

Regulatory B-cell induction by helminths: Implications for allergic disease

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Chronic helminth infections are often associated with a reduced prevalence of inflammatory disorders, including allergic diseases. Helminths influence the host immune system by downregulating T-cell responses; the cytokine IL-10 appears to play a central role in this process. Over the last decade, evidence has emerged toward a new regulatory cell type: IL-10-producing B cells, capable of regulating immunity and therefore termed regulatory B cells. Initially, regulatory B cells have been described in autoimmunity models where they dampen inflammation, but recently they were also found in several helminth infection models. Importantly, regulatory B cells have recently been identified in humans, and it has been suggested that patients suffering from autoimmunity have an impaired regulatory B-cell function. As such, it is of therapeutic interest to study the conditions in which IL-10-producing B cells can be induced. Chronic helminth infections appear to hold promise in this context as emerging evidence suggests that helminth-induced regulatory B cells strongly suppress allergic inflammation. In this review, we will discuss the conditions under which regulatory B cells are present, leading to a state of tolerance, as well as the conditions where their absence or functional impairment leads to exacerbated disease. We will summarize their phenotypic characteristics and their mechanisms of action and elaborate on possible mechanisms whereby regulatory B cells can be induced or expanded, as this may open novel avenues for the treatment of inflammatory diseases, such as allergic asthma. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: *Regulatory B cells, IL-10, regulatory T cells, helminths, allergy, asthma*

Affluent countries are facing an increase in the prevalence of hyperinflammatory disorders, such as allergies or autoimmunities. It has been suggested that (parasitic) infections suppress the development of these diseases. Changes in lifestyle and

Abbreviations used

BAFF: B cell-activating factor
DC: Dendritic cell
EAE: Experimental autoimmune encephalomyelitis
MS: Multiple sclerosis
MZ: Marginal zone
T2: Type 2
TLR: Toll-like receptor

improved health care have resulted in a substantial reduction in infectious diseases. Consequently, this may lead to insufficient maturation of the regulatory arm of the immune system, allowing uncontrolled expression of inflammatory responses against either innocuous or self-antigens later in life. This hypothesis is supported by evidence from epidemiological studies showing that in human populations with high rates of parasitic infections, particularly helminth infections, the prevalence of allergic diseases is considerably lower. The protective effect of helminths is most likely explained by the downregulation of the immune system during chronic helminth infection, causing spillover suppression to bystander allergens. Immunosuppression during helminth infection has been attributed to the increased activity of regulatory T cells (Treg cells), alternatively activated macrophages, and, more recently, regulatory B cells (Breg cells).

Traditionally, B cells are known for their capacity to produce antibodies, thereby contributing to humoral immunity and clearance of pathogens. B cells can also be pathogenic: in autoimmune disease, they contribute to destruction of self by the production of autoantibodies. Indeed, experimental depletion of B cells in humans by using CD20 monoclonal antibody (rituximab) proved an effective treatment for patients suffering from various autoimmune disorders such as systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody-associated vasculitis, or rheumatoid arthritis. Unexpectedly, B-cell depletion in models for experimental autoimmune encephalomyelitis (EAE) or chronic colitis exacerbated disease. This led to the hypothesis that B cells may also play an immunoregulatory role. Dissection of the underlying mechanisms revealed that in addition to pathogenic B cells, protective B cells are induced throughout the course of autoimmune disease. Fillatreau and coworkers were one of the first to show that these protective B cells negatively regulated EAE progression through provision of IL-10 and termed them Breg cells. Additional studies by Mizoguchi, Mauri, and others confirmed the presence of active IL-10-producing Breg cells in other autoimmune models, that is, inflammatory bowel disease or collagen-induced arthritis. Soon it was discovered that IL-10-producing Breg cells could be induced by

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TABLE I. Overview of different Breg cell subsets, their phenotypic characteristics, and their mechanism of action

