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B cells in allergic diseases: Bad or Better?

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Abstract
IgE-producing B cells are always considered as 'bad' guys in allergic diseases, as they play a direct role in promoting inflammatory responses against inhaled or ingested allergens and contribute to the development of subsequent clinical symptoms. During the past decade, mouse studies have shown that B cells may also have a 'better' side, producing IL-10 and suppressing inflammatory responses; those cells are called regulatory B (Breg) cells. There is evidence now that impairment of Breg cell activity may play a role in the development of inflammatory diseases. New transgenic models and renewed interest have expanded our knowledge on different B cell phenotypes, signals to promote their activity and their function in health and disease. This review will highlight the current knowledge on disease-promoting or disease-protecting activities of B cells and discuss its potential for therapeutic applications in allergies.

Keywords: *Regulatory B cells, IL-10, IgE, allergy, asthma, parasites*

Introduction

Allergic asthma is characterized by bronchial hyper-responsiveness and a variable degree of airflow obstruction, leading to episodes of wheezing and breathlessness. These clinical manifestations generally result from chronic inflammatory processes in the lower airways in response to normally harmless aero-allergens, like faecal products from house dust mite (HDM), tree, grass or flower pollen, mold and animal dander from e.g., cat, dog or horses. It should be noted that also processes like structural remodeling of the airway in response to damaging stimuli or retention in lung development and growth can be a fundamental risk factor for the development of asthma.

Allergic rhinitis, or hay fever, is a disease characterized by irritation and inflammation of the nasal airways upon aero-allergen exposure. This results in excessive mucus production, itching, conjunctiva and eyelid swelling, middle ear effusion and lateral crease on the nose. Importantly, up to 80% of the asthmatic patients have concomitant rhinitis symptoms in the upper airways. Importantly, allergic rhinitis (AR) patients have a strongly increased risk to develop asthma and the current concept is that AR precedes asthma in most patients. Likewise, when AR symptoms in asthma patients worsen, it negatively affects the course of asthma [1].

In food allergies, allergic responses can be found against food products such as peanuts, fruits or milk, characterised by mild or more severe gastrointestinal and respiratory distress, or even life-threatening anaphylactic responses, which require immediate emergency intervention. There are cross reactive responses to certain food allergens and aeroallergens, resulting in overlapping symptoms in different mucosal compartments, examples are birch pollen and fruits or grass pollen and peanut, soybean or tomato. Common inflammatory immune responses can be found in allergic diseases that are manifested in mucosal tissues and which are characterised by an expansion of polarized Th2 lymphocytes, secreting typical cytokines like interleukin (IL)-4, IL-5, IL-9 and IL-13, elevated IgE production, eosinophilia, goblet cell hyperplasia and an excess of mucus production [2].

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From 1960 onwards, the incidence of childhood asthma and allergies has strongly increased in westernized areas and seems to have reached a peak over the past decade [3]. However also in Africa, Latin America and parts of Asia, the prevalence is rising in the past few years. This has lessened the global differences in prevalence but underlines that the global burden of asthma and allergies is continuing to rise [3] and that new therapies are warranted.

During the past few years there is a growing awareness that allergic diseases, like asthma in part stems from a defect in the regulatory compartment of the immune system. There is evidence that environmental and microbial exposures may drive strong regulatory responses and this may drive provide protection against the development of allergic diseases. This review focuses on the role of a relative unknown player in the regulatory network, the regulatory B cell, and discuss the current understanding of these cells and its value for therapeutic applications in allergic disease.

Effector B cells in allergic responses

Traditionally, B cells are known for their capacity to produce antibodies, contributing to humoral immunity and clearance of pathogens. However, they can also perform pathogenic functions by producing autoantibodies, which contribute to destruction of self and the development of auto-immune disease. In addition, B cells producing allergen-specific IgE antibody isotypes are central in immediate and late-phase allergic responses, leading to clinical symptoms of allergic diseases. In terms of evolution, it is highly unlikely that IgE evolved to contribute to the pathology of allergy, but it has been shown that the dominant role of IgE is to protect the host from helminth infections. Hence, it is believed that IgE has evolved to protect the human from helminth infections, which was until very recently, and in tropical areas still is, one of the major threats of the human species.

Regulation of IgE synthesis

In the bone marrow, mature B cells are generated which produce IgD and IgM of a defined antigen specificity. They have the capacity to modify their isotype to IgG, IgA or IgE, each with distinct biological effector functions but with the same committed antigenic specificity of the parent cell. This process of class switching will occur when both B cells and $CD4^+$ T cells encounter their cognate antigen. Antigen binding to surface Ig triggers internalization, degradation into peptides and their subsequent presentation in major histocompatibility complex (MHC) class II molecules at the surface of the B cell and antigen presentation to $CD4^+$ T cells.

