Regulatory B cells and Allergy: uncovering the link

Role of Breg cells in allergic disorders

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Abstract

Regulatory B (Breg) cells are recognized as immunosuppressive cells. During the last years, several subsets of Breg cells, with different phenotypes and suppressive mechanisms, have been described in the literature. We aim to present a review based on an extensive literature research in PubMed, about the role of Breg cells on allergy.

We describe the types and mechanisms of action of B cells and their role in the pathogenesis of several allergic diseases (allergic asthma, allergic rhinitis, food allergy, contact hypersensitivity and anaphylaxis).

Key-words: regulatory B cells; allergy; allergic disease; allergen tolerance; B10; Br1; asthma; food allergy; *Hymenoptera* venom allergy; pregnancy.

RESUMEN:

Los linfocitos reguladores del tipo B (B reg.) juegan un papel importante en el funcionamiento del sistema inmunitario. Durante los últimos años, se han descrito varios subgrupos de linfocitos B reg., con diferentes fenotipos y mecanismos supresores. Nuestro objetivo es recopilar la información existente sobre el papel de los linfocitos B reg. en Alergología, en base a una profunda investigación bibliográfica en PubMed.

Describimos los tipos y mecanismos de acción de los linfocitos B y su función en la patogénesis de varias enfermedades alérgicas (asma alérgica, rinitis alérgica, alergia alimentaria, eccema de contacto y anafilaxia).

PALABRAS CLAVE:

linfocitos B reguladores; alergia; enfermedad alérgica; tolerancia a alérgenos; B10; Br1; asma; alergia alimentaria; alergia al veneno de himenópteros; embarazo.

Introduction

Regulatory cells are essential to preserve immunological homeostasis and self-tolerance. Within this group of cells, research has been focused primarily on the role of $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells. The role of Treg cells has been extensively studied on the pathogenesis of autoimmune and allergic diseases as well as on the maintenance of tolerance to allergens. [1-5] Comparing to T cells or even to dendritic cells, the role of B cells on immune regulation has been relegated for a long time.

Evidence supporting the regulatory function of B cells has been accumulated over the last 20 years, mainly in animal models. In 1996, compelling evidence on this field was brought by Wolf *et al.* [6] through the induction of experimental autoimmune encephalomyelitis in genetically B cell-deficient mice. Afterwards in 2002, through animal models of intestinal inflammation, Mizoguchi *et al.* [7] demonstrated that a B cell subset, $CD1d^{hi}$, producing interleukin-10 (IL-10), could suppress the progression of intestinal inflammation. At same time, Fillatreau *et al*. [8] showed that IL-10 produced by B cell plays a key role in controlling autoimmunity. These studies have put forward the concept of a specific regulatory B cell (Breg) subset that produces IL-10. Lately, several other studies have described a significant role for B cells in suppressing allergic and autoimmune responses.

This paper is focused on the role of Breg cells on allergy. We describe the types and mechanisms of action of B cells and their role in the pathogenesis of several allergic diseases (allergic asthma, allergic rhinitis, food allergy, contact hypersensitivity and anaphylaxis).

B Regs: types and mechanisms of action and their role in allergy

Several subsets of Breg cells with different phenotypes and suppressive mechanisms have been described in both mice and humans (Table 1).

Murine Breg subsets, subdivided into $CD5^+$ B1a and $CD5^-$ B1a, are mainly found in the peritoneal and pleural cavities. B1a-like cells have been identified as a relevant source of IL-10. Furthermore, in mice, $CD5^+CD1d^{hi}$ (B10) cells have been identified. These cells share some characteristics with B1a B cells but also with other B cell subsets. Other phenotypes of Breg resembling B2 B cells have been described. B2 cells can be divided into follicular B cells, which are found in circulation and secondary lymphoid tissues, and marginal zone (MZ) B cells. Follicular and MZ B cells come from immature precursors in bone marrow, called transitional B cells. In mice both transitional MZ precursor B cells ($CD19^+$ $CD21^{hi}$ $CD23^{hi}$ $CD24^{hi}$ $IgM^{hi}IgD^{hi}CD1d^{hi}$) and MZ B cells ($CD19^+CD21^{hi}CD23^-CD24^{hi}IgM^{hi}IgD^{lo}CD1d^{hi}$) have been associated with IL-10–mediated immunoregulatory functions. Briefly, in mice, several types of Breg cells have been described, such as transitional 2 marginal-zone precursor (T2-MZP) cells, $CD5^+CD1d^{hi}$ B (B10) cells, marginal-zone (MZ) B cells, $CD138^+$ plasma cells, and plasmablasts. [9] Phenotypically, murine B10 cells are cells that secrete IL-10 and are

