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Regulatory B Cells - Implications in Autoimmune and Allergic Disorders

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1. Introduction

B lymphocytes represent a major component of the immune system and their best understood effector functions are antibody production, presentation of antigens to T cells and the modulation of immune responses via cytokine production. Although most of these functions serve to amplify immune responses, B cells have also been demonstrated to downregulate inflammatory reactions and induce tolerance. As such, regulatory B (Breg) cells have been implicated in various inflammatory conditions. There is evidence for Breg cell deficiencies in human autoimmune diseases and various adoptive transfer experiments in mouse models of autoimmune and allergic conditions indicate that Breg cells are capable of suppressing disease development. In this review we endeavour to give an overview of the current knowledge about regulatory B cell immunobiology and their implications in autoimmune and allergic disorders.

2. Regulatory B cells

B cells with regulatory capacity have become the focus of intense investigations in recent years. However, the general concept that B cells might have the ability to induce tolerance, was introduced already in the 1970s by Katz et al., who demonstrated that depletion of B cells from splenocytes abolished their ability to inhibit an inflammatory reaction in a delayed type hypersensitivity (DTH) model (Katz, Parker et al. 1974; Mauri and Ehrenstein 2008). More than 20 years later, Janeway and co-workers were the first to demonstrate a role of B cells in protection from autoimmunity, showing that B cell-deficient mice failed to undergo spontaneous remission from experimental autoimmune encephalomyelitis (EAE) (Wolf, Dittel et al. 1996). The term 'regulatory B cells' was introduced shortly afterwards, by Mizoguchi and Bhan, who identified an IL-10 producing B cell subset in gut-associated lymphoid tissues (GALT) with upregulated CD1d expression, which suppressed progression of intestinal inflammation by downregulating inflammatory cascades (Mizoguchi, Mizoguchi et al. 2002). Breg cells are now considered a key regulatory cell type

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capable of suppressing effector functions of various target cells including T cells, dendritic cells (DC) and macrophages, and can even convert effector T cells into regulatory T cells (Tian, Zekzer et al. 2001; Matsushita, Horikawa et al. 2010; Ronet, Hauyon-La Torre et al. 2010; Wong, Puaux et al. 2010).

2.1 Breg cell populations in mice and humans

Although the existence of a regulatory subset of B cells is generally accepted, there is still some controversy concerning their origin and relationship to other B cell populations (Vitale, Mion et al. 2010). In mice, B cells are classified according to their developmental origin, into B1 and B2 cells. B1 lymphocytes are considered an innate type of lymphocytes and appear early in life. They produce antibodies with a limited diversity to common pathogens and can respond quickly and independently of T cells. B2 lymphocytes on the other hand are further subdivided into marginal zone (MZ) and follicular B cells in the spleen and circulating B cells in the peripheral blood, each with very specific characteristics and functions (Hardy and Hayakawa 2001). Regulatory B cells or their precursors seem to be able to arise from different subpopulations of both B1 and B2 cells. As shown in Table 1, several Breg cell populations with varying surface phenotypes have been identified in various mouse model systems as well as in different human disease conditions. Some regulatory B cell populations have also been shown to be induced in diverse disease settings and in response to many different exogenous and endogenous stimuli. Toll-like receptor (TLR) signalling via TLR-2, 4 and 9 as well as B cell receptor (BCR) signalling and co-stimulation mediated by CD40, CD80/CD86 or B-cell activating factor (BAFF) has been demonstrated to induce B cells with suppressive activity (Fillatreau, Sweenie et al. 2002; Mauri, Gray et al. 2003; Blair, Chavez-Rueda et al. 2009; Kala, Rhodes et al. 2010; Lampropoulou, Calderon-Gomez et al. 2010; Yang, Sun et al. 2010). One prominent type of 'natural' B cells with regulatory capacity has been isolated from naive mouse spleens and termed B10 cells by reason of their IL-10-dependent suppressive function. Phenotypically these B cells seem to be predominantly $CD1d^{hi}CD5^{+}$, thus they share surface markers with $CD5^{+}$ B1 cells ($CD21^{hi}CD23^{+}IgM^{hi}CD1d^{hi}Cd93^{int}$), MZ B cells ($CD1d^{hi}CD21^{hi}CD23^{lo}IgM^{hi}$) and transitional 2 (T2)-MZ precursor B cells ($CD1d^{hi}CD21^{hi}CD23^{hi}IgM^{hi}$), but do not exclusively belong to one of these B cell subpopulations (Yanaba, Bouaziz et al. 2008). The human equivalent to mouse B10 cells has been identified recently as a small population within peripheral blood $CD24^{hi}CD27^{+}$B cells (Iwata, Matsushita et al. 2011). In analogy to regulatory-type T cells, which can been subdivided into Treg, Tr1 and Th3 according to their expression of FoxP3, IL-10 and transforming growth factor (TGF)-β, respectively, it has been proposed to classify human regulatory B cells into 'Breg', Br1 (B10) and Br3 (Noh and Lee 2011).

Because of the variety of Breg cell populations and inducing factors, several models have been proposed that try to explain their origin and development. The first model put forward by Mizoguchi et al. states that distinct Breg cell populations are generated from already existing B cell subsets depending on distinct activation processes (Mizoguchi and Bhan 2006). According to this hypothesis, innate type regulatory B cells are generated from MZ B cells in the spleen upon stimulation with inflammatory signals such as lipopolysaccharides (LPS) or CpG via toll-like receptors (TLR). On the other hand, acquired type regulatory B cells develop from follicular B cells following activation with CD40 ligand and/or B cell receptor (BCR) ligation with self-antigen. A second model proposed by Lampropoulou et al. states that B cells acquire suppressive function due to a hierarchical process of stepwise B

species	phenotype	initial identification	organ of origin	major effector function	disease condition
mouse	B10	(Yanaba, Bouaziz et al. 2008)	spleen	IL-10	CHS
mouse	T2 MZ	(Carter, Vasconcellos et al. 2011) (Evans, Chavez-Rueda et al. 2007)	spleen	IL-10	arthritis
mouse	MZ	(Gray, Miles et al. 2007)	spleen	IL-10	CIA
mouse	B1	(Nakashima, Hamaguchi et al. 2010)	peri-toneum	IL-10	CHS
mouse	$CD1d^{hi}$	(Amu, Saunders et al. 2010) (Mizoguchi, Mizoguchi et al. 2002)	spleen	IL-10	AAI, IBD anaphylaxis
mouse	$CD23^{+}$	(Wilson, Taylor et al. 2010)	mes. LN	?	AAI, EAE
sheep	$CD21^{+}$ B2	(Booth, Griebel et al. 2009)	Peyer's patches	IL-10	healthy
human	immature trans B	(Blair, Norena et al. 2010)	blood	IL-10 CD80/ CD86	SLE
human	'B10 (Br1)'	(Iwata, Matsushita et al. 2011)	blood	IL-10	healthy and autoimmune
human	$CD1d^{hi}$	(Correale, Farez et al. 2008)		IL-10	
human	'Br3'	(Lotz, Ranheim et al. 1994)	blood	TGF-β	CLL
human	'Breg'	(Noh, Choi et al. 2010)	blood	FoxP3	healthy