Breg cell phenotype	Additional markers	Mouse/human	Organ	Mechanism of action	Disease model/patients	Helminths	References
T2 precursor MZ	CD1d ^{hi} CD5 ⁺	Mouse	Spleen	IL-10, Treg cells, T _H 1/T _H 17 suppression	CIA, lupus	None	6-8
CD1d ^{hi}	CD21 ^{hi} CD23 ^{hi}	Mouse	Spleen	IL-10, Treg cells	AAI (ovalbumin)	<i>S. mansoni</i>	1,2
CD1d ⁺ CD5 ⁺	CD21 ^{hi}	Mouse	Spleen, peripheral LNs	IL-10, APC suppression	EAE, CHS, lupus	None	9-11
CD23 ^{hi}	None	Mouse	Mesenteric LNs	Unknown	AAI (Der P1) & EAE	<i>H. polygyrus</i>	3
B1 cells	CD5	Mouse	Peritoneal cavity	IL-10, CD22	CHS	None	12
CD1d ^{hi}	None	Human	Peripheral blood	IL-10, T-cell suppression	MS	Mixed helminth infections	13
CD24 ^{hi} CD38 ^{hi}	CD1d ^{hi} CD5 ⁺	Human	Peripheral blood	IL-10, T-cell suppression	SLE		14
CD24 ^{hi} CD27 ⁺	CD1d ^{hi} CD5 ⁺ CD38 ⁺	Human	Peripheral blood	IL-10, APC suppression	None	None	15
CD5 ⁺	None	Human	Peripheral blood	IL-10	Food allergy (milk)	None	16

AAI, Allergen-induced airway inflammation; APC, antigen-presenting cell; CHS, oxazolone-induced contact hypersensitivity; CIA, collagen-induced arthritis; LNs, lymph nodes.

extrinsic factors such as helminth parasites. In this review, we highlight the latest findings on both mouse and human Breg cells, with emphasis on helminth-induced Breg cells and their capacity to protect against allergic inflammation (in mice) or autoimmunity (in humans).

DIFFERENT HELMINTHS INDUCE BREG CELLS AND PROTECT AGAINST ALLERGIC DISEASES

Schistosoma mansoni

The majority of studies on Breg cells in helminth infection employed adoptive transfer experiments and used suppression of disease symptoms, protection against disease development, or both as a read-out for Breg activity. It has been demonstrated that B cells induced by *Schistosoma mansoni* worms protect mice against allergic reactions in both anaphylaxis and allergic airway inflammation models in an IL-10-dependent manner.¹ In this model, only male parasites were used for inducing infection, yielding infections without eggs. Instead, we studied Breg cell function during different stages of natural *S. mansoni* infections and showed the existence of active regulatory mechanisms during chronic, but not acute, infection. Both splenic B cells and CD4⁺ T cells isolated from chronically, but not acutely, infected mice protected against allergic airway inflammation via IL-10, revealing active roles for both IL-10-producing B cells and CD4⁺ T cells.²

Heligiosomoides polygyrus

The concept that helminth-induced B cells can protect against allergic inflammation has been extended to other helminth infections that are natural for mice: in *H. polygyrus*-infected mice, adoptive transfer of mesenteric lymph node B cells suppressed both DerP1-specific airway inflammation and EAE.³ However, in contrast to other models, IL-10 production by *H. polygyrus*-induced B cells was not required to provide protection against either disease. This finding may suggest that other molecules or mechanisms such as direct interactions with host cells may be involved in suppressing disease symptoms.

Taken together, these studies show that helminths can induce Breg cells that can protect against allergic diseases and that this process is particularly active during the chronic stage of infection. Furthermore, it can be concluded that the suppressive ability of Breg cells is not restricted to T_H1 immune responses associated with autoimmunity.

Other pathogens

Interestingly, recent reports indicated that Breg cell development is restricted not only to helminth parasites but can also be seen during other infections, such as those caused by *Leishmania major*⁴; during these infections, IL-10-producing B cells were critical for the development of unprotective T_H2 responses and susceptibility to infection. In addition, murine cytomegalovirus has been shown to induce IL-10-producing Breg cells, resulting in decreased virus-specific CD8⁺ T-cell responses and plasma cell expansion.⁵ These data indicate that as for Treg cells, infections other than those caused by helminths can lead to the development of Breg cells.