Distinct signals, including both cell-cell interactions and secreted cytokines, from the activated Th cells will determine the degree of class switching in the B cells. In the case of IgE class switching both the ligation of CD40 on the B cells by T cell derived CD40L and the Th2 cytokines IL-4 and/or IL-13 are necessary, leading to a subsequent downstream activation of nuclear factor κB (NFκB) and nuclear translocation of signal transducer and activator of transcription 6 (STAT6) and the initiation of Cε exon transcription [4]. This means that activated Th2 cells are instrumental and necessary to generate IgE class switch and IgE producing B cells.

Cellular receptors for IgE

There are two types of IgE receptors: the FcεRI and the FcεRII, also known as CD23. The expression of both receptors is enhanced by IgE [5]. FcεRI is the high affinity receptor for IgE and consists of three subunits, an α subunit that binds the Fc region of the IgE antibody, a β subunit that provides additional accessory signaling, and the FcR γ-chain, which is shared with FcγRIII and activates intracellular signaling [4]. FcεRI is expressed as a $\alpha\beta\gamma_2$ tetramer on mast cells and basophils, or as $\alpha\gamma_2$ trimer in a wide variety of other cell types. FcεRI has a very avid dissociation constant (K_d), allowing full saturation at physiological concentrations of IgE and persistence of IgE bound to cellular receptors for weeks or months despite its low half-life of only a few days in serum [4].

FcεRII or CD23, is structurally not related to other immunoglobulin receptors and belongs to the family of the C type lectin receptors. In the membrane form, CD23 consists of a trimeric long stalk-like coiled structure with three globular lectin domains that bind IgE. However, the stalk region is also susceptible to proteolysis by endogenous proteases, leading to soluble fragments of CD23 with various sizes; those still containing stalks are able to form trimers, whereas those lacking any stalk region remain monomeric [6]. CD23 is called the 'low-affinity'-receptor for IgE, but this name is not entirely applicable: although the affinity of monomeric CD23 for IgE is less compared to FcεRI, the overall avidity of the trimeric membrane-bound form of CD23 is not much less than that of FcεRI [7].

CD23 has both negative and positive regulatory effects on the level of IgE. For this regulatory function, one of its co-receptors, CD21 (also known as complement receptor 2 (CR2)), is important. In humans, soluble CD23-membrane IgE complexes interacting with CD21 can stimulate IgE synthesis when CD23 is trimeric or repress it with monomeric CD23 [7]. Binding of membrane CD23 by IgE prevents the release of soluble CD23, thereby abrogating positive signaling for IgE synthesis. In addition, co-ligation of membrane CD23 and

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membrane IgE by allergen-IgE complexes results in negative signaling for IgE synthesis [8].

CD23 can also interact with MHCII molecules, using structures in the CD23 protein that are located in the stalk region of the molecule [9]. This interaction is believed to facilitate antigen processing and presentation by antigen-IgE complexes captured by CD23, generating enhanced immune responses over immunization with antigen alone [10–12]. In this way CD23-expressing B cells are able to present a variety of peptides, even from totally unrelated antigens, to cognate T cells, regardless of the specificity of the B cell's own antigen receptor. This phenomenon is the basis for 'epitope spreading' [13], not just within a single allergen, but also to unrelated allergens and serves as a positive feed-back mechanism to enhance allergic sensitization. This process may explain the fact that mono-specific allergies often deteriorate into poly-specific allergies.

Allergens and IgE

Cross-linking of IgE-FcεRI complexes by allergens on mast cells and basophils lead within minutes, to the so-called immediate hypersensitivity reaction or early phase of the allergic reaction, involving mast cell degranulation and synthesis of lipid mediators [14,15]. For example, histamine stimulates nerve endings to produce itching and mucus secretion and smooth muscle contraction that block the airways. Serotonin acts on the nervous system, giving rise to tachycardia, bronchoconstriction, diarrhoea and pain [15,16]. Vasoactive amines (histamine, serotine) and the lipid mediators (platelet-activating factor (PAF), prostaglandins, leukotriens) also increase cutaneous blood flow and enhance local vascular permeability leading to the leakage of plasma proteins causing swelling and trapped erythrocytes, which redden the area [14].

The subsequent released cytokines and chemokines initiate the late phase, which peaks several hours later and results from the recruitment and activation of inflammatory cells, like T cells and eosinophils, at the site of allergen exposure. At the same time allergens also activate antigen presenting cells with loaded IgE-FcεRI, which in turn activate allergen-specific Th2 cells and promote further IgE production by B cells [6].