Table 1. B cell populations with regulatory phenotypes in different species. B cell populations with regulatory capacity have been identified in various different experimental settings or disease conditions in mice, humans and sheep. CHS: contact hypersensitivity, T2-MZ: transitional 2 marginal zone, CIA: collagen induced arthritis, AAI: allergic airway inflammation, IBD: inflammatory bowel disease, mes.LN: mesenteric lymphnodes, EAE: experimental autoimmune encephalomyelitis, SLE: systemic lupus erythematosus, CLL: chronic lymphocytic leukemia.

cell activation, with TLR ligands initiating the process and BCR and CD40 engagement serving to further reinforce this differentiation. According to this model, all activated B cells have the capacity to become regulatory B cells after activation (Lampropoulou, Calderon-Gomez et al. 2010). A third model, based on shared phenotypic markers between most described IL-10 producing B cell populations, claims that all different B cell populations contain distinct Breg cell precursors, which mature to IL-10 producing cells upon activation (DiLillo, Matsushita et al. 2010). Taken together, currently available information suggests, that in addition to distinct 'natural' Breg cell populations arising from specific Breg cell progenitors, members of many B cells subsets are potentially able to acquire suppressive functions as a negative feedback mechanism in response to activation.

2.2 Immunological effector functions of regulatory B cells

Regulatory B cells employ a variety of mechanisms to modulate immune responses and target many different immune cell types, such as dendritic cells (DC) (Matsushita, Horikawa

et al. 2010), macrophages (Wong, Puaux et al. 2010) as well as both T helper 1 (Th1) and Th2 cells (Tian, Zekzer et al. 2001; Ronet, Hauyon-La Torre et al. 2010). Their most prominent effector function is the production of the potent immunosupressive cytokine IL-10, however different subsets also produce TGF-β (Fig. 1) or suppress target cells via cell contact-dependent mechanisms (Fig. 2).

2.2.1 Release of cytokines

As depicted in figure 1, many Breg cell functions have been demonstrated to be mediated by the release of immunosuppressive cytokines. **IL-10** is the hallmark cytokine of regulatory B cells. It has been shown to be essential for the Breg cell suppressive functions in many autoimmune models. Accordingly, the protective function of Breg cells in collagen induced arthritis (CIA), experimental autoimmune encephalomyelitis (EAE), non-obese diabetes (NOD) and inflammatory bowel disease (IBD) is abrogated if B cells are deficient in IL-10 production (Fillatreau, Sweenie et al. 2002; Dalwadi, Wei et al. 2003; Mauri, Gray et al. 2003; Hussain and Delovitch 2007; Booth, Griebel et al. 2009). B cell derived IL-10 efficiently suppresses proliferation and inflammatory cytokine production of T cells (Fillatreau, Sweenie et al. 2002; Mauri, Gray et al. 2003) and can also induce forkhead box P3 (FoxP3) positive regulatory T cells (Gray, Miles et al. 2007; Blair, Chavez-Rueda et al. 2009). Some of these effects might be indirect and due to the effects of IL-10 on innate cell types, as IL-10 is well known to inhibit antigen presentation and pro-inflammatory cytokine production by DC, monocytes and macrophages (Moore, de Waal Malefyt et al. 2001).

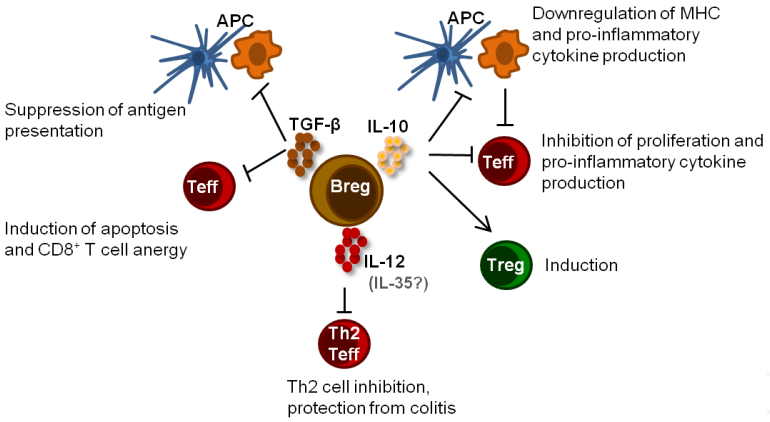

Fig. 1. Suppressive functions of Breg cells mediated by the release of cytokines. Breg cells secrete immunosuppressive cytokines causing downregulation of antigen presenting cell (APC) function, inhibition of T effector cell function and induction of regulatory T cells. Breg: regulatory B cells, Teff/reg: effector/regulatory T cells, APC: antigen presenting cells.

IL-10, **TGF-β** is the second immunosuppressive cytokine found to be secreted by some Breg cell populations to downregulate inflammatory immune responses (Tian, Zekzer et al. 2001; Parekh, Prasad et al. 2003). Similar to IL-10, TGF-β suppresses inflammatory cytokine production by T cells and inhibits the function of antigen presenting cells (APC). In

addition, TGF-β induces apoptosis in target effector cells and acts as a negative regulator of mucosal immune responses (Takenoshita, Fukushima et al. 2002).

Interestingly, although not generally considered suppressive, **IL-12** production by B cells has also been demonstrated to have immunomodulatory capacity in a T cell receptor (TCR)α knockout mouse model of Th2-mediated colitis. In this model, IL-10 mediated induction of IL-12 secreting B cells is involved in protection from colitis, as IL-12p35-deficient double knockout mice as well as mice treated with anti-IL-12p40 antibodies developed a more severe colitis compared to control mice (Sugimoto, Ogawa et al. 2007).

2.2.2 Cell contact-dependent suppressive mechanisms

Independent of cytokine secretion, several B cell surface molecules have been implicated in the suppressive functions of regulatory B cells (Fig. 2). **CD1d** is not only a major phenotypic marker highly expressed on many Breg cell populations, it has also been suggested to have an active role in Breg cell-mediated suppression. CD1d is a major histocompatibility complex (MHC) class I-like molecule and is responsible for the presentation of lipid antigens to Natural Killer T (NKT) cells (Chiu, Park et al. 2002; Borg, Wun et al. 2007). Mizoguchi et al. showed that upregulation of CD1d on B cells is associated with B cell-mediated protection against intestinal mucosal inflammation (Mizoguchi, Mizoguchi et al. 2002).