IDENTIFICATION OF B-CELL SUBSETS ASSOCIATED WITH A REGULATORY FUNCTION

Regulatory B-cell subsets in models of autoimmunity

In the last few years, several studies focusing on the splenic compartment identified marginal zone (MZ) and transitional type 2 (T2)-MZ precursor B cells as B cells with a putative suppressive function. In addition, IL-10 production by splenic B cells has been linked to B cells expressing high levels of CD1d with or without the expression of CD5 (Table I). In this respect, pioneering work has been performed in models of EAE¹⁷ and oxazolone-induced contact hypersensitivity⁹ where an IL-10-dependent protective role for splenic CD1d^{hi}CD5⁺ B cells was identified. This relatively rare regulatory B cell subset was termed B10 cells.⁹ Further characterization revealed that approximately half of the splenic CD1d^{hi}CD5⁺ IL-10-producing B cells expressed high levels of CD21, similar to MZ B cells (CD21^{hi}CD23^{low}IgM^{hi}).⁹ Another major contribution to the field was made by the use of chimeric mice lacking endogenous IL-10 producing B cells in an arthritis model. These mice showed the exacerbation of the disease with a marked increase in T_H1 and T_H17 cells compared with wild-type B-cell mice.⁶ Reconstitution of B-cell-deficient mice showed that transitional T2-MZ precursor B cells (CD21^{hi}CD23^{hi}IgM^{hi}) coexpressing CD1d prevented disease and ameliorated established disease in mice with collagen-induced arthritis^{6,7} (Table I). Moreover, a recent report describes another subset, peritoneal B1 cells, as a source for IL-10 and essential for suppressing the late remission phase of contact hypersensitivity. Interestingly, the authors found an additional role for CD22, a sialic-binding

Ig-like lectin, which was expressed on the IL-10-producing peritoneal B1 cells and was involved in their protective abilities¹² (Table I).

Regulatory B-cell subsets in helminth-infection models

Studies in adult-stage *S. mansoni*-infected mice indicated that splenic CD1d^{hi} B cells have a regulatory function as these cells provided protection against allergic airway inflammation.¹ Analogous to what had been found in the models of autoimmunity (detailed earlier), the CD1d^{hi} B cells expressed CD5, CD21^{hi}, CD23⁺, and high levels of IgM, resembling T2-MZ precursor B cells¹ (Table I). During natural infections with *S. mansoni*, we also found a splenic subset of IL-10-producing B cells that protected against allergic airway disease²; however, in our model, the Breg cells were identified within the MZ B-cell compartment (CD21^{hi}CD23^{low}), with a majority (>80%) coexpressing CD1d (van der Vlugt et al, unpublished data). As T2-MZ precursor B cells can differentiate into MZ B cells, it can be speculated that the splenic Breg cell subsets identified by several laboratories are in fact all similar (Table I).

Interestingly, yet another phenotype of parasite-induced Breg cells is found in the mesenteric lymph node upon infection with *H. polygyrus*. These Breg cells express high levels of CD23, but no CD5 or CD1d, and suppress allergic inflammation in an IL-10-independent manner.³ These results suggest that protection against allergic inflammation is not limited to one subset of Breg cells, raising the question whether differences exist in effector mechanisms of different Breg subsets.

BREG CELL EFFECTOR MECHANISMS

Breg cells can induce suppression by several effector mechanisms and by targeting different cell subsets, as discussed in the following subsections.

Suppression of T-cell responses

The capacity of B cells to suppress T-cell proliferation and/or T-cell cytokine production has been studied in several disease settings. Early work showed that lethal T_H1 responses are expanded in schistosome-infected B-cell-deficient mice, suggesting that in wild-type mice T_H1 cells are suppressed by schistosome-induced B cells. In addition, applying different allergy models^{1,2} clearly indicated that schistosome-induced B cells can also inhibit ovalbumin-specific T_H2 cytokine responses in an IL-10-dependent manner, resulting in reduced allergic symptoms. These findings are in line with studies in autoimmunity models, where IL-10-induced suppression of inflammation was found in EAE,^{10,17} lupus,⁸ or arthritis⁷ by modulating T_H cell proliferation and reducing IFN- γ , IL-2, IL-17, or TNF- α levels; in some studies,^{7,8,10} this suppressive effect was potentiated via CD40 ligation. Furthermore, IL-10-producing B cells were described to inhibit T_H2-mediated colitis in a T-cell receptor alpha knockout model by yet another mechanism that involved the induction of IL-12-producing B cells.¹⁸ Interestingly, IL-10-independent downregulation of T_H2 responses has also been reported by B cells from *H. polygyrus*-infected mice,³ suggesting the involvement of cell-cell interaction or other soluble mediators (Table I).