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characterized by expression of CD5 and CD1d. In fact, this specific subset, B10 cells, but also splenic transitional 2-marginal zone precursor B cells (T2-MZP), are both know to inhibit immune responses through the production of IL-10. [10]

In humans, several B cell subsets have been described as having regulatory capacities. Two main populations were identified: $CD19^{+}CD24^{hi}CD38^{hi}CD1d^{hi}$ and $CD19^{+}CD24^{hi}CD27^{+}$ Breg cells. The most common definition of Breg cells, however, includes cells with the phenotype $CD19^{+}CD38^{+}CD24^{+}$ and intracellular IL-10 expression [11] found among immature transitional B cells. Human Br1 cells are characterized by a $CD73^{-}CD25^{+}CD71^{+}$ phenotype and have been studied in the context of allergen tolerance induction. [12] Functionally, Br1 or B10 cells are IL-10-producing regulatory B cells, and both nomenclatures are used in literature.

The "hygiene hypothesis" postulated by Strachan[13], states that the increasingly clean and sterile environment of modern life has promoted the development of many diseases, including asthma. Subsequent substantial evidence has supported this theory.[14] During the last decades, the lifestyle changes have transformed the non-harmful coexistence with our commensal microbiome, leading to a loss of opportunities to acquire microorganisms, considered "microbial friends". Some of these organisms have beneficial properties. [15] According to this hypothesis, the loss of exposure to microorganisms increase the prevalence of many diseases such as asthma. [14]

Epidemiological studies have reported an inverse association between parasitic infections, extremely prevalent in developing countries, and allergic disorders. [16, 17] Helminth infections induce strong Th2 responses and IgE production. The incidence of allergic disorders is lower among subjects infected by helminths than among non-infected subjects. [17] Moreover, Breg cells production might be induced by bacterial or parasitic infections. [12]

Breg cells that are induced by helminths are typically from the $CD5^{+}CD1d^{hi}$ B10 subset, and their effect is mostly mediated through IL-10 secretion. [12] Additionally, other types of Bregs can be induced on helminth infection. The follicular $CD19^{+}CD23^{hi}$ B cell subset, might also suppress inflammatory responses. Adoptive transfer of these cells strongly suppresses allergic airway inflammation in an ovalbumin-sensitized mice model. [12]

An *in vitro* culture system showed that *Schistosoma mansoni* induces IL-10-producing $CD1d^{hi}$ Breg cells, and the transfer of this Breg subset suppresses allergic airway inflammation in ovalbumin-sensitized mice. [17] These findings suggest that helminthic infections have a direct impact on Breg cells function.

Infection with *S. mansoni* has been associated with high levels of IL-10– and TGF-β1–producing B cells that can inhibit the production of IL-4, IFN-γ (interferon-gamma), and IL-17 by T cells and mediate conversion of effector T cells into $CD25^{hi}Foxp3^{+}$ IL-10-producing Treg cells. Thus, helminth infections can contribute to an immunoregulatory environment and promote dampening of Th1 and Th17, but also

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Th2-skewed pathologies. [12] Infection with *S. mansoni* showed to be protective in an experimental model of systemic anaphylaxis. [18] This effect was dependent on induction of IL-10–producing B cells, which had a 2-fold increase in *S. mansoni*–infected mice and can protect against allergic hypersensitivity. [18] These data illustrate the delicate balance between protective regulatory (IL-10) responses mediated by parasite induction and harmful (IL-4) allergic responses. [18]

