ago. Mice with B-cell deficiency failed to recover fully from EAE (Wolf et al., 1996). When B cells from WT mice had been depleted by monoclonal antibody (mAb) CD20 7 days before EAE induction, it was found that the total number of $CD4^+$ T cells in the CNS was significantly expanded, and disease symptoms were exacerbated. However, the adoptive transfer of IL-10-producing regulatory $CD5^+CD1d^{hi}$ potent B cells, but not of other B cells, suppressed disease symptoms (Fillatreau et al., 2002; Matsushita et al., 2008). Additional experimental data supported similar effects in EAE that had been treated with a B-targeted mAb that blocks CD22 (Matsushita et al., 2010). Additionally, B-cell depletion during the progression of EAE dramatically ameliorated symptoms and the inflammatory response (Matsushita et al., 2008). Another study identified plasmablasts in the draining lymph nodes as the IL-10-producing Bregs that negatively regulate EAE inflammation. EAE progression was enhanced by their deletion in mice lacking plasmablasts (Matsumoto et al., 2014). In addition, infiltrating T cells were significantly reduced in B-cell-deficient mice that had been treated with E2 and Bregs. Thus, coadministration of Bregs and E2 might provide a promising future immunotherapy for treatment of EAE (Zhang et al., 2015a,b).

Phenotypic characterization of Bregs in human neuroimmunologic disorders is presented in Table II. MS is primarily a chronic progressive autoimmune demyelinating disease, caused by migration of T cells in the CNS (Compston and Coles, 2008; Roosendaal and Barkhof, 2015). Cumulative evidence emphasizes the significance of B-cell subsets in the pathogenesis (Lucchinetti et al., 2000) and therapy (Keegan et al., 2005) of MS. Specifically, Bregs play an important role in the pathophysiological basis of MS (Krumbholz and Meinl, 2014). Helminth infection in MS patients induced more Bregs capable of dampening the immune response through production of high levels of IL-10 (Correale et al., 2008; Correale and Equiza, 2014). In a recent study, fewer IL-10 producing B cells were found in the peripheral blood of MS patients during both relapse and remission compared with healthy controls (Knippenberg et al., 2011).

However, contradictory findings have been reported by researchers describing other studies in which normal frequency and phenotype of Bregs was observed in the peripheral blood of patients with MS (Michel et al., 2014). No differences were observed between MS patients and healthy controls in the frequency and function of $CD19^+CD24^{hi}CD38^{hi}$ Bregs, suggesting that the lack of peripheral Bregs may not contribute to the pathophysiology of MS (Michel et al., 2014). However, these discrepancies could be due to differences in the protocols in terms of time of cell culture and nature of stimulation, both of which have been shown to have an impact on cytokine secretion by B cells.

Researchers identified a new type of Bregs ($CD19^+CD25^+$), in low but readily appreciable numbers, in human peripheral circulation of MS patients and healthy controls. In one study, MS patients had a higher frequency of circulating $CD19^+CD25^+$ B cells during relapse compared with those in remission. The frequency of circulating $CD19^+CD25^+$ Bregs was also higher in MS patients in remission compared with healthy controls (de Andres et al., 2014). Understanding the complex role of Bregs will help to illuminate the immunopathogenesis of MS, which may offer new opportunities for targeting MS.

NMOSD

NMO is a severe inflammatory demyelinating disorder of the CNS that is characterized by typical attacks of optic neuritis and longitudinally extended transverse myelitis (Wingerchuk et al., 2007, 2015). Several studies have indicated a crucial role of B cells in the pathogenesis of

NMO-spectrum disorder (NMOSD; Krumbholz and Meinl, 2014; Bennett et al., 2015). The central role of autoantibodies against water channel protein aquaporin 4 (AQP4; Lennon et al., 2004) and MOG (Probstel et al., 2015) in the pathogenesis of NMOSD has provided a new hope for treatment of this rapidly disabling disorder.

A few researchers have reported on the role of Bregs in the pathogenesis of NMOSD. Recently, two articles from Chinese researchers indicated significantly lower frequencies of different subsets of Bregs in patients with NMOSD compared with both MS patients and healthy controls (Quan et al., 2013; Yang et al., 2015). One of these studies demonstrated significantly lower frequencies of $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs and IL-10 levels in NMOSD. Additionally, the frequency of $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs was even lower in the NMOSD patients who tested positive for AQP4 antibody compared with those testing negative for AQP4 antibody (Quan et al., 2013).

Another study appeared to mirror these findings in that the proportion of $CD19^{+}CD5^{+}CD1d^{hi}$ Bregs was significantly less in NMOSD patients compared with those in MS patients and healthy controls. Furthermore, the proportion of $CD19^{+}CD5^{+}CD1d^{hi}$ Bregs in $CD19^{+}$B cells was lower in AQP4 antibody-positive NMOSD patients than that in antibody-negative patients (Yang et al., 2015). These findings appear to implicate the reduced expression of Bregs in the pathogenesis of neuroautoimmune disorders.

MG

MG is a B-cell-mediated neuroautoimmune disorder in which the main target autoantigens are either the muscle-specific tyrosine kinase (MuSK) or the acetylcholine receptor (AchR) at the postsynaptic membrane of the neuromuscular junction, leading to muscle weakness and fatigue (Vincent et al., 2001; Guptill et al., 2015). CD72 has been demonstrated to act as a B-cell-inhibitory receptor in several autoimmune disorders (Smith et al., 2004; Nakano et al., 2007). Preliminary studies have shown that CD72 appears to be significantly decreased in MG patients and negatively correlates with anti-AchR-IgG levels. This suggests an inhibitory effect of CD72 on B-cell activation in MG and implicates CD72 in the causation of MG (Lu et al., 2013).

It has recently been demonstrated that the frequency and function of Bregs ($CD19^{+}CD24^{hi}CD38^{hi}$ phenotype as well as $CD19^{+}CD5^{+}CD1d^{hi}$ phenotype) were both reduced in MG patients compared with healthy controls. In addition, the frequency and function of Bregs were associated with disease activity (Sun et al., 2014). Another study appeared to mirror these findings in that a lower percentage of B10 cells was detected in patients with MuSK MG (Guptill et al., 2015). Thus, Bregs may serve as a marker for disease activity in MG patients and is a potential future therapeutic target.

CONCLUSIONS

Available evidence indicates that Bregs can downregulate excessive inflammatory responses in neuroimmunologic disorders. Because of the obvious limitations of obtaining human peripheral blood samples, there are only a few studies on regulatory B cells have been published, except for the most common neuroimmunologic diseases, such as MS, NMOSD, and MG. Undoubtedly, there will be further significant advances in other important neuroimmunologic diseases in the coming years. We equally anticipate the precise identification of additional Bregs subpopulations that produce different cytokines or mediate distinct functions. However, whether i35-Bregs and IL-10-producing B cells are overlapping subpopulations or simply represent different stages of B cells is yet to be understood, and this must be addressed in the future. We must understand how to expand Bregs efficiently *in vitro* and how to achieve maximal regulatory function of B cells. This crucial knowledge will open the gates for a promising, novel approach to treatment of human immune-related disorders.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

ROLE OF AUTHORS

Primary authorship: JH, LS. Significant contributing authorship and editing of intellectual content: XF, ZW, YC. Critical review and editing of intellectual content: JZ, TJ.

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