Recruitment of Treg cells

The concept that B cells can induce Treg cells was first introduced in a model of anterior chamber-associated immune deviation by Ashour and Niederkorn. These findings can be extended to helminth infections, as schistosome-induced CD1d^{hi} B cells promoted expansion of Foxp3⁺ Treg cells in the lung via IL-10.¹ Similar results were found in autoimmunity models, such as lupus,¹¹ where B10 cells reduced inflammation by the induction of Treg cells. Another example is shown in a model of collagen-induced arthritis, where adoptive transfer of T2 MZ precursor B cells induced FoxP3 Treg cells, resulting in reduced T_H1 and T_H17 frequencies and decreased inflammation.⁶ In a model for EAE, B-cell-deficient mice displayed delayed emergence of Foxp3⁺ and IL-10⁺ T cells in the central nervous system, which was corrected by reconstitution with B cells and resulted in recovery from disease.¹⁹ Of note, Breg and Treg cell numbers appear to peak at different disease stages in EAE, with enhanced Breg cell activity during early EAE initiation and Treg cells providing protection during late-phase EAE.¹⁰ Therefore, even though Breg cells may induce Treg cells, Breg cells and Treg cells may have partly independent roles in controlling inflammation.

Antibody-mediated regulation

Recent studies indicate that antibodies may also be involved in the suppression of immune responses. Potential mechanisms include suppression of dendritic cell (DC) activation through the binding of IgG to Fc γ RIIB, as well as IgG-mediated clearance of potentially pathogenic host apoptotic cells. In addition, van de Veen et al have suggested that human IL-10-producing B cells are designated to switch to IgG4 (World Immune Regulation Meeting-V in Davos, Switzerland, personal communication). This may be potentiated by IL-10, which is an important switch factor for IgG4. IgG4 belongs to the group of anti-inflammatory antibody isotypes as it is unable to activate complement. IgA also belongs to this group, and we have recently reported that microbial modulation of DC function was crucial to induce allergen-specific secretory IgA in the mucosa, which suppressed the salient features of asthma.²⁰ Helminths are strong inducers of IgG4 in humans. However, the question remains whether the IgG4-producing B cells present in helminth-infected individuals originate from IL-10-producing B cells and whether helminths harbor similar mucosal IgA-inducing capacities.

DC impairment

It is well known that IL-10 can inhibit DC antigen processing and presentation and expression of costimulatory molecules, such as CD80/CD86. This has clear consequences for their T-cell stimulatory capacity as shown by a recent report, in which purified splenic DCs from mice with EAE were cultured with MOG-specific CD4⁺ T cells. Less T-cell proliferation was seen when DCs were conditioned by CD1d^{hi}CD5⁺ B cells compared with conditioning by CD1d^{low}CD5⁺ B cells. This effect was IL-10 dependent.¹⁰ These findings may be extended to parasite-induced Breg cells as *L. major*-exposed B cells were shown to suppress DC cytokines in an IL-10-dependent manner *in vitro*.⁴ Interestingly, we observed that myeloid DC function was impaired in *Schistosoma heamatobium*-infected individuals.²¹ Although not proven, it is tempting to speculate that the increased Breg activity during schistosome infection, as shown in animal models,^{1,2} is responsible for the altered DC function.

HUMAN BREG CELLS: DO THEY EXIST?

Helminth-induced CD1d^{hi} B cells

The majority of the studies on Breg cells have been conducted in murine models, and little is known about their existence in humans. In 2008, it was first demonstrated by Correale and coworkers that CD1d⁺ B cells were present in the peripheral blood of helminth-infected patients with multiple sclerosis (MS), producing high levels of IL-10 in response to CD40 ligation. B cells from healthy controls and infected patients with MS, but not from uninfected patients with MS, were able to suppress T-cell proliferation in an IL-10-dependent manner *in vitro*.¹³ Phenotypically, the IL-10-producing B cells were similar to their murine counterpart, as they expressed high levels of CD1d, supporting the view that helminths also induce enhanced Breg cell activity in humans.