Thus, the capacity of Breg cells to suppress allergic airway inflammation seems to depend on the expression of CD1d, particularly in the mouse, but also presents an IL-10-dependent mechanism. [7, 19-21] Studies performed by van der Vlugt [16, 22] have shown that Schistosomes induce regulatory responses in both human and mouse $CD1d^{hi}$ B cells, and that they can restore allergic inflammation by IL-10 production. Schistosoma-infected children had an overexpression of $CD1d^{hi}$ B cells in peripheral blood compared to uninfected children. Moreover, these cells produced higher levels of IL-10. [16]

The recognition of microbial antigens through toll-like receptors (TLR) and the TLR signal mediator MyD88 induces B cells which can suppress inflammation during microbial infection. Several works in both animals and humans have demonstrated the protective role TLR activation (by parasites and other microbes) towards allergy. [23] Infection with parasites promotes the development of Breg cells and protects from allergic inflammation. [16, 17] According to this, animal models with B-cell-specific deficiency in both TLR2 and TLR4 developed a chronic form of experimental autoimmune encephalomyelitis, similar to chimeric models with IL-10-deficient B cells. [23] Microarray analysis of $CD19^{+}CD1d^{hi}$ Breg cells from mice infected with *S. mansoni* demonstrated increased expression levels of TLR7. [24] The activation of the TLR7 pathway in $CD19^{+}CD1d^{hi}$ B cells increases their capacity to produce IL-10. The adoptive transfer of TLR7-elicited $CD19^{+}CD1d^{hi}$ B cells could reduce airway inflammation and was associated with airway hyperresponsiveness. TLR7 stimulation leads to the expansion of IL-10-producing $CD19^{+}CD1d^{hi}$ B cells, which can suppress allergic lung inflammation through induction of Treg cells. [24]

Breg cells have shown to induce pulmonary infiltration of Treg cells, in a Transforming Growth Factor (TGF)-β independent way, leading to a suppression of allergic airway inflammation. [21] Breg cells generated *ex vivo* also suppressed the development of allergic airway inflammation. Furthermore, the transfer of these regulatory B cells did reverse the established airway inflammation in sensitized mice.[21] Helminth-induced Bregs cells were able to suppress Th2 cells and induce Treg cells, which further inhibited the Th2 responses during allergic inflammation. [21, 25, 26]

Specific immunotherapy has proven to induce an allergen-specific expansion of Breg cells, supporting their role in the establishment of allergen tolerance. The regulatory functions of B cells are not exclusively IL-10 dependent. There are other regulatory mechanisms mediated by B cells such as the production of TGF-β, the

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promotion of T-cell apoptosis by Fas–Fas ligand or granzyme-B pathways, and the capacity to produce inhibitory IgG4 and sialylated IgG, both able to mediate anti-inflammatory mechanisms. [3, 23, 26] Considering this, Breg cells are regarded as interesting targets for the development of new therapies to induce allergen tolerance.

Allergic Asthma

Animal studies have demonstrated that IL-10-producing B cells can modulate T-cell responses, by induction of IL-10-producing T cells or $Foxp3^+$ Treg cells. [25, 27, 28] The $CD24^{hi}CD27^+$ Breg subset is responsible for the induction of $IL\text{-}10^+$ $CD4^+$ T cells. In patients with allergic asthma, Breg cells were significantly reduced and they also had a lower capacity to produce IL-10 in response to lipopolysaccharide (LPS). Besides the lower numbers of $CD24^{hi}CD27^+$ B cells, asthmatic patients also had lower IL-10 production by T and B cell co-culture in response to house dust mite allergen. This impaired regulatory activity, particularly the impaired ability of $CD24^{hi}CD27^+$ B cells to induce $IL\text{-}10^+$ T cells, supports the idea of a weakened Breg function in patients with allergic asthma. [29]