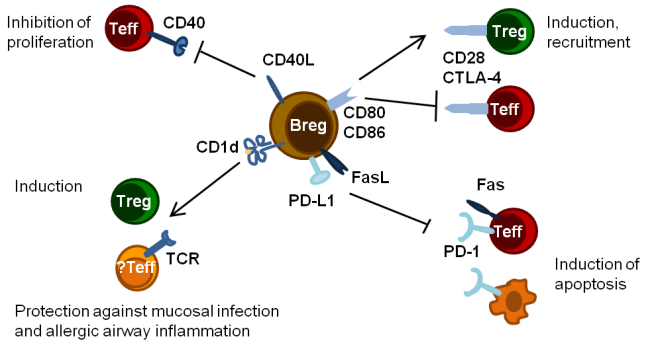

Fig. 2. Suppressive functions of Breg cells mediated by cell contact-dependent mechanisms. Breg cells express several cell surface molecules that cause inhibition of T effector cell function, induction of target cell apoptosis and induction of regulatory T cells. Breg: regulatory B cells, Teff/reg: effector/regulatory T cells, TCR: T cell receptor, PD-1: programmed death-1, PD-L1: programmed death-ligand1, FasL: Fas-Ligand, CTLA-4: cytotoxic T-lymphocyte protein 4, CD40L: CD40-Ligand.

As NKT cells had earlier been shown to be protective in mouse models of diabetes (Lehuen, Lantz et al. 1998) and colitis (Saubermann, Beck et al. 2000), it was feasible to assume that the activation of NKT cells was the underlying mechanism of protection in these models. However, as the TCRα knockout mice used in the studies by Mizoguchi et al., do not have NKT cells, the protective effect in this experimental setting has to be mediated by another CD1d responsive cell type. Amu et al. later confirmed a $CD1d^{high}$ Breg cell-dependent, but

NKT cell-independent mechanism of protection in a model of worm mediated protection from allergic airway inflammation (Amu, Saunders et al. 2010). Another group reported, that CD1d expression on APC and splenic MZ B cells was necessary for efficient generation of regulatory T cells in CD1d-reactive NKT cell-dependent tolerance in immune privileged sites such as the eye (Sonoda and Stein-Streilein 2002).

As described earlier, **CD40-CD40L** interaction seems to play an important role in the differentiation of regulatory B cells. In addition, there are reports indicating that CD40 signalling on target cells might also be involved in the suppressive mechanisms of B cells. Upon activation, B cells express CD40L on their surface (Wykes, Poudrier et al. 1998) and CD40-CD40L interaction has been shown to mediate suppression of colonic inflammation by inhibition of T cells (Bhan, Mizoguchi et al. 2000). Other costimulatory molecules involved in cell contact-dependent suppressive functions of B cells, are the B7 costimulatory receptors **CD80 and CD86**. Interaction of B7 surface receptors with their inhibitory ligands cytotoxic T-lymphocyte protein 4 (CTLA-4) or CD28 on target cells is crucial in regulating T cell activation and peripheral tolerance (Fife and Bluestone 2008). Expression of B7 molecules has been shown to be essential for recovery from EAE due to B cell-mediated generation and recruitment of regulatory T cells (Mann, Maresz et al. 2007) as well as for the suppression of colonic inflammation through inhibition of effector T cell proliferation (Bhan, Mizoguchi et al. 2000).

Moreover, evidence exists that Breg cells upregulate surface molecules like Fas ligand (FasL) and programmed death-ligand 1 (PDL-1), which upon interaction with their receptors can directly induce apoptosis in target cells. Lundy and Fox demonstrated that in a mouse model of rheumatoid arthritis, splenic $CD5^+$ B cells express high levels of FasL and that induced T cell apoptosis indeed was due to FasL-mediated direct killing by B cells (Lundy and Fox 2009). In EAE, Bodhankar et al. showed that the well established protective effect of estrogen is mediated by B cells. The treatment, besides increasing the percentage of IL-10-producing regulatory B cells, also induced upregulation of **PD-L1** expression on B cells (Bodhankar, Wang et al. 2011). Furthermore, in murine experimental stroke, PD-L1 and PD-L2 expressing B cells were found to be protective due to their capacity to inhibit the activation of inflammatory T cells, macrophages and microglial cells through upregulation of PD-1 expression (Ren, Akiyoshi et al. 2011).

3. Regulatory B cells in autoimmune diseases

In homeostasis as well as during acute immune responses a delicate balance between activating and suppressing subsets of immune cells has to be maintained. Disrupting this balance often leads to immunodeficiencies or autoimmune diseases. In particular, the balanced ratio between effector and regulatory T cells has been demonstrated to be of crucial importance in maintaining immune homeostasis, and the role of Treg cells has been well established in autoimmune diseases (O'Connor and Anderton 2008; Yang, Tian et al. 2008; Huang and Sattler 2011). Recently, various studies have also found critical roles and possible clinical relevance of regulatory B cells in both systemic and organ-specific autoimmune diseases (Lemoine, Morva et al. 2009).

3.1 Regulatory B cells in systemic autoimmune diseases

Systemic autoimmune diseases are defined by their multi-organ involvement. Antibodies reactive to a wide variety of ubiquitous autoantigens including DNA, cell surface molecules

as well as intracellular matrix proteins can cause tissue damage in various target organs. Although the underlying cause leading to systemic autoimmunity remains unclear, several genetic and environmental factors and immunological mechanisms have been implicated.

3.1.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune condition often considered the prototype of autoimmune diseases. It is mainly characterised by the presence of auto-antibodies to a variety of self antigens, particularly against nuclear components (Mills 1994). Because of the high production of pathogenic auto-antibodies, B cells are considered a major contributor to SLE pathogenesis and several therapies targeting B cells in SLE patients have been introduced (Sabahi and Anolik 2006). In addition however, there is evidence for the existence of a subset of B cells with regulatory capacity in lupus (Amano, Amano et al. 2003). Furthermore, human SLE patients have been shown to have an increased percentage of B10 and B10pro cells in peripheral blood (Iwata, Matsushita et al. 2011). However, regulatory B cells isolated from the peripheral blood of SLE patients might be functionally impaired, as they appeared to be unresponsive to CD40 stimulation, produced less IL-10 and lacked the capacity to suppress T cells (Blair, Norena et al. 2010).