Anti-IgE therapy: omalizumab

The main treatment consists of suppressing clinical symptoms by the use of bronchodilators, inhaled steroids or simply allergen avoidance. Yet, a novel treatment approach is omalizumab, a humanized non-anaphylactic monoclonal antibody that binds circulating IgE antibody, preventing it from binding to its high-affinity receptor on basophils and mast cells [17]. In patients with allergic asthma, omaluzimab treatment improves symptoms and reduces exacerbations [18]. Although this antibody seem to prove its value for therapy of allergic diseases, the costs of this therapy are huge and therefore it is currently only used for moderate to severe cases of asthma and then only in cases when other less costly treatments did not result in any improvement.

In addition to its function in neutralizing IgE, it may also cause apoptosis in B cells by cross-linking membrane IgE. However, it is unlikely that it will affect long-lived plasma cells that express little of the membrane form of IgE. As the tendency in allergic asthmatic patients to mount Th2 responses remains, there is a clear change of a relapse if the treatment with the antibody ceases. Therefore new therapy strategies should focus on allergen-specific immunotherapy to achieve immune modulation either or not in combination with omalizumab. During immunotherapy immunoregulatory cytokines like IL-10 are being enhanced, while Th2 cytokines are downregulated. An interesting approach would be to explore methods to further enhance and maintain this population of IL-10 producing cells.

Regulatory B cells: suppression of auto-immune or allergic inflammation

T cells and antigen presenting cells (APC) are well known for their capacity to produce IL-10, but these cells are not the only ones. An increasing number of papers are now pointing at B cells as an alternative source of IL-10. These studies imply that B cells are not merely antibody-producing factories, but that subsets of B cells can actively serve an antibody-independent function by regulating T cell-mediated inflammatory processes and inducing tolerance by producing IL-10. Because of their capacity to maintain immune homeostasis these B cells were therefore named regulatory (Breg) B cells.

Regulatory B cells in mouse models of inflammation

About a decade ago, a series of landmark papers were published coining the concept of IL-10 producing B cells as regulatory cells in a number of autoimmunity models [19–22]. Mizoguchi and colleagues identified IL-10 producing B cells in a model of chronic colitis [23], which were characterized by the enhanced expression of CD1d [24]. Adoptive transfer of those IL-10 expressing B cells could mediate protection against intestinal inflammation in recipient animals [24]. In addition, Fillatreau and colleagues investigated the regulatory potential of IL-10 producing B cells in a model of experimental autoimmune encephalomyelitis (EAE). Here, adoptive transfer of IL-10-competent B cells could reduce disease severity, while B cells from IL-10-deficient mice

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could not [25]. Finally, Mauri and colleagues established the inhibitory capacity of IL-10 producing B cells in a collagen-induced arthritis (CIA) model [26] also comparing IL-10-competent and IL-10-deficient B cells.

Since then, a large number of other mouse studies have confirmed the regulatory potential of IL-10 producing B cells in either similar or other models of auto-immunity, including inflammatory bowel disease (IHB) [27,28], EAE [29,30], type 1 diabetes [31] or systemic lupus erythematosus (SLE) [32–34]. The potential of IL-10 producing Breg cells is not restricted to auto-immune diseases; several papers have also shown inflammation suppressing activities of B cells in models of contact hypersensitivity [35,36], in prevention of graft transplant rejections [37–40] or in allergy models.

For example, continuous allergen exposure of the lungs generated local B cells that were responsible for the induction of inhalation tolerance and could transfer protection against allergic airway inflammation (AAI) to recipient mice [41]. In a model of allergic conjunctivitis, CpG administration generated splenic IL-10 producing B cells that protected against eosinophilia in the conjunctiva, a process that was abrogated when CpG-treated B cells were derived from IL-10-deficient mice [42]. Furthermore, in models for anaphylaxis or AAI, transfer of IL-10 producing Breg cells from helminth-infected animals also strongly reduced allergic inflammation [43–47]. In the majority of the previously indicated models, the role of splenic IL-10 producing B cells was investigated.

Several surfaces markers have been suggested to phenotype these cells: $CD23^{hi}$ follicular B cells [42], marginal zone precursor (MZP) B cells, characterized by a high expression of CD21, CD23 and IgM [48], marginal zone (MZ) B cells, with high expression of CD21 and IgM, but not of CD23 [24,32,47,49], and in some studies combined with the expression of $CD1d^{hi}$ [24,47,50]. Also splenic $CD19^{+}CD5^{+}$ $CD1d^{hi}$ B cells, named B10 cells, have been identified with IL-10 dependent suppressive capacities [24,33,51]. Interestingly, there are also a number of studies demonstrating a regulatory function for mesenteric B cells, in which the expression of either CD1d [52] or CD23 [45] seemed to be specific for the Breg cells.

There is a considerable overlap between the expressions of several of these markers, questioning whether these are all distinct subsets or that the variation between the markers could be explained by the option that they represent either precursors or mature stages of the same Breg cell subset. More recently, the protein T cell Ig domain and mucin domain protein 1 (TIM-1) was identified as a specific marker (more than 70%) for IL-10 producing B cells [40].