Deeper analysis of the Breg cells phenotype has revealed that CD9 is a specific marker for Breg cells in mice and humans. [30, 31] In humans, the expression of CD9 is dramatically increased at the surface of $CD24^{hi}CD38^{hi}$ immature B cells, described as an important IL-10-secreting Breg subset, able to control T-cell inflammation. [32-34] Recently, Braza *et al.* [30] showed that this new regulatory B cell subset, $CD9^+$ Breg cells, inhibits house dust mite–induced allergic airway inflammation. Initially the authors showed that the induction of allergic asthma alters the homeostasis of $IL\text{-}10^+$ Breg cells, increasing the production of inflammatory cytokines by B cells. The frequency of $IL\text{-}10^+$ Breg cells was decreased in the spleen and lungs of asthmatic mice. Moreover, the adoptive transfer of $CD9^+$ B cells normalized airway inflammation and lung function by inhibiting Th2- and Th17-driven inflammation in an IL-10-dependent manner, restoring a favorable immunological balance in lung tissues. Interestingly, the adoptive transfer of $CD9^+$ Breg cells controlled the expansion of lung effector T cells resulting in a higher local regulatory/effector T cells ratio. Thus, $CD9^+$ Breg cells may prevent the development of asthma by inhibiting allergic airway inflammation via IL-10-dependent mechanisms, and likely contribute to immunological tolerance induction in allergic airway inflammation.

Allergic rhinitis

Recently, Kim *et al*. found that subjects with allergic rhinitis had lower levels of Breg cells than nonallergic controls. [35] This study demonstrated a significant reduction in T follicular helper (TFH)-like cells ($CD4^+PD\text{-}1^+CXCR5^+$) and their corresponding IL-21 production in individuals with allergic rhinitis comparing with nonallergic subjects. The authors made the novel observation that Breg cells and TFH cells are both present in human lung lymph nodes. Considering that the production of

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Breg cells is influenced by TFH cells, the decrease of TFH-like cells in allergic rhinitis may contribute to the reduced numbers of Breg cells. [35]

Food allergy

In food allergic patients, the inhibitory role of IL-10-producing $CD5^+$ B cells has been described. [19] Interesting results showing the clinical relevance of B reg cells came up from some studies on specific oral immunotherapy (SOIT) protocols in patients with cow's milk allergy (CMA). [36]

However, another regulatory B cell subset that produces TGF-β was recognized. These cells play essential roles in the induction of tolerance to non-IgE mediated food allergy in atopic dermatitis. [19] TGF-β-producing Breg cells (Br3) were characterized in allergic responses to cow's milk. [37] A study performed by Lee *et al* [37] with milk-allergic and milk-tolerant subjects, submitted to *in vitro* casein stimulation, has shown that Br3 proliferated in response to allergen stimulation in the milk-tolerant group, but not in the milk-allergy group. Hence, Br3 may be involved in allergy tolerance by negative regulation with TGF-β.

Noh *et al.* [38] performed *in vitro* allergen (casein) stimulation of blood mononuclear cells from CMA patients and milk-tolerant subjects who had already outgrown CMA. Patients with CMA showed decreased levels of peripheral IL-10-producing regulatory B cells (Br1). In response to casein stimulation, Br1 decreased in the CMA group and significantly increased in the milk-tolerant group. Allergen stimulation in the milk-tolerant subjects induced the proliferation of Br1, suggesting a role for these cells on allergen tolerance. On the other hand, apoptotic non-IL-10-producing Breg cells increased by allergen stimulation in the milk allergy group. Considering these results, Br1 cells appear to be involved in the acquisition of immune tolerance in patients with food allergies, probably through IL-10 production. [38]