CD24^{hi}CD38^{hi} immature B cells

Another human regulatory B-cell subset, which is CD19⁺CD24^{hi}CD38^{hi} (so-called immature transitional B cells), was identified by Blair and coworkers in the peripheral blood of healthy individuals. Approximately 70% of these B cells also expressed CD5 and CD1d.¹⁴ The CD24^{hi}CD38^{hi} B-cell population was capable of suppressing IFN- γ and TNF- α secretion by anti-CD3-stimulated T helper cells, and this suppression was dependent on IL-10 and CD80/CD86 costimulation. Interestingly, CD19⁺CD24^{hi}CD38^{hi} B cells isolated from patients with systemic lupus erythematosus were functionally impaired as they could not suppress autologous T helper cytokine production.¹⁴

CD24^{hi}CD27⁺ B cells

Recently, the human equivalent¹⁵ of the mouse B10 cell was identified in several autoimmunity models.^{9,10,11} A rare population was described within peripheral blood B cells that either already produced IL-10 or first required 48 hours of priming before acquiring the ability to express IL-10. B10 cells represented a small subset within the CD24^{hi}CD27⁺ B-cell population, with about 60% coexpressing CD38.¹⁵ Interestingly, both stimulated CD24^{hi}CD27⁺ and CD24^{low}CD27⁻ B cells inhibited IFN- γ and TNF- α production in T helper cells in an IL-10-independent manner. In contrast, CD24^{hi}CD27⁺ B cells inhibited TNF α production by monocytes via IL-10. In contradiction to what had been published previously,¹⁴ increased frequencies of IL-10-producing peripheral blood B cells were found in patients suffering from different autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, blistering skin disease, and MS) compared with healthy controls upon stimulation with CD40 ligand and CpG motifs.¹⁵ However, these studies did not evaluate the functional abilities of human B10 cells from autoimmune patients compared with those from healthy controls with respect to their capacity to reduce T-cell cytokine responses or whether other cytokines were simultaneously expressed in B10 cells from the patients.¹⁵

Other IL-10-producing peripheral blood B cells

In addition to these well-defined Breg cell subsets, IL-10-producing B cells were recently described, which were diffusely scattered throughout the B-cell lineage and not restricted to either the immature transitional B-cell compartment

(CD24^{hi}CD38^{hi}) or the memory B-cell compartment (IgD⁺CD27⁺).²² It was demonstrated that these B cells, obtained from human peripheral blood or spleen, were induced by stimulation with oligonucleotides that contained CpG motifs and anti-Ig and that these cells inhibited T-cell proliferation in an IL-10-dependent manner. Interestingly, stimulation also induced high levels of other cytokines, such as IL-6, IL-12, IFN- γ , and TGF- β . However, as this was not measured at a per-cell basis (ie, by flow cytometry), it is still unclear to what extent IL-10-producing B cells express other cytokines and how this may affect their Breg cell functionality.

All together, these studies show that IL-10-producing Breg cells exist in humans; however, further research is required to fully characterize and functionally define these cells.

SIGNALS FOR BREG CELL INDUCTION

Working models

In many of the previously described studies applying autoimmunity models, MyD88-dependent Toll-like receptor (TLR) signaling (TLR2, 4, and 9) and CD40 ligation, with or without B cell receptor triggering, proved to be important for Breg development (Fig 1). Many of these findings have been paralleled in human *in vitro* studies.^{14,15,22} To integrate all the information on distinct signals required for Breg cell activation and development, several working models have been put forward: Mizoguchi and Bhan have suggested that more than one Breg cell subset exists, with different subsets requiring different activation signals. Innate-type Breg cells are induced by TLR ligands, whereas adaptive-type Breg cells are induced by CD40 and (self) antigens that trigger BCRs. Instead, Fillatreau, Gray, and coworkers have proposed that during autoimmunity, all activated B cells can become suppressors and that these B-cell suppressive functions are acquired during a stepwise activation process initiated by TLR ligands followed by BCR and CD40 reinforcement. Alternatively, Tedder and coworkers have suggested a model in which immature progenitor cells progress into mature B10 cells following ligation by TLRs and CD40.