Ligation of TIM-1 (by an agonistic antibody) enhanced IL-10 production in splenic B cells, suggesting that TIM-1 is not a simple identification marker but may also be of functional significance [40]. However, at present it is not known whether TIM-1 expression is specific for other IL-10 producing B cell subsets and further studies need to be done to find out.

All these studies combined underline the broad potential of regulatory B cells in inhibiting inflammatory conditions of both auto-immune and allergic diseases and to maintain immune homeostasis. Therefore, a great deal of attention has been paid to elucidate the effector mechanisms of Breg cells.

Effector mechanisms of Breg cells

By definition, regulatory B cells suppress inflammatory processes and inducing tolerance. To achieve this they display a number of activities of which some are directly related to their capacity to produce IL-10, while for others this is less clear and may involve additional or alternative inhibitory pathways.

First, they inhibit antigen-specific T cell proliferation and cytokine production of Th1, Th2 and Th17 effector cells. This was demonstrated in models of EAE [29,51], lupus [53] or arthritis [48], where IFNγ, IL-2, IL-17 or TNFα levels were reduced and part of the suppressive effect was potentiated by CD40. In addition, in several allergy models cytokine responses of allergen-specific Th2 cells, like IL-4, IL-5 and IL-13, were downmodulated by splenic Breg cells in an IL-10 dependent manner [43,44,46,47].

Second, one of the major effector functions of Breg cells centers around the induction and/or recruitment of $FoxP3^{+}$ Treg cells, in which various pathways may to be involved. For example, in auto-immunity models for lupus [33], EAE [51] or arthritis [54] or in models of allergic lung inflammation [46,47], there was a clear role found for IL-10.

However, in two other models for either oral tolerance [55] or inhalation tolerance [41] against allergens, $FoxP3^{+}$ Treg cell induction by Breg cells was dependent on TGFβ, rather than IL-10. Of note, although Treg cell induction is dependent on Breg cell activity, they can act independently in controlling inflammation. This is highlighted in a model of Breg cell-induced protection against AAI, showing that temporal Treg ablation only partly restored allergic inflammation [47]. Furthermore, in EAE Breg and Treg cell numbers appear to peak at different disease stages with enhanced Breg cell activity during early EAE initiation, while Treg cells were found to provide protection during late-phase EAE [51].

Third, Breg cells may induce apoptosis of effector T cells by mechanisms related to the expression of death receptor Fas ligand (FasL). For example, Lipopolyssacharide (LPS)-activated FasL-expressing

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B cells suppressed the onset of auto-immune diabetes in non-obese diabetic (NOD) mice [56] and the number of FasL-expressing splenic B cells inversely correlated with the severity of diabetes. In addition, FasL-expressing B cells could mediate immune tolerance in a skin graft model against the male H-Y antigen, where adoptive transfer of splenic B cells from male control mice tolerised female graft recipients, but B cells from FasL-defective mice did not [57].

Furthermore, the role of FasL-expressing B cells was studied in an asthma model based on cockroach antigens comparing X-linked immunodeficiency (Xid) B cell-deficient mice and WT mice, showing elevated numbers of FasL-expressing B cells in WT mice and more pronounced lung inflammation and reduced lung T cell apoptosis in the Xid mice [58]. It should be noted that the apoptosis-related activities have all been attributed to CD5-expressing B cell subsets, as recently reviewed by Klinker and Lundy [59].

Last, Breg cells reduce migration and activation of dendritic cells and macrophages. It is well known that IL-10 can inhibit antigen processing and presentation and the expression of co-stimulatory molecules, like CD80 and CD86, including the release of pro-inflammatory cytokines [60]. This has clear consequences for their T cell stimulatory capacity as is illustrated by in vitro cultures of cultures of splenic DCs from mice with EAE and MOG-specific $CD4^+$ T cells. Conditioning of DCs by $CD5^+CD1d^{hi}$ B cells resulted in less T cell proliferation compared to conditioning by non-Breg cells [51].

Human Breg cells

So far most evidence comes from murine models and needs to be confirmed in humans. Nevertheless, there are studies emerging now on human B cells that point at conditions in which either an increased presence or a lack of regulatory B cells can be found. Sofar, three distinct human Breg cells have been described. (i) In healthy individuals the population $CD24^{hi}CD38^{hi}$ immature B cells was found to have regulatory capacities: this subset expressed elevated levels of IL-10 and could inhibit TNFα and IFNγ expression by $CD4^+$ T cells. Interestingly, in SLE patients this B cell subset was functionally impaired and did not suppress cytokine production from $CD4^+$ T cells [61]. We have studied this population in allergic asthma (AA) patients and although we found an increased frequency $CD24^{hi}CD38^{hi}$ B cells in peripheral blood, they had a similar capacity to produce IL-10 as healthy controls [62].