Interesting insights into a possible dual role of B cells in lupus were obtained from CD19 deficient lupus-prone mice (NZB/W mice). Although, auto-antibody accumulation was significantly delayed in these mice, nephritis appeared earlier and survival was reduced compared to wild type NZB/W mice. Adoptive transfer of wild type $CD1d^{hi}CD5^{+}$ splenic B cells containing IL-10 producing regulatory B cells into CD19 deficient recipients significantly prolonged survival (Watanabe, Ishiura et al. 2010). Adoptive transfer of *in vitro* anti-CD40 stimulated T2 B cells into lupus-prone mice also improved renal disease and survival by an IL-10-dependent mechanism. This effect was explained by the suppression of Th1 responses and the induction of IL-10 producing and regulatory T cells. Direct *in vivo* administration of anti-CD40 also reversed established lupus disease (Blair, Chavez-Rueda et al. 2009). A possible role for innate immune signalling in the pathogenesis of SLE has been suggested previously (Lenert, Goeken et al. 2003) and TLR-9 signalling in marginal zone B cells has been demonstrated to induce higher IL-10 production in lupus-prone mice compared to controls. These high levels of B cell derived IL-10 inhibits the production of IL-12 by macrophages and DC and consequently can modulate T cell mediated inflammatory responses (Lenert, Brummel et al. 2005).

3.1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common T cell-dependent chronic inflammatory disease characterised by synovial proliferation and excessive pro-inflammatory cytokine production, resulting in cartilage and bone destruction (Firestein 2003). Data available on Breg cells in human rheumatoid arthritis are limited, however similar to lupus patients, an increased percentage of B10 and B10pro cells in the peripheral blood of rheumatoid arthritis patients has been observed, indicating that regulatory B cells might play a role in this autoimmune condition too (Iwata, Matsushita et al. 2011). To date, the majority of the experimental data available on arthritis, has been obtained from the murine model of collagen-induced arthritis (CIA), which mimics the immunopathogenesis of human rheumatoid arthritis (Trentham, Townes et al. 1977). Using this model, adoptive transfer of

IL-10 producing B cells has been demonstrated by different groups to prevent the development of arthritis as well as to ameliorate already established disease (Mauri, Gray et al. 2003; Evans, Chavez-Rueda et al. 2007; Gray, Miles et al. 2007).

Mauri and co-workers were the first to show that adoptive transfer of *in vitro* anti-CD40 activated splenic B cells prevented the development of arthritis. The B cells used in these experiments were shown to produce increased amounts of IL-10 and inhibited Th1 differentiation (Mauri, Gray et al. 2003). Work by Evans et al. demonstrated that the number of endogenous IL-10 producing MZ and their precursors T2 MZP B cells were increased during the remission phase of arthritis and that adoptive transfer of T2 MZP to CIA mice prevented disease progression and alleviated established disease. Again, the underlying mechanism seemed to be the reduction of a Th1 type immune response in the presence of immunosuppressive cytokines, rather than cell contact-dependent mechanisms (Evans, Chavez-Rueda et al. 2007). Gray et al. induced IL-10 producing regulatory B cells in the spleen of CIA mice by administration of apoptotic thymocytes. Regulatory B cells induced in this manner *in vivo* as well as upon passive transfer after *in vitro* induction, were effective in protecting mice from autoimmune joint inflammation (Gray, Miles et al. 2007).

3.2 Regulatory B cells in organ-specific autoimmune diseases

In contrast to systemic autoimmune diseases, organ-specific autoimmune conditions are characterised by cell- and auto-antibody-mediated immune responses directed specifically against antigens which are only localised in a particular organ such as the pancreatic islets in type I diabetes or the central nervous system in multiple sclerosis.

3.2.1 Inflammatory bowel disease

Inflammatory Bowel Disease (IBD) refers to a group of conditions characterised by inflammation in the intestinal tract, with Crohn's disease (CD) and ulcerative colitis (UC) accounting for the majority of cases. While in CD chronic inflammation is mainly mediated by the Th1 pathway, UC is also associated with the presence of auto-antibodies, leading to the initial assumption that B cells might play a role in disease initiation (Mizoguchi, Mizoguchi et al. 1996; Bhan, Mizoguchi et al. 1999).

Studies in various mouse models of IBD demonstrating the protective roles of B cells, were among the earliest publications to document the existence and relevance of regulatory B cells. Mizoguchi et al. used a mouse model deficient in TCRα that spontaneously develops UC-like chronic colitis and demonstrated that B cells were not required to initiate disease at all, but could actually suppress colitis (Mizoguchi, Mizoguchi et al. 1997). These B cells were later shown to appear during chronic intestinal inflammation, exhibit upregulated CD1d expression and release IL-10 (Mizoguchi, Mizoguchi et al. 2002). Furthermore, adoptive transfer experiments confirmed a protective role of B cells via mechanisms like IL-10 production and induction of regulatory T cells (Bhan, Mizoguchi et al. 2000; Mizoguchi, Mizoguchi et al. 2002; Wei, Velazquez et al. 2005). Several additional studies performed by different groups using various mouse models have confirmed that B cells can regulate UC-like intestinal inflammation (Gerth, Lin et al. 2004; Hokama, Mizoguchi et al. 2004; Su, Guo et al. 2004; Sugimoto, Ogawa et al. 2007) as well as Crohn's disease-like conditions (Dalwadi, Wei et al. 2003; Wei, Velazquez et al. 2005; Ostanin, Pavlick et al. 2006).

Interestingly, B cells producing IL-12 in an IL-10-dependent manner, have also been demonstrated to be protective in a mouse model of UC-like Th2-mediated colitis (Sugimoto, Ogawa et al. 2007). In Crohn's disease-like Th1-mediated colitis, IL-12 was initially considered to be pathogenic, however a recent report suggests that IL-23 sharing the common subunit p40 (p19/p40) rather than IL-12 (p35/p40) is pro-inflammatory and the one to mediate disease (Cua, Sherlock et al. 2003; Yen, Cheung et al. 2006). Importantly, both IL-12 subunits p35 and p40 have been demonstrated to be crucial in B cell mediated attenuation of colitis (Sugimoto, Ogawa et al. 2007). However, it needs to be noted that a possible contribution of another potent suppressive cytokine sharing the p35 subunit, namely IL-35, has not been taken into account (Collison, Workman et al. 2007; Niedbala, Wei et al. 2007).