Signals from helminth antigens: TLR, BCR, and CD40 ligation

How can this information be applied to helminth-induced Breg cell activation and development (Fig 1)? Several reports have suggested that *S mansoni* eggs and adult worm antigens contain TLR ligands: the egg-derived carbohydrate lacto-N-fucopentaose (LNFPIII) ligates TLR4, at least on DCs, and induced B lymphocyte IL-10 production. Furthermore, we previously reported that lysophosphatidylserine, a lipid derived from soluble *S mansoni* worm antigens, can bind to TLR2 on human monocytes-derived DCs and promote Treg cells activity. Moreover, it was demonstrated that soluble egg antigen (SEA) could modify immune responses by both human B cells and DCs via TLR2.²³ More evidence for the involvement of TLR signaling in microbial-induced Breg cell development comes from reports describing nonparasitic infections: B cell ligation by TLR2 ligands from *Helicobacter* species suppressed *Helicobacter*-induced immunopathology by inducing Treg cells.²⁴ MyD88 signaling in B cells suppressed protective immunity during *Salmonella typhimurium* infections via IL-10, affecting neutrophils, natural killer cells, and effector T cells.²⁵ Lastly, Amu et al

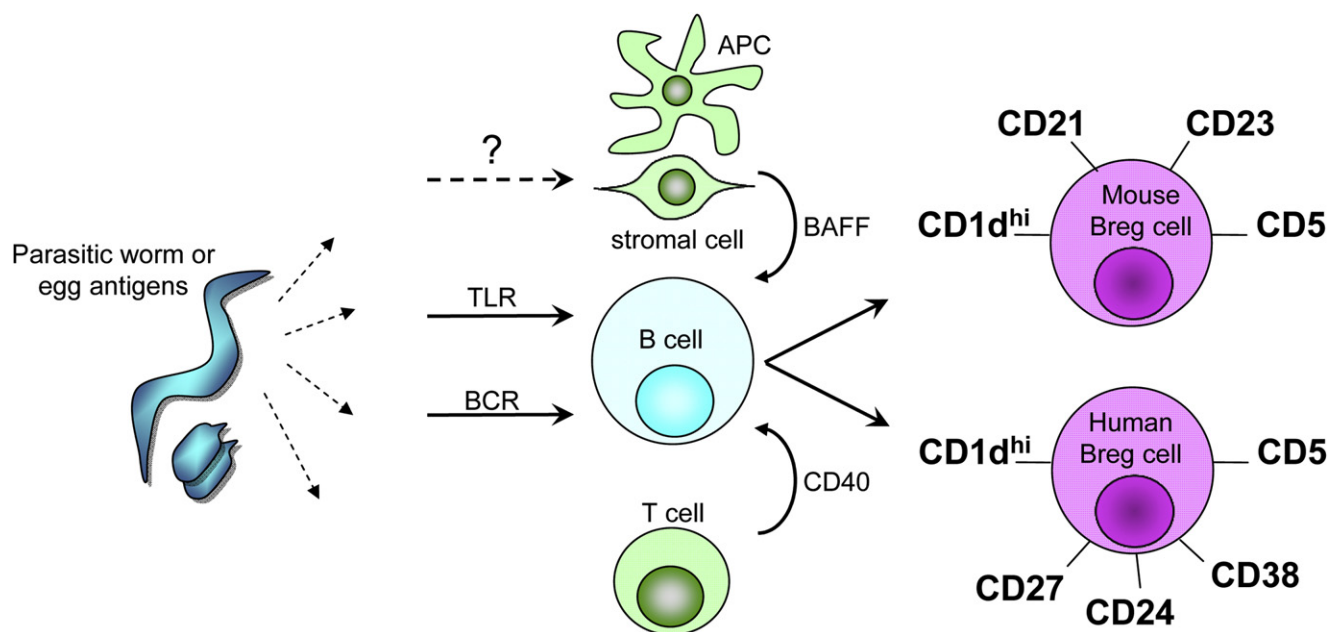


FIG 1. Signals for Breg cell development. Helminth antigens support Breg cell development either directly via TLRs and/or BCR cross-linking plus CD40 ligation or indirectly via BAFF produced by stromal cells or local antigen-presenting cells. Typical mouse Breg cell markers are CD1d^{hi}, CD5, CD21, and/or CD23. Typical human Breg cell markers are CD1d^{hi}, CD5, CD24, CD27, and/or CD38.