Based on these data, we have no indications yet that this Breg subset behaves differently or is impaired in AA patients. (ii) In helminth-infected individuals an increased population of $CD1d^+$ B cells is found in peripheral blood, which expressed elevated levels of IL-10 [47]. Interestingly, helminth-infected multiple sclerosis (MS) patients displayed reduced disease activity compared to non-infected MS patients and had an increased population of IL-10 producing $CD1d^+$B cells that were capable of suppressing T cell proliferation in vitro [63].

In this stage it is unclear whether helminth-induced human IL-10-producing $CD1d^+$B cells are equally able to suppress allergic T cell responses as described for the auto-reactive T cells in MS patients or as their murine counterparts in the allergy models. However, as helminth-induced IL-10 production is positively associated with the absence of HDM-specific skin prick test (SPT) positivity in helminth-infected individuals [64], it is tempting to suggest that IL-10 producing $CD1d^+$ B cells at least partly contribute to the suppression of immune responses to allergens. (iii) A third B cell subset associated with increased IL-10 production and immune regulation is found within $CD24^+CD27^+$B cells and was first described by Iwata and colleagues [65].

Within this population they identified the human equivalent of the mouse B10 cells, a rare population expressing CD5, CD1d and IL-10. There was also a considerable co-expression with CD38 with this $CD24^+CD27^+$ B cell population. The $CD24^+CD27^+$ B cells could inhibit cytokine production by both $CD4^+$ T cells and monocytes, although only in the case of monocytes this inhibition was IL-10 dependent. Surprisingly, increased frequencies of those B10 cells were found in patients suffering from various auto-immune disorders (SLE, rheumatoid arthritis (RA), Sjögren syndrome, blister skin disease or MS) compared to healthy controls. However, the functional capacities of those B10 cells from the auto-immune patients were not investigated, so in this stage it is not possible to draw conclusions whether this subset is impaired or not in autoimmunity.

In contrast, we clearly observed a significant decrease of $CD24^+CD27^+$ B cells in peripheral blood of AA patients compared to healthy controls. $CD24^+CD27^+$ B cells from AA patients expressed less IL-10 in response to LPS and induced less IL-10 producing T cells in subsequent co-cultures with $CD4^+$ T cells and Der P1 compared to similar cultures from control subjects [62]. These data indicate a selective impairment of $CD24^+CD27^+$ B cells from AA patients in their responsiveness to LPS, which may contribute to increased inflammation found in asthma.

Although a number of distinct human Breg cell populations have been identified and clear parallels can been drawn in function and phenotype with several mouse Breg subsets, it may still to early to conclude that either one of those subsets has truly unique capacities or that one specific subset is more associated to a certain disease type. To be able to fully

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exploit the benefits of this relative novel regulatory subset for therapeutic application, signals to induce or increase their activity need to be identified.

Induction of regulatory B cells: signals from the past

A concept has been postulated that regulatory B cells not only serve to maintain immune homeostasis, preventing the initial development of auto-immune or allergic diseases, but also have evolved as a mechanism to limit otherwise vigorous adaptive pathogen-specific inflammation preventing excessive tissue damage [66]. Pathogens may have exploited these host protective mechanisms to enhance their survival and may have adapted during the course of evolution to develop signals for Breg cell development or to enhance their activity.

Link between microbial exposure and protection against allergic diseases

The fact that childhood asthma prevalence has increased up to 15% in westernized countries in a relatively short period argues against genetic changes but favors short-term environmental changes. It is conceivable that environmental exposures, the number and the type of infections in industrialized countries is completely different compared to 100 yrs ago due to drastic changes in health care, sanitation, vaccination programs, lifestyle, housing, food patterns, socioeconomical status and education level.

It is hypothesized that the rise in allergic diseases is in part related to an immune disbalance, caused by a reduced infectious pressure [67]. Indeed, there are many epidemiological studies showing a negative association between chronic infections or microbial exposure and allergic diseases [68].

Helminths strongly influence host immunity by the formation of a regulatory network, in which the cytokine IL-10 plays a central role [69]. IL-10 is not only produced by Treg cells, but also by helminth-induced B cells. The link between helminths and Breg cells is clear from a number of papers showing IL-10 producing B cells associated with reduced pathology and modulation of T cell responses [70,71] in various models of chronic parasitic inflammation, such as chronic schistosomiasis, filariasis or Leishmaniasis [43,44,72,73].

Another example is given by farm studies, showing that children being raised on farms in rural Europe were protected from allergic rhinitis, wheeze and asthma. The most important contributors to the protective farm effect were identified as intake of unpasteurised farm milk and frequent livestock exposure in particular during the first year of life [74].