Whereas oral tolerance induced by ingestion of milk alone did not improve clinical outcomes, milk intake associated to IFN-γ injections completely suppressed the disease. SOIT protocols with IFN-γ have been associated with tolerance induction in IgE-mediated[39, 40] and non-IgE-mediated food allergies. [40] IFN-γ is a representative Th1 cytokine and Th1/Th2 imbalance is the critical immune mechanism of allergic diseases, including food allergy. [41] IFN-γ seems to contribute as an immunomodulatory agent with tolerogenic effects, increasing allergen-specific Br1 cells. [41] Immunotherapy with IFN-γ was first attempted to desensitize against house dust mites for atopic dermatitis[42], and subsequently applied in SOTI (specific oral tolerance induction) protocols for food allergy. [36] Patients receiving IFN-γ and milk showed significantly higher proportions of Br1 cells, and after *in vitro* restimulation of peripheral blood mononuclear cells with casein. [36] Considering the total numbers, Br1 cells decreased following allergen stimulation before SOTI protocols, but increased after. [36]

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In vitro stimulation of peripheral blood mononuclear cells from milk allergy patients (non-IgE mediated) and milk-tolerant subjects, showed that Br1 responses were not induced by IFN-γ alone, without allergen (casein) stimulation, but were induced when IFN-γ was simultaneously administered with casein. [41]

Br3 cells demonstrated similar responses in non-IgE-mediated food allergy and proliferated in response to allergen stimulation in milk-tolerant subjects. [37]

Both Br1 and Br3 cells seem to be critical to induce immune tolerance in non-IgE-mediated food allergy related to atopic dermatitis. [19]

SOTI protocols were attempted using IFN-γ as an adjuvant in a study performed by Noh *et al.* [39], which included 25 patients with IgE-mediated anaphylactic food allergy to milk, egg, or wheat. IFN-γ-induced SOTI (ISOTI) was conducted in 10 patients, while five patients were treated only with food, five patients received only IFN-γ, and five patients did not receive any treatment. Tolerance was successfully induced in all patients with ISOTI, while no patients acquired tolerance in the control groups. Simultaneous allergen stimulation with nonspecific immunomodulation of IFN-γ was important to achieve specific tolerance in IgE-mediated anaphylactic food allergy. [39]

Kim *et al.* [43] demonstrated that MLN (mesenteric lymph node)-derived IL-10-producing $CD5^+$ B cells can suppress casein-induced allergic responses in a mouse model via induction of $Foxp3^+$ regulatory T cells in an IL-10-dependent manner. IL-10-producing $CD5^+$ B cells appear to be critical to promote the development of oral tolerance to casein. IL-10-producing $CD5^+$ B cells were increased in MLN, but not in spleen nor peritoneal cavity, in casein-tolerant mice. Interestingly, previous reports had already showed that oral tolerance cannot be induced in mice lacking MLN. [44, 45] Moreover, the adoptive transfer of mesenteric $CD5^+$ B cells from casein-tolerant mice suppressed allergic symptoms, highlighting the role of this subset in tolerance induction.

A particular Breg population, tolerogenic B cells ($CD5^+CD19^+CX3CR1^+$), is capable of inducing Treg cells in the intestine and suppress food allergy-related Th2-mediated pattern of intestinal inflammation in mice. [46]

Hymenoptera venom allergy

IL-10-producing regulatory B cells suppress immune responses through T cell-dependent mechanisms. Human $IL\text{-}10^+$ Br1 cells, namely those with the phenotype $CD73^-CD25^+CD71^+$, known to produce high levels of IL-10, can potently suppress antigen-specific $CD4^+$ T cell proliferation. [47] Also, IgG4 production appears to be selectively confined to human Br1 cells. [47] Concerning hymenoptera venom allergy, specific B cells for the major bee venom allergen phospholipase A2 (PLA), isolated from nonallergic beekeepers, showed increased production of IL-10 and IgG4. Furthermore, the frequency of $IL\text{-}10^+$ PLA-specific B cells (Br1) increased in allergic patients receiving

allergen-specific immunotherapy, supporting the concept that Breg cells are important for the establishment of allergen tolerance. [47]

A recent study provided a detailed characterization of the allergen-specific B-cell response before and during bee venom immunotherapy, comparing allergic patients to healthy beekeepers, before and during the beekeeping season. The authors observed that a high-dose bee venom exposure induces similar tolerogenic B cell responses in allergic patients and healthy beekeepers, after venom exposure. Both groups showed increased frequencies of plasmablasts, PLA-specific memory B cells, and IL-10-secreting $CD73^{-}CD25^{+}CD71^{+}$ Br1 cells. PLA-specific IgG4-switched memory B cells expanded after bee venom exposure. These findings suggested a similar functional immunoregulatory role for B cells in allergen tolerance in both groups. [48]