3.2.2 Multiple sclerosis

Multiple sclerosis (MS) is considered a T cell-mediated autoimmune condition that results in inflammatory lesions, demyelination and axonal damage in the central nervous system (CNS). A mouse model mimicking human MS, experimental autoimmune encephalomyelitis (EAE) has been used widely to investigate the underlying immunological mechanisms and the components of the immune system involved in disease pathogenesis (Baxter 2007). Similar to other autoimmune diseases, clonal expansion of B cells and the production of auto-antibodies, indicate that B cells contribute to the pathogenesis of MS (Colombo, Dono et al. 2000; Fraussen, Vrolix et al. 2009). However, the effects of anti-CD20-mediated B cell depletion in the EAE model depend crucially on timing, as treatment shortly after disease onset reduced disease severity, while depletion prior to disease induction or at the peak of disease did not change the disease course or even led to disease exacerbation (Matsushita, Yanaba et al. 2008). Exacerbation of disease indicates a protective role of B cells and Wolf et al. were one of the first groups to show that there might indeed be an additional protective function of B cells in EAE. They demonstrated that although the incidence and severity of disease was comparable between mice genetically deficient in mature B cells and wild type control mice, B cell deficient mice failed to undergo spontaneous recovery and developed chronic disease instead (Wolf, Dittel et al. 1996).

Several recent studies confirm these findings showing in addition that IL-10 producing B cells are responsible for this protective effect (Fillatreau, Sweenie et al. 2002; Matsushita, Fujimoto et al. 2006; Lampropoulou, Hoehlig et al. 2008). Furthermore, adoptive transfer experiments revealed a possible therapeutic potential of isolated regulatory B cells in EAE (Mann, Maresz et al. 2007; Matsushita, Yanaba et al. 2008; Rafei, Hsieh et al. 2009; Kala, Rhodes et al. 2010). Considering the extensive use of MS treatments that are dependent on B cell depletion, it seems crucial to define this dual role of B cells in the progression of disease. Lee-Chang et al. demonstrated that homeostasis of the B cell subsets is altered during the preclinical and acute phases of EAE, where the percentage of B cells with regulatory phenotype are significantly reduced (Lee-Chang, Lefranc et al. 2011), indicating again that timing is an important consideration when targeting B cells during therapy. It was also shown that B cell depletion reduced the frequency of regulatory T cells, and increased the pro-inflammatory polarising capacity of the remaining myeloid APC (Weber, Prod'homme et al. 2010).

Interestingly, in human MS patients, peripheral blood B cells produced less IL-10 in response to TLR-9 as well as CD40 and BCR stimulation compared to healthy controls (Duddy, Niino et al. 2007; Hirotani, Niino et al. 2010). This might indicate that Breg cells in human MS patients are functionally impaired, or simply exhausted due to chronic pro-inflammatory stimulation, and thereby are implicated in disease development.

3.2.3 Type 1 diabetes

Type 1 diabetes (T1D) and the spontaneous disease that develops in the corresponding mouse model (non-obese diabetic (NOD) mouse), is characterised by autoimmune destruction of the insulin-producing pancreatic β cells. Attack on β cells is primarily mediated by T cells (Anderson and Bluestone 2005), however B cells and humoral immunity also play a role, especially in disease initiation (Silveira and Grey 2006; Xiu, Wong et al. 2008). Despite the pathogenic role of B cells in disease initiation, B cells activated *in vitro* can maintain tolerance and transfer protection from disease in NOD mice (Tian, Zekzer et al. 2001; Hussain and Delovitch 2007). Transfusion of BCR-stimulated B cells reduced the incidence and delayed the onset of disease, when given repeatedly starting at a young age before disease onset. Disease protection was dependent on IL-10 and correlated with the polarisation of T cells towards a Th2 phenotype (Hussain and Delovitch 2007). In a different experimental setting, transfer of *in vitro* LPS-stimulated B cells protected NOD mice from spontaneous diabetes. As these B cells were shown to express FasL and secrete TGF-β, this effect was attributed to the triggering of apoptosis in Th1 cells and/or the inhibition of APC activity (Tian, Zekzer et al. 2001).

4. Regulatory B cells in allergic diseases

The vast majority of studies on regulatory B cells has been focused on autoimmunity models. However, recent studies indicate that Breg cells may also be instrumental in reducing T-helper 2 (Th2) skewed immune diseases, such as allergies. Allergies are dysregulated immune responses towards normally harmless allergens that result in an expansion of polarised Th2 cells, elevated immunoglobulin E (IgE) production and eosinophilia (Kay 2000). Common allergic diseases include allergic asthma, rhinitis, atopic dermatitis, and food allergies. Allergic asthma is characterised by reversible airway obstruction and airway remodelling upon exposure to inhaled aeroallergens such as house dust mite (HDM), grass pollen, or pet dander. In allergic rhinitis (hay fever), allergen exposure leads to irritation and inflammation of the nasal airways, whereas atopic dermatitis is an inflammatory, chronically relapsing, non-contagious and pruritic skin disorder. In food allergies, exposure to food products such as peanuts, fruits or milk may lead to allergic symptoms including gastrointestinal and respiratory distress, or life-threatening anaphylactic responses (Kay 2000).

Traditionally, B cells have been known for their capacity to produce antibodies, thereby contributing to humoral immunity and clearance of pathogens. During allergic disorders, B cells are driven to preferentially class-switch to IgE isotypes in the presence of local IL-4 and this forms a central element in the acute inflammatory responses to allergens. Allergen-specific IgE binds to Fc-receptors (FcR) on mast cells and basophils and subsequent exposure to the same allergen leads to degranulation and inflammation. So far, reports evaluating B cell function other than Ig(E) production in allergies are limited. Nevertheless,

a few reports suggest that in allergic inflammation, like in autoimmunity, B cells can have a regulatory role (Hussaarts, van der Vlugt et al. 2011). For example, B cells isolated from OVA tolerant mice were able to dampen acute allergic airway inflammation via the TGF-β induced conversion of $CD4^+CD25^-$T cells into functionally suppressive $CD4^+CD25^+FoxP3^+$ T regulatory cells (Singh, Carson et al. 2008). In addition, B cells were also shown to control experimental cockroach allergen-induced inflammation by the induction of FasL-mediated apoptosis of $CD4^+$ T cells. In mice lacking B1a B cells, it was demonstrated that in particular the $CD5^+$ B1a B cell population was important for protective $CD4^+$ T cell apoptosis (Lundy, Berlin et al. 2005). Furthermore, two reports have studied the presence of human IL-10 or TGF-β producing B cells in non-IgE mediated food allergy. In response to the milk antigen, casein, the frequency of IL-10 or TGF-β producing $CD5^+$ peripheral blood B cells increased in healthy donors whereas the frequency declined in allergic donors (Noh, Choi et al. 2010; Lee, Noh et al. 2011). In addition, our group observed less IL-10 producing B cells in response to LPS in house dust mite allergic asthma patients compared to healthy controls (Mlejnek and van der Vlugt 2012). These findings support the notion that Breg cells may form an important regulatory arm of the immune system and seem to be dysfunctional in allergic disorders.