Frequent contact with livestock will lead to an increased microbial exposure, which may actively influence allergen-specific immune responses and protect against allergic disease. Indeed, Ege and colleagues showed recently that exposure to gram negative bacteria and certain fungi were critical for the protective 'farm-effect' [75]. As these regulatory processes may have taken thousands of years to develop, we may regards those pathogen-derived signals as ancient signals from the past [76]. We will outline the influence of microbial signals on the development or activity of Breg cells below and how this can be exploited to 're-introduce' the signals from the past for therapeutic application.

Role of helminth infections and microbial compounds

Crucial elements that determine the development of Breg cells were studied In various mouse models and there is a general consensus that alt least two factors proved to be important: receptors controlling antibody production [B cell receptor (BCR) and/or CD40] and/or MyD88-dependent Toll-like receptor (TLR) signaling. Several models have been designed to explain how the different signals can be integrated or act at different subsets, e.g., naïve or memory B cells or alternatively at precursors of Breg cells [77,78]. In view of the above described association between microbial exposure and protection against allergic disease, the role of TLR ligation by pathogen-derived molecules is particularly interesting. Indeed, several TLR agonists, such as LPS, peptidoglycan or CpG-containing oligonucleotides are potent inducers of IL-10 in both human and mouse B cells [65,79,80]. Furthermore, it was demonstrated in a model of EAE that TLR were directly involved in the regulatory function of B cells, as mice with a B cell-specific deletion of both TLR2 and TLR4 or of the TLR-adaptor molecule Myd88 did not recover from EAE [81].

Interestingly, we observed that B cells from patients with allergic asthma expressed less IL-10 in response to LPS, while IL-10 expression in response BCR stimulation was similar to healthy controls [62]. Furthermore, in healthy individuals allergens (dog hair, grass pollen and HDM-derived Der p1) were also capable of inducing IL-10 production in purified memory B cells, although here it was not clear in what way contaminating endotoxin may have contributed to these findings. Nevertheless, allergen-stimulated B cells produced less IgE upon stimulation by anti-CD40 and IL-4 through autocrine secretion of IL-10 [82]. Further studies need to find out whether a reduced exposure to microbial molecules like LPS at early age results in an irreversible impaired capacity to induce B cell IL-10 at later ages.

Live infections with certain pathogens or exposure to crude extracts can also induce IL-10 expression in

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B cells by TLR2 or TLR4 signaling. For example, the oncogenic polyoma virus [83], parasites such as *Leishmania major*, microfilarial extracts from *Brugia malayi* or egg glycans from schistosomes all enhanced IL-10 expression from B cells by triggering TLR4 [72,84]. While TLR2 proved to be critical for B cell IL-10 production by TLR2 ligands from the bacterium *Helicobacter felis*, which suppressed helicobacter-induced immunopathology by promoting IL-10-producing T cells [85]. In addition, soluble egg antigens (SEA) from *Schistosoma mansoni* stimulation of human B cells resulted in a TLR-2 mediated IL-10 production [86].

MyD88-signaling in B cells suppressed protective immunity during *Salmonella typhimurium* infections via IL-10, influencing the activity of effector T cells [87]. Lastly, in vitro cultures of splenocytes and live schistosome worms generated IL-10 producing B cells that could suppress AAI upon transfer in allergen-sensitized mice, proving their functional capacity [46]. While in this study the involvement of TLR signaling was not addressed, these findings do suggest that direct interactions between helminth molecules and B cells seem to be important for the induction of Breg cells.

Although it is clear that various infectious agents can directly influence B cell function by ligation TLRs on the surface of B cells, pathogens or pathogen-derived molecules may also use indirect mechanisms to support the development of IL-10 producing B cells. They may do so by activating resident cells in the surrounding tissue or immune cells in their close proximity as a consequence of TLR ligation. For example, mouse mammary tumour virus stimulates IL-10 production from B cells by triggering TLR4 on accessory cells; B cell TLR4 triggering was not required in this model [88]. In addition, soluble factors produced by local cells such as B cell-activating factor (BAFF) [89] or type 1 interferons [90] have also been shown to drive IL-10 producing Breg cell development. Now, the question remains whether this knowledge can be exploited to use regulatory B cells for therapeutic applications.

Regulatory B cells for therapy: option or utopia?

At present the treatment of allergic diseases mainly consists of alleviating the symptoms through the use of anti-histamine drugs, bronchodilators and inhalation or topical steroids and need to be applied all one's life. Due to daily use, these drugs may have serious side effects, like osteoporosis, atrophy of the skin and cataract. Also, little is known about the long-term effects of steroid use by children. Immunotherapy would have the advantage of lacking side effects of steroids and the induction of long lasting protective immune responses, curing or even preventing childhood asthma. Would it be possible to design an immunotherapy that targets for Breg cells?

Allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) induces allergen desensitization by either subcutaneous or sublingual administration of increasing dosages of allergen. Drawbacks of the current protocol is the application of large quantities of allergens, the risk on severe side effects like anaphylaxis and the fact that this therapy has to be applied up to 3 years to ensure clinical improvement, which may last several years before fading off.