Contact hypersensitivity

The lack, or loss, of regulatory B cells can exacerbate symptoms of contact hypersensitivity (CHS) [10, 19]. B10 cells were regarded as regulators of inflammation in murine models of CHS. [11, 49] CHS is exacerbated in CD19-deficient mice. CD19 expression is critical and CD19 loss resulted in increased and prolonged reaction of CHS, suggesting an inhibitory role of CD19 expression in CHS. [50] Yanaba et al. [51] reported the existence of a B cell subset characterized by the phenotype $CD19^{hi}CD1d^{hi}CD5^{+}$, capable of suppressing experimental induced CHS in an antigen-restricted and IL-10-dependent manner. [51, 52] Adoptive transfer of this specific B cell subset, derived from sensitized animals, showed to be effective in reducing inflammation in recipients sensitized with the same chemical, but not with a different one. Apparently, these data expose an underlying specificity in Breg cells response in CHS. [51, 52]

Pregnancy and allergy

Pregnancy represents an unpredictable challenge to the immune system, requiring a critical balance to assume tolerance towards the fetus, without compromising immunological competence.

A prospective observational study performed by Lima *et al.* [53] reported that the absolute counts and percentages of the majority of the B cell subsets were significantly lower in the third trimester of pregnancy and on the delivery day, comparing to non-pregnant women. Moreover, the percentages of naïve B cells were significantly higher in the third trimester and on delivery day and $CD24^{hi}CD38^{hi}$ Breg cells were significantly higher in the postpartum. [53] These data support the idea that the peripheral B cell compartment undergoes quantitative changes during normal late pregnancy and postpartum.

Modifications in T and B cell subsets in asthmatic pregnant women have also been reported. [54] Martins *et al.* described that, in asthmatic pregnant women, $CD24^{hi}CD38^{hi}$ Breg cells were decreased during pregnancy and increased significantly in the postpartum, as observed in healthy pregnant women. Similar levels of Treg cells were observed in both asthmatic and pregnant women, compared to non-pregnant women. However, Foxp3 expression in Treg cells was impaired during pregnancy in asthmatic and healthy pregnant women, recovering postpartum. Though the reduction is more noticeable in healthy pregnant women than in asthmatics, both groups significantly downregulated Foxp3 expression in the third trimester of pregnancy compared to non-pregnant women. At postpartum, Foxp3 expression levels increased significantly in both groups. These results, describing similar patterns for Breg cells and Fox p3 expression within T reg cells, corroborate a close interaction between T and B regulatory cells in immune responses during pregnancy, also present in asthmatic patients.

Maternal exposure to an environment rich in microbial compounds might protect against the development of atopic sensitization. [55] It was demonstrated that in early life, immune cells preferentially produce IL-10 after stimulation with TLR ligands. [56] Accordingly, neonate mice exhibited higher levels of Breg cells than adult mice. [51] Lower TLR4-mediated IL-10 production might play a causal role in the development of atopic dermatitis in children. [51] Patients with allergic asthma showed reduced TLR4-induced IL-10 production by B10 cells when compared to healthy controls. [29] All these findings support a potential role for IL-10 Breg cells in the early control of allergic diseases. It is speculated that early exposure to pathogens can enhance the generation of Breg cells, being an important protection against allergy, probably through the maintenance of Treg cells. [16, 21, 23]

Conclusions

There is strong evidence to accept the prominent role of regulatory B cells in allergic inflammation. Moreover, human studies have found elevated levels of allergen-specific IL-10-producing Breg cells after immunotherapy, suggesting that Breg cells have a critical role in tolerance induction. However, further investigations are needed, mainly human studies, to clarify the exact mechanisms and the influence of Breg cells.