showed that *in vitro* exposure of splenic B cells to live schistosome worms induced functional IL-10-producing Breg cells,¹ supporting the notion that direct interactions between helminth molecules and B cells may be involved in the induction of Breg cells. However, in this study, the involvement of TLR signaling was not assessed. Therefore, further studies need to be conducted to identify the (nature of) helminth antigens and the molecular details of their interaction with the immune system, answering the question whether different B cell subsets can be stimulated, depending on the stimuli (helminth molecules), to secrete IL-10. In addition, a possible role for CD40 ligation, either alone or with BCR triggering, to mediate helminth-induced Breg cell development needs to be clarified.

Signals from helminth: Soluble factors

Interestingly, endogenous apoptotic cells²⁶ or soluble factors, such as B cell-activating factor (BAFF),²⁷ may also provide signals for Breg cell activation (Fig 1). BAFF induced IL-10-producing splenic Breg cells *in vitro*, which were mainly derived from MZ B cells and had a distinct CD1d^{hi}CD5⁺ phenotype. In addition, intraperitoneal injection of BAFF increased IL-10-producing B cells in the MZ areas.²⁷ As BAFF can be produced by local DCs or stromal cells, it is possible that both direct effects of helminth-derived antigens on B cells and indirect signals, such as helminth infection-induced antigen-presenting cells production of BAFF, form an important stimulus for the development of Breg cells. As this point of view may open a totally new area of research, it is worth noting that in a recent study by Phytian-Adams et al, depletion of antigen-presenting CD11c-expressing cells during natural schistosome infections completely abolished infection-induced changes in the frequency of MZ B cells, but not other B-cell subsets. Although these findings suggest that splenic CD11c⁺ cells can strongly affect MZ B cells, it is still

unclear whether this has any consequences for the induction of IL-10-producing (MZ) Breg cells by schistosomes.

APPLICATION OF BREG CELLS FOR THE TREATMENT OF ALLERGY AND ASTHMA?

As illustrated earlier, evidence from animal studies and a few human studies points toward a significant role for IL-10-producing Breg cells in the modulation of pathogenic responses in both type 1 and type 2 inflammation models. Although it has become clear from a number of reports that at least the Treg cell compartment of patients with allergic diseases, such as asthma, rhinitis, or dermatitis, is impaired in number and activity, there are not many reports on Breg cell numbers and activity in these patients as yet. One report has evaluated IL-10-producing B cells in allergic patients and controls, describing an increased frequency of IL-10-producing CD5⁺ peripheral blood B cells from healthy individuals in response to the milk antigen casein, which was not observed in PBMC cultures from individuals allergic to cow's milk.¹⁶ Notably, this area of research is relatively unexplored and shows an important gap that needs to be studied in the coming period.

Therapies such as allergen-specific immunotherapy or non-specific treatments such as glucocorticoids, which are used to treat allergies, have been shown to induce IL-10-secreting Treg cells. Nevertheless, these therapies are mostly reducing symptoms and require lifelong application. Therefore, it is warranted to search for other, longer-lasting sources of IL-10-producing cells or methods that in a self-sustaining manner induce or activate IL-10-producing Treg cells in patients with asthma. Studies on Breg cells described in this review show promising leads and may have therapeutic potential, particularly as IL-10-producing B cells can also lead to the induction/recruitment