It has been hypothesized that successful AIT induces allergen-specific tolerance [91], most probably affecting both the T- and B cell compartment, as IL-10 producing Treg cells have been demonstrated together with increased IgG_4 and IgA responses and simultaneous decreased IgE [92,93].

These type of allergen-specific responses have also been demonstrated in sensitized but clinically healthy individuals [94]. Indeed, both inducible $CD4^+CD25^+FoxP3^+$ Treg cells [95] and Tr1 cells [96], defined by their ability to produce high levels of IL-10 and TGF-β, were found to suppress endogenous allergen-specific T cell proliferation and cytokine production.

Clearly, having a functional Treg cell compartment is crucial to reduce or prevent allergic disease. Patients with mutations in the *FOXP3* gene leading to a loss in the natural Treg cell compartment show a number of immune-mediated pathologies, including allergy [97] and the activity of allergen-specific Treg cells from asthmatic patients appears to be impaired [98]. However, current IL-10 producing Treg cell therapies like allergen-specific immunotherapy or nonspecific treatments like glucocorticoids [99] mostly reducing symptoms and need to be applied repeatedly all one's life.

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 asthmatic patients. The above described IL-10 producing regulatory B cells seem to promising in this context. Adding regulatory B cells to the spectrum of regulatory cells will expand our choices to more than one area of regulation. In addition, as IL-10 producing B cells also induce and/or recruit Treg cells, it may offer the advantage of inducing two regulatory populations of lymphocytes simultaneously that may act in concert and thus offer superior immunosuppression when compared to Treg cells alone.

Therefore, new therapy strategies should not only focus at inhibiting aberrant effector immune responses but also at actively inducing regulatory immune responses to allergens, as observed in healthy

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individuals. This could include stratagems aiming to improve current AIT protocols by adding active Breg cell inducing adjuvants, not only enhancing the efficacy of the treatment but also allowing decreased allergen quantities applied during AIT, thereby significantly reducing the risk on acute anaphylaxis. In this stage, it is still hypothetical what those adjuvants could be, although TLR2, 4 or 9 ligands seem to be logic candidates. New studies need to point out whether those molecules can be used safely and whether their addition gives any clinical advantage compared to classical protocols and medication.

Induction of Breg cells by chemical drugs

Recent studies on the working mechanisms of some successful drugs for multiple sclerosis (MS) or arthritis have suggested that IL-10 producing Breg cells were affected during their application and may therefore also be interesting candidates as Breg cell inducing agents in the treatment of allergic diseases.

B cells from multiple sclerosis (MS) patients displayed an enhanced production of pro-inflammatory cytokines (TNF-α, LT-α, IL-12 and IL-6) and a decreased capacity to produce IL-10, which could be restored by application of the chemotherapeutic agent mitoxantrone [100] or by Rituximab (blocking antibody against CD20: a B cell depleting antibody) [101] and was associated with reduced disease activity, a shift towards IL-10 producing B cells and increased in vitro inhibition of T cell proliferation by the B cells. Also the treatment of MS patients with IFNβ seemed to affect their B cell responses, as isolated B cells showed a lower proliferative response and a shifted cytokine expression of less IL-1β and IL-23 but more IL-12 and IL-27 compared to untreated patients. In vitro stimulated of B cells by IFNβ enhanced their IL-10 expression, which may mediate their regulatory effect [102]. The stimulatory effect of type 1 interferons on IL-10 producing B cells has also been demonstrated in mice [90]. Recently Tocilizumab (blocking antibody against IL-6R) was introduced in therapy against rheumatoid arthritis (RA). Application of Tocilizumab for 3 months enhanced TGFβ expression on peripheral blood $CD25^{+}$B cells and reduced the expression of CD69, altering their activation status [103], suggesting that this treatment influences the balance between effector