5. Implications of pathogen-induced Breg cells in autoimmunity and allergy

The onset of hyperinflammatory disorders such as allergies and autoimmunities seems to be partly genetic, as the risk for developing disease increases when a parent or a sibling is affected (Mariani 2004; von Mutius 2009). However, the steep increase in the incidence of hyperinflammatory disorders over the last few decades in the Western world has suggested that environmental factors may also have a major impact. Fast changes in lifestyle, housing, improved hygiene and vaccinations in industrialised countries have resulted in reduced microbial exposure during early childhood (Wills-Karp, Santeliz et al. 2001; Yazdanbakhsh, Kremsner et al. 2002), which may allow for uncontrolled inflammatory responses against either innocuous or self-antigens later in life. In support of this 'hygiene' hypothesis, several epidemiological studies have pointed towards a reversed relationship between hyperinflammatory disorders and microbial exposure, such as bacterial, viral and helminth infections.

5.1 Hyperinflammatory disorders and the 'hygiene hypothesis'

Parasites are regarded to be master manipulators of the host immune system. A negative correlation between the rates of parasitic infections in developing countries and the prevalence of allergic symptoms and atopic sensitisation in children has been highlighted in a number of studies in different geographical areas (Flohr, Quinnell et al. 2009). Strikingly, long-term anti-helminth treatment resulted in increased atopic reactivity to house dust mite, supporting a direct link between helminth exposure and protection against allergic diseases (Lynch, Hagel et al. 1993; van den Biggelaar, Rodrigues et al. 2004). In addition, helminth infected MS patients showed better clinical disease outcome compared to control MS patients (Correale, Farez et al. 2008). A relationship between helminth infections and protection against hyperinflammatory disorders has also been established in various mouse models for food allergy (Nagler-Anderson 2006), asthma (Smits, Hammad et al. 2007; Amu, Saunders et al. 2010), T1D (Zaccone, Fehervari et al. 2003; Liu, Sundar et al. 2009), CIA

(Osada, Shimizu et al. 2009) and EAE (La Flamme, Ruddenklau et al. 2003; Wilson, Taylor et al. 2010). Furthermore, different cross-sectional studies show that children living in farming environments are protected from childhood asthma and atopy and this correlation has been attributed to contact with livestock (Ege, Frei et al. 2007) and hay and the consumption of raw cow's milk (Douwes, Cheng et al. 2008; Loss, Apprich et al. 2011). In farming environments, both outdoor and indoor microbial exposure are higher and more diverse compared to nonfarming environments (von Mutius, Braun-Fahrlander et al. 2000; Ege, Mayer et al. 2011). More detailed analysis of the dust composition showed that a lower risk of asthma was associated with Gram-negative bacteria and fungi of the *Eurotium* and *Penicillium* species (Ege, Frei et al. 2007; Ege, Mayer et al. 2011). Inhalation is a main route of exposure to pathogens, but ingestion of orofecal microbes (Matricardi, Rosmini et al. 1997) or colonization of certain probiotic bacteria stimulating the gut associated lymphoid tissue (GALT) may also help to avoid allergic responses or certain autoimmune conditions. A direct association between the composition of the gastrointestinal microbiome and the risk of developing allergies has been described in several studies, suggesting that *Lactobacilli* and *Bifidobacterium bifidum* have a protective effect (Bjorksten, Sepp et al. 2001; Johansson, Sjogren et al. 2011). Also in line with this data, changes in faecal microbiota were detected in autoimmune patients suffering from Crohn's disease and ulcerative colitis (Manichanh, Rigottier-Gois et al. 2006; Frank, St Amand et al. 2007).

Altogether these findings indicate that microbial exposure during early life seems to be important to prevent hyperinflammatory conditions. Various studies have indicated that the development of the regulatory arm of the immune system is instrumental for this protection, and so far have highlighted a role for Treg cells (Wohlfert and Belkaid 2008). However, there is a growing amount of evidence showing a protective role for Breg cells induced by infectious agents.

5.2 Pathogen-induced Breg cells are protective in autoimmune and allergic conditions

One of the first observations that helminths, such as *Schisostoma mansoni*, could induce suppressive B cells was made in µMT mice, which lack mature B cells. These mice show increased *S.mansoni*-induced tissue pathology compared to infected wild-type mice (Jankovic, Cheever et al. 1998). Subsequent studies with *S. mansoni* demonstrated that B cells isolated from helminth-infected mice could play a protective role in allergy, as transfer of B cells protected recipient mice against systemic fatal anaphylaxis or OVA-induced airway inflammation via the production of IL-10 (Mangan, Fallon et al. 2004; Mangan, van Rooijen et al. 2006; Amu, Saunders et al. 2010). Interestingly, these regulatory mechanisms were only active during the chronic phase of infection (Smits, Hammad et al. 2007). Similar results were obtained in *Heligosomoides polygyrus*-infected mice, where $CD19^{+}CD5^{-}CD23^{hi}$ B cells isolated from mesenteric lymph nodes of chronically infected mice were able to suppress Derp1-induced airway inflammation, although independently of IL-10 (Wilson, Taylor et al. 2010). Interestingly, *S. mansoni*-induced Breg cells also incurred protection against allergic airway inflammation via the induction of regulatory T cells (Amu, Saunders et al. 2010). However, Breg-induced immune regulation was only partially dependent on Treg cell induction as we could demonstrate in conditional FoxP3 knockout mice (van der Vlugt and Labuda 2012). In addition, B cell induced FasL-mediated apoptosis of $CD4^{+}$ T cells appeared to be another

mechanism used by Breg cells to control inflammation during schistosome infections (Lundy and Boros 2002). Helminth-induced Breg cells also ameliorated symptoms of several autoimmune diseases. Adoptive transfer of B cells isolated from *H. polygyrus* infected mice, dramatically reduced EAE severity in uninfected recipients (Wilson, Taylor et al. 2010) and B cells from helminth infected MS patients suppressed T cell activation *in vitro* (Correale, Farez et al. 2008). The production of B cell IL-10 and the induction of Treg cells were important in the reduction of inflammation. Treg cell induction was further shown to be dependent on expression of B7 costimulatory molecules, as B7 deficient B cells failed to efficiently recruit Treg cells into the CNS and mediate recovery from EAE clinical disease (Mann, Maresz et al. 2007). In addition to helminthic infection, bacterial exposure may also enhance the activity of Breg cells. For example, TLR signaling on B cells is required for the recovery from EAE. Interestingly, although both TLR-4 (LPS) and TLR-9 (CpG) signaling induced IL-10 expression in B cells, only LPS stimulation via TLR-2/4 was capable of inducing recovery from EAE (Lampropoulou, Hoehlig et al. 2008). Furthermore, tissue damage as a result of invading pathogens may induce apoptosis and can influence the development of Breg cells. Injection of apoptotic cells into mice has been shown to induce Breg cells and reduce inflammatory processes in a collagen-induced arthritis model (Gray, Miles et al. 2007). Overall, there is a strong case for the capacity of various pathogens to induce functional Breg cells that are protective against inflammation-driven pathology.