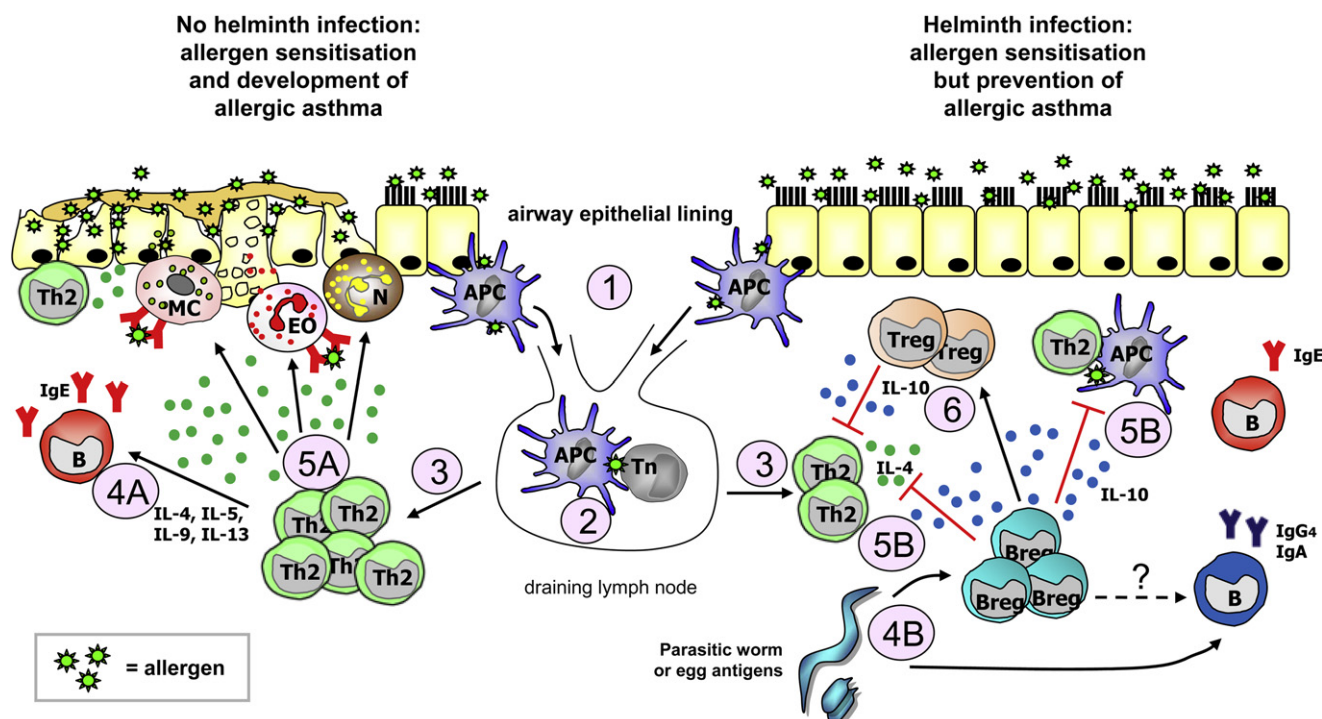


FIG 2. Breg cell-induced protection against allergic airway inflammation. In noninfected individuals, allergic sensitization leads to allergen-loaded airway DCs, driving polarized Th₂ cells (1-3). These Th₂ cells will subsequently drive the allergic effector cascade in the lung (4a, 5a). In helminth-infected individuals, steps 1 till 3 are similar. At the same time, however, helminth antigens will prime Breg cells (4b) secreting IL-10 and suppressing DCs and Th₂ cells (5b). In addition, Breg cells will induce/recruit Treg cells (6), further suppressing the Th₂ immune response. APC, Antigen-presenting cell; EO, eosinophil; MC, mast cell; N, neutrophil.

of Treg cells and amplification of the regulatory response (Fig 2). This emphasizes that targeting for Breg cells may offer superior immunosuppression when compared with Treg cells alone (Fig 2).

CONCLUDING REMARKS

This review describes a relatively new regulatory cell type, the Breg cells. They excel in suppressing hyperinflammatory responses in both models of autoimmune and allergic airway inflammation. Therefore, their induction may be of particular interest to treat a range of diseases. For this, helminth infections may be of particular value, as helminths appear to be potent inducers of Breg cells. Therefore, in addition to further characterization of Breg subtypes and their mechanism of action, it would be important to unravel the mechanisms underlying Breg cell induction by helminths and to identify the helminth-derived molecules involved, as this may open novel avenues for the treatment of hyperinflammatory diseases such as allergy and autoimmunity.

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