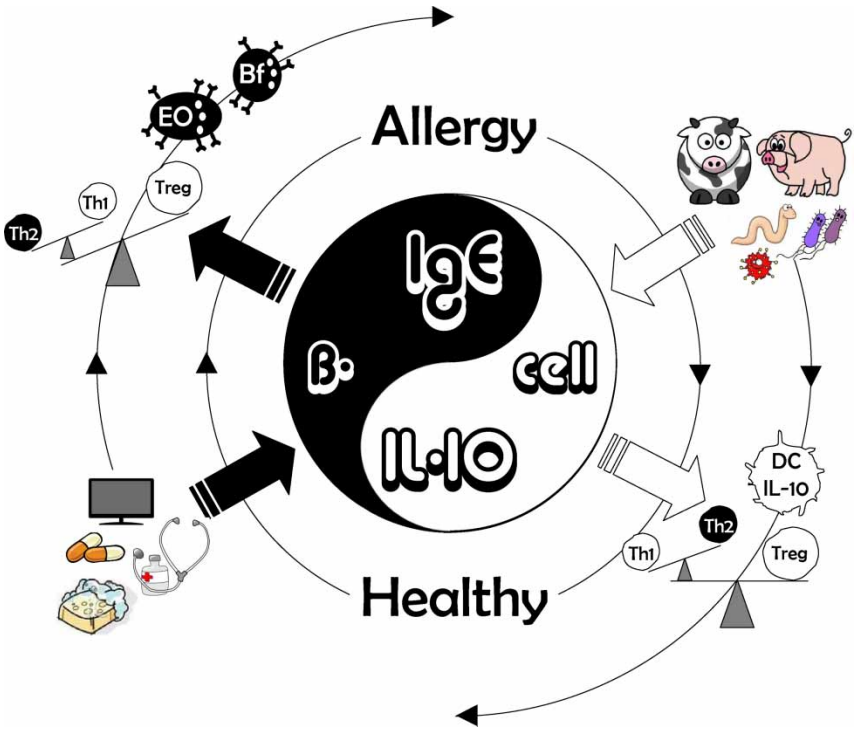


Figure 1. Ying and Yang of effector and regulatory B cells in allergic diseases. In a Th2-dominated cytokine milieu, effector B cells will produce IgE, which is involved in the effector cascade of allergic reactions, causing degranulation of eosinophils (EO) and basophils (BF) in response to allergens. In contrast, IL-10 producing Breg cells reduce inflammatory (Th2) responses and enhance the regulatory arm of the immune system by stimulating Treg cell activity and influence the activation status of dendritic cells (DC) and macrophages. The development of effector or regulatory B cells is a balance, which in genetically susceptible people, is influenced by environmental signals. The presence of rich sources of microbial or parasitic signals (like at traditional farms with cattle or in tropical areas with high prevalence of helminth parasites), will influence this balance and favor the development of IL-10 producing Breg cells and the full repertoire of a regulatory network in the immune system; while the absence of those signals due to improvements in hygiene, health care and a changed life style (spending more time indoors), will provide the space in genetically susceptible children, to allow the development of inflammatory responses to e.g. allergens, creating a Th2-rich environment and subsequent IgE producing B cells, leading to allergic symptoms.

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and regulatory B cells. Finally, several mouse studies have investigated the influence of the drugs glatiramer acetate (GA) and a hormone drug estrogen (both used for treatment of MS) on B cell immunology. GA treatment of mice reduced EAE, while adoptive transfer of B cells from GA-treated mice suppressed disease activity in recipient mice, inhibited proliferation of auto-reactive T cells, prevented the development of Th1 and Th17 cells and increased IL-10 expression in recipient mice but Treg cell levels remained unchanged [104,105]. Estrogen-mediated protection from EAE was accompanied by increases in the numbers of IL-10 producing B cells and the upregulation of PD-L1 expression on those cells, which may have consequences for T cell apoptosis [106]. Collectively, these studies show that there are already registered drugs that are able to drive Breg cell development and/or activation and as such may form interesting alternative candidates or additives for the treatment of allergic diseases by enhancing Breg cell activity.

Concluding remarks

Both in auto-immunity and in allergic diseases, effector B cells have always considered as the 'bad' guys, responsible for the induction of clinical symptoms via the production of auto-antibodies or allergen-specific IgE molecules. However, research in the past decade may have adapted this view: B cells can also execute inflammation suppressing activities pointing out the 'better' side of B cells. At present, both human and mouse IL-10 producing regulatory B cells have been identified and their impaired activity may play a role in the development of inflammatory diseases (Figure 1).

As a regulatory cell, B cells have a broad range of activities, influencing both innate immune responses by DCs and macrophages and adaptive immune responses by effector T cells. In addition, they also enhance the regulatory arm of the immune system by inducing Treg cell activity (Figure 1). Therefore targeting Breg cells for therapeutic purposes would provide the benefit that also Treg cell activity will be induced, making it a more efficient approach. Certain micro-organisms and parasites can stimulate Breg cell activity. Exposure to those signals were readily available in the past, but due changes in our lifestyle over the past 50 years, with improved hygiene and healthcare and less time spend outdoors, this is reduced in modern society (Figure 1). Future studies should point out whether we can learn the old tricks from nature and adapt those for therapeutic purposes.

Nevertheless, it seems that some drugs that are already used for the treatment of auto-immune diseases may also activate Breg cells, and it might be interesting to investigate its potential for treatment of allergic diseases as drugs that target Breg cells. To appreciate its full potential, further studies on Breg cell biology and its activity in humans need give more information on whether Breg cells will develop into antibody producers, their flexibility, their antigen-specificity or their life span. Despite all these open questions, the results so far at least suggest that this is a promising regulatory subset, worthwhile to explore its possibilities for future drugs.

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