In the future, it will be important to evaluate, in large cohorts, the impact of Breg cells for the modulation of allergic diseases and the potential use of this knowledge for targeted therapies in allergic disorders.

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Table 1. Historic perspective and phenotypic characterization of human and mice Breg cell subsets. [adapted from van de Veen [12]]

Model	Date	Phenotype (designation)	Associations
Human	2008	$C1d^{hi}$	MS, [57] CHB, CHCC[58]
	2010-12	$CD19^{+}CD24^{hi}CD38^{hi}$ (immature cells)	SLE, RA,[34] CHB[59]
	2011	$CD27^{+}CD24^{hi}CD148^{hi}CD48^{hi}$ (B10 cells)	RA, SLE, SS, autoimmune vesiculobullous skin disease, MS (higher levels compared with healthy controls) [60]
	2013	$CD73^{-}CD25^{+}CD71^{+}$ (Br1 cells)	Nonallergic beekeepers and patients receiving allergen-specific immunotherapy (allergen tolerance)[47]
	2014	$CD27^{int}CD38^{+}$ (plasmablast)	Healthy donors (regulatory role in autoimmune inflammation) [61]
	2014	$CD19^{+}CD25^{+}$	MS[62]
	2015	$CD5^{+}CD24^{hi}CD38^{hi}$	ANCA-associated vasculitis[63]
	2013-15	$CD19^{+}CD24^{hi}CD38^{hi}$	ITP,[64] pemphigus,[65] RA,[66] SS[67]
Mice	2002, 2013	$IgM^{hi}CD5^{+}CD1d^{hi}$ $FasL^{+}$ (killer B1a cells)	*S mansoni* infection[68, 69]
	2007-08	$CD19^{+}CD5^{+}$ (B1a cells)	Neonatal acute inflammation,[70] chronic colitis[71]
	2008-2015	$CD19^{+}CD1d^{hi}CD5^{+}$ (B10 cells)	Contact hypersensitivity,[72] EAE,[73] lupus,[74] EAMG,[75] collagen-induced arthritis,[76] colitis,[77] allergic airway inflammation[21, 24]
	2013	Tolerogenic $CX3CR1^{+}$ B cells	Food allergy-induced intestinal inflammation[46]
	2007, 2009, 2015	$CD19^{+}CD21^{hi}CD23^{hi}$ $CD24^{hi}IgM^{hi}IgD^{hi}CD1d^{hi}$ (transitional 2 B cells)	Experimental arthritis,[78] lupus,[79] tolerance induction and allograft survival[80]
	2009	$B220^{+}CD21^{+}CD22^{+}CD23^{+}CD24^{+}$ $CD1d^{+}CD138^{+}IgD^{+}IgM^{+}$ (GIFT-15 B cells)	EAE[81]
	2012	$CD24^{hi}IgM^{hi}IgD^{lo}CD1d^{hi}$ (MZ B cells)	*Leishmania donvani* infection[82]
	2016	$CD19^{+}CD21^{hi}CD23^{-}$ (MZ precursor B cells)	Allograft survival[83]
	2014-15	$IgM^{+}CD138^{hi}TACI^{+}CXCR4^{+}$ $CD1d^{int}TIM1^{int}$ $CD138^{hi}PD\text{-}L1^{+}B220^{+}IgA^{+}$ (plasma cells)	EAE, *S enterica* infection,[84] tumors[85]
	2014	$CD138^{+}CD44^{hi}$ (plasmablast)	EAE[61]
	2014-16	$IL\text{-}35^{+}$Breg (i35-Breg)	EAE,[84] EUA[86-88]

ANCA, antineutrophil cytoplasmic autoantibody; CHB, chronic hepatitis B; CHC, chronic hepatitis C; EAE, experimental autoimmune encephalomyelitis; EAMG, experimental autoimmune myasthenia gravis; EAU, experimental autoimmune uveitis; GIFT15, granulocyte-macrophage colony-stimulating factor and interleukin-15 'fusokine'; ITP, immune thrombocytopenia; MS, multiple sclerosis; MZ, marginal zone; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren syndrome