6. Possible therapeutic applications targeting Breg cells in autoimmune and allergic disorders

Several studies have highlighted the relevance of Breg cells in downmodulating inflammation in autoimmune and allergic disorders. In addition to the direct effects via cytokine production, Breg cells also function indirectly via the induction or recruitment of regulatory T cells and therefore may have promising therapeutic potential. However, the mechanism underlying the formation of regulatory B cells and their implications in existing therapies must be fully understood, before these pathways can be exploited for therapeutic purposes.

6.1 Pathogen-driven pathways for the induction and expansion of Breg cells

As demonstrated in figure 3, Breg cells can be induced by bacterial or parasitic infections. Therefore, the identification of the secreted or excreted pathogenic compound(s) driving Breg cell induction provides useful information for the development of therapeutic interventions. Indeed, the fact that live schistosome worms could induce IL-10 producing Breg cells from splenic B cells in an *in vitro* culture system, suggests that helminth antigens have a direct effect on B cells (Amu, Saunders et al. 2010). Helminth-related TLR ligands may be a likely candidate responsible for helminth-induced Breg cell formation, given the implication of certain TLR ligands in the induction of Breg cells in autoimmune models (as discussed above). Notably, lacto-N-fucopentaose-III (LNFPIII), a sugar found on soluble egg antigens (SEA) interacts with TLR-4 and stimulates splenic B cells to produce IL-10 (Velupillai and Harn 1994). Likewise, microfilarial extracts from *Leishmania major*, and *Brugia malayi*, which both bind to TLR-4, can induce IL-10 production by B cells (Palanivel, Posey et al. 1996). Furthermore, lyso-phosphatidylserine, a lipid derived from *S. mansoni* worms

ligated TLR-2 on human monocyte-derived DC and promoted Treg cell activity (van der Kleij, Latz et al. 2002). Although it is unclear whether this TLR-2 ligating molecule has an effect on the formation of Breg cells, SEA stimulation of human B cells did result in TLR-2 mediated elevated IL-10 production (Correale and Farez 2009).

Bacterial infections such as *Helicobacter felis* induced IL-10 producing B cells via TLR-2 signalling and were also able to suppress *Helicobacter*-induced pathology via the induction of IL-10 producing T cells (Sayi, Kohler et al. 2011). Other bacterial structures, such as CpG oligonucleotides (ODN) binding to TLR-9, are also well known to be strong inducers of B cell IL-10 production (Barr, Brown et al. 2007; Bouaziz, Calbo et al. 2010). Interestingly, administration of CpG ODN to mice potently inhibited acute and established asthma, allergic rhinitis and conjunctivitis (Fonseca and Kline 2009). Additionally, human clinical trials with CpG ODN conjugated with ragweed antigen revealed that ragweed allergy subjects developed a shift in immune response from Th2 towards a dominant Th1 profile (Simons, Shikishima et al. 2004) and a decrease in clinical allergy symptoms two years after treatment (Tulic, Fiset et al. 2004). Although the role of IL-10 producing B cells was not studied in those clinical trials, a recent study in mice clearly showed that immunosuppressive IL-10 producing follicular B cells appeared after CpG treatment. These Breg cells were responsible for the reduction in late phase experimental allergic conjunctivitis (Miyazaki, Kuo et al. 2009), suggesting that the administration of CpG can also form an important therapeutic approach to induce Breg cell activity.

6.2 Induction and expansion of Breg cells by chemical drugs used in medical treatment

Clonal expansion of B cells and the production of auto-antibodies indicate that B cells contribute to the pathogenesis of several autoimmune diseases. Accordingly, B cell depletion therapy using Rituximab (anti-CD20) has shown promising effects in clinical trials (Bar-Or, Calabresi et al. 2008; Hauser, Waubant et al. 2008). However, possible implications for regulatory B cells in the treatment of human autoimmune diseases have been indicated by recent studies investigating the immunological mechanisms of drugs already used for medical treatment of human patients (Fig. 3). A very recent report shows that an antibody acting as an IL-6R antagonist (Tocilizumab), which has recently been introduced as therapy for rheumatoid arthritis, causes regulatory $CD25^+$ B cells to increase their TGF-β expression and alter their activation status, indicating that the beneficial effects of Tocilizumab are due to an induction or expansion of regulatory B cells (Snir, Kessel et al. 2011).

Beneficial effects of several drugs used in the treatment of multiple sclerosis also seem to be mediated by regulatory B cells. Glatiramer acetate (GA) is a drug safely used in MS patients, and it has been demonstrated that the beneficial effects of GA were abrogated in B cell-deficient mice. Furthermore, adoptive transfer of B cells from GA-treated mice inhibited the proliferation of autoreactive T cells as well as the development of Th1 and Th17 cells, but promoted IL-10 production in recipient mice (Kala, Rhodes et al. 2010; Begum-Haque, Christy et al. 2011). Estrogen, a hormone drug with well established therapeutic effects on MS, was shown to depend on B cells as well. In EAE, estrogen-mediated protection from disease was associated with a general increase in the percentage of IL-10-producing regulatory B cells as well as an upregulation of PD-L1 expression on B cells, possibly leading

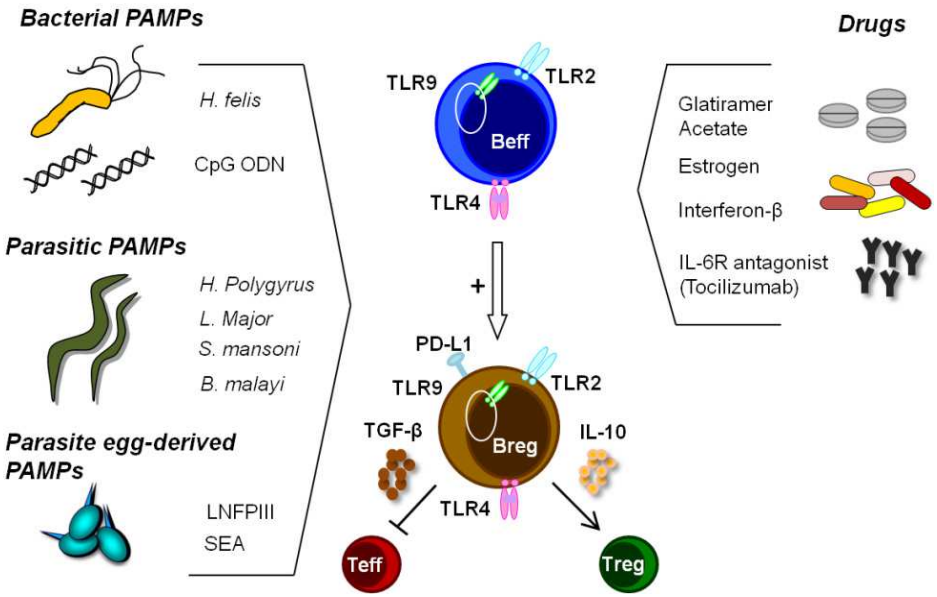

Fig. 3. Pathways for the induction and expansion of Breg cells. Different secreted or excreted (non)pathogenic compounds of bacteria, parasites or their eggs can drive Breg cell induction. These compounds have been shown to bind to TLR and thereby induce Breg cell development. Additionally, Breg cell promoting activities were found in several registered drug-based treatments for autoimmune diseases. As a consequence, Breg cells start to produce anti-inflammatory cytokines IL-10 and TGF-β, inhibit Teff cell proliferation and induce Treg cells. PAMPs: pathogen associated molecular patterns, TLR: Toll-like receptor, Breg: regulatory B cells, Teff/reg: effector/regulatory T cells, LNFPIII: lacto-N-fucopentaose-III, SEA: soluble egg antigens.

to direct target cell apoptosis (Bodhankar, Wang et al. 2011). As previous studies on B cells from human MS patients have demonstrated a defective IL-10 producing capacity (Duddy, Niino et al. 2007; Hirotani, Niino et al. 2010), upregulation of IL-10 production by B cells might be of importance in disease resolution in MS patients undergoing treatment. Indeed, a study on human patients treated with IFN-β demonstrated that their B cells showed a lower proliferative response *in vitro* than B cells from untreated patients. *In vitro* IFN-β treatment of B cells shifted their cytokine profile and induced IL-10 secretion (Ramgolam, Sha et al. 2011).

7. Concluding remarks

The underlying mechanisms leading to inflammatory conditions such as autoimmune diseases and allergies are diverse and far from being fully understood. However, it has become obvious that a balance between effector and regulatory functions of different subsets of immune cells is crucially important in the maintenance of a healthy steady-state situation.

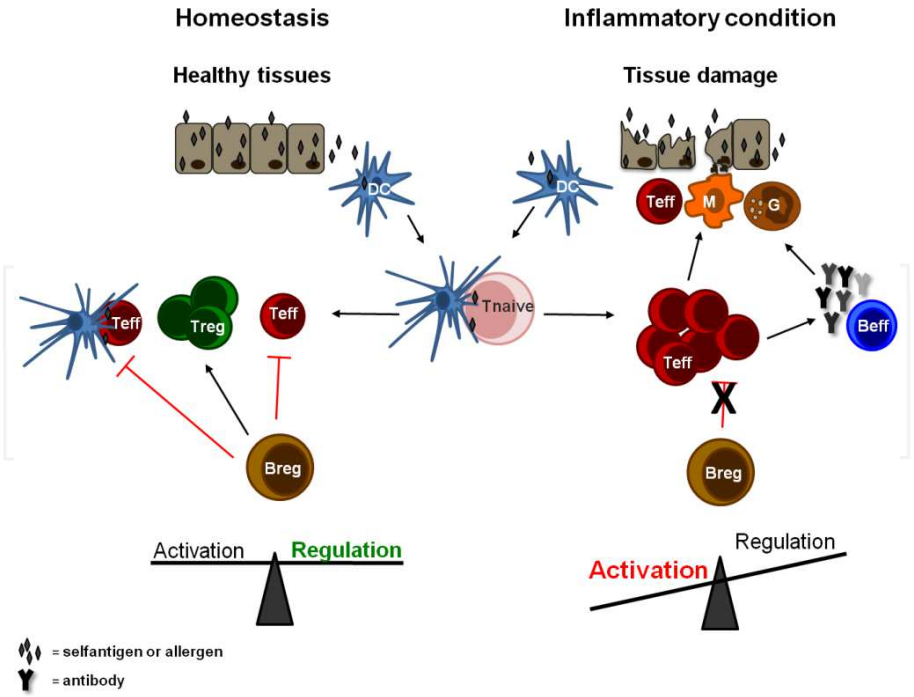

Fig. 4. Regulatory B cells in homeostasis and disease. Under normal conditions regulatory B cells control T effector cell activation and proliferation in response to harmless self antigens and allergens, and induce and activate regulatory T cells. If Breg cell mediated control fails, effector T cells can proliferate and activate antibody producing B cells as well as innate immune cell types causing tissue damage. Beff/reg: effector/regulatory B cells, Teff/reg: effector/regulatory T cells, Tnaive: naive T cells, DC: dendritic cells, M: macrophages, G: granulocytes.

Regulatory B cells are an exciting new player on the regulatory side of this constant struggle for balance. As depicted in figure 4, in the healthy immune system Breg cells help to control effector cell activation, by releasing immunosuppressive cytokines and inducing target cell apoptosis. The broad target cell range of their cytokines allows them to inhibit pro-inflammatory functions of both innate immune cells, such as DC and macrophages as well as cells of the adaptive immune system, such as effector T cells of both the Th1 and Th2 lineage. On the other hand they also amplify the regulatory arm of immune responses by inducing regulatory T cells. Impaired regulatory capacity of Breg cells might play a role in the development of inflammatory diseases. Uncontrolled effector T and B cell activation can ultimately lead to inflammation and tissue damage in various target organs. Correspondingly, several treatments demonstrated to be beneficial in autoimmune and allergic diseases seem to affect the immune system at the level of B cells by amplifying their regulatory capacity. Currently much effort is put into therapies aiming to induce regulatory T cells. However, targeting regulatory B cells instead holds the added benefit of indirectly affecting all target cell types of Breg cells, including regulatory T cells, making it a more

efficient approach. Therefore, further research is needed to increase our understanding of Breg cell biology in health and disease, as targeting Breg cells for therapeutic applications holds great promise for the future treatment of autoimmune and allergic inflammatory conditions.

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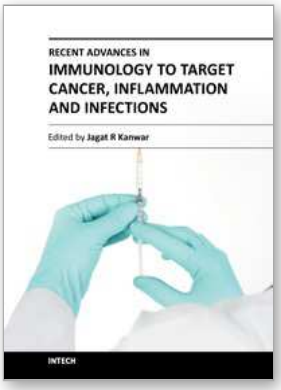

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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