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Review

The regulatory role of B cells in autoimmunity, infections and cancer: Perspectives beyond IL10 production

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ABSTRACT

The term regulatory B cells (B regs) is ascribed to a heterogeneous population of B cells with the function of suppressing inflammatory responses. They have been described mainly during the last decade in the context of different immune-mediated diseases. Most of the work on B regs has been focused on IL-10-producing B cells. However, B cells can exert regulatory functions independently of IL-10 production. Here we discuss the phenotypes, development and effector mechanisms of B regs and advances in their role in autoimmunity, infections and cancer.

1. Introduction

B lymphocytes are the only cell type in the organism capable of producing antibodies (Abs). In addition, this population can influence immunity in multiple ways such as antigen presentation to T cells, expression of surface co-stimulatory/inhibitory molecules and cytokine secretion. Consequently, B cells can act as drivers of innate and adaptive immunity. The name of regulatory B cells (B regs) is ascribed to a heterogeneous population of B cells with the function of suppressing directly or indirectly inflammatory responses. They have been described mainly during the last decade in the context of different autoimmune and infectious diseases, and cancer.

2. Regulatory B cells: phenotypes and suppression mechanisms

Many efforts have been made to associate a particular B cell phenotype to the regulatory function. The term "regulatory" B cell to designate a B cell with inhibitory properties was used for the first time by Mizoguchi and Bhan [1]. Initially, B cells with recognized regulatory functions were the IL-10-producing B cells described in the autoimmune models of colitis, experimental autoimmune encephalitis (EAE) and arthritis [2–4]. These cells can present different phenotypes in mice. Several subsets of IL-10-producing B regs show expression of CD1d, such as $CD1d^{hi}CD5^{-}B220^{low}CD11b^{+}IgM^{+}$ [2], $CD1d^{hi}CD5^{+}$ (denominated B10 cells) [5] and $CD1d^{hi}Tim^{+}CD5^{+}$ [6], which were linked with the protection from autoimmune diseases. However, it is important to point out that CD1d is expressed on a wide variety of cell types. Indeed, it is constitutively expressed in most B cells (not only those secreting IL-10), with the highest expression on MZ B cells ($CD21^{hi}IgM^{hi}IgD^{lo}CD24^{int}CD23^{-}CD43^{-}$) and T2 B cells ($CD21^{hi}IgM^{hi}IgD^{hi}CD23^{+}$) [7]. Peritoneal $CD5^{+}$B1 cells have been described as the main source of B cell-derived IL-10 [8]; however, these cells were associated more to autoimmunity promotion than to immunoregulation [9]. In addition, it has been demonstrated that $CD5^{+}$ B cells synthesize as much IL-10 as $CD5^{neg}$ B cells after mitogen- or antigen-stimulation, indicating that B cells produce IL-10 independently of CD5 expression [10].

Although little is known about human B regs, it has been reported that B cells from healthy individuals and patients with active Rheumatoid Arthritis (RA) presenting a phenotype $CD19^{+}CD24^{hi}CD38^{hi}CD1d^{+}$ were able to suppress the release of IFN-γ by $CD4^{+}$T cells but did not suppress IL-6 and IL-8 production [11]. In addition, a subset of IL-10-producing $CD24^{hi}CD27^{+}$ B cells analogous to murine B10 cells was also shown to exist in humans [12]. There are also descriptions of human IL-10 and TGF-β producing-$CD25^{hi}CD27^{hi}CD86^{hi}CD1d^{hi}$ B cells able to suppress autologous T cell proliferation and to induce the generation of $Foxp3^{+}CTLA4^{+}$ regulatory T cells (Tregs) in a cell-to-cell

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contact-mediated and TGF-β-dependent mechanism [13]. Finally, Griffin and Rothstein reported the capacity of CD11b$^+$ B1 cells, a recently described subpopulation of B1 cells [14], to spontaneously produce IL-10 and suppress T-cell activation [15]. Owing to their capacity to either stimulate T-cell proliferation [14] or suppress T-cell activation [15], these B cells should be able to guide the immune response.

Taking into account that IL-10-producing B cells express different surface markers, it is not possible to assign the regulatory function to a unique phenotype, and it is probable that surface phenotypes are more related to the origin of the B cell subset rather than to their function. In addition, detection of intracellular cytokines involves stimulation, fixation and permeabilization, which is likely to alter the initial phenotype of B cells, hindering the correct phenotypification of the B cell subset in study.

As a result of the impossibility to define a particular phenotype for the B reg cell subset, one of the main challenges of B reg cell research is the identification of a B reg cell-specific transcription factor analogous to Foxp3 in Tregs [16], as it has been previously proposed [17]. The identification of such molecule would allow the direct association of the regulatory function to a transcription factor instead of to a surface phenotype or functional assay. This may accelerate B reg identification in different diseases as well as the design of therapeutic trials for B reg induction and tolerance restoration.

As we mentioned, B regs may regulate different scenarios through the expression of cytokines other than IL-10, including TGF-β, IL-35, and IL-17. Through TGF-β production, lipopolysaccharide (LPS)-activated B cells can induce apoptosis of CD4$^+$ [18] and anergy in CD8$^+$ [19] effector T cells. TGF-β is produced by both CD5$^+$ and CD5$^-$ B cells from autoimmune-prone NZB mice [20] and it is also expressed by normal human B cells [21]. These TGF-β$^+$ B cells play essential roles in the induction of tolerance to non-IgE mediated food allergy in atopic dermatitis [21]. IL-35-producing B cells were identified as key players in the negative regulation of immunity as mice in which only B cells did not express IL-35 failed to recover from the T-cell-mediated demyelinating autoimmune disease EAE [22]. We reported that B cells were the main splenic population producing IL-17 during *Trypanosoma cruzi* infection. Furthermore and in agreement with the regulatory role of IL-17 during this parasite infection [23], transfer of WT B cells but not of IL-17-deficient B cells decreased the inflammatory response and mortality of *T. cruzi* infected B cell-deficient mice [24]. These results highlight that IL-17$^+$ B cells play critical roles in the regulation of inflammation.

It was of great interest to find that within the cytokine-producing B regs described in infections by Shen et al. [22] and our group (Bermejo et al. [24]), there was an important proportion of CD138$^+$ plasma cells. In 2012, Maseda et al. [25] first suggested that splenic Pax5$^+$ B10 cells could rapidly convert into plasmablasts after in vivo or in vitro activation; nevertheless, they did not test the regulatory capacity of the arising plasmablasts/-plasma cells. Furthermore, during the characterization of B cells with potential regulatory function generated in the draining lymph node during EAE, IL-10-producing plasmablasts with a mixed phenotype in terms of IgM and IgG expression and a reasonable degree of class switching were detected [26]. However, it is not clear which plasmablast population, whether the IgM$^+$ or the IgG$^+$, is expressing more IL-10. The generation of these regulatory plasmablasts was dependent on Blimp-1 and IRF-4 as mice lacking plasmablasts by genetic ablation of the transcription factors Blimp-1 or IRF-4 in B lineage cells developed an exacerbated EAE. In contrast, disruption of Bcl-6, a transcription factor that controls B cell germinal center formation, did not reduce CD138$^+$CD44^{hi} plasmablast numbers and did not exacerbate EAE development, suggesting that regulatory plasmablast generation was mainly in extrafollicular foci and not dependent on germinal center responses [26]. Accordingly, we observed that IL-17-producing plasmablasts and plasma cells with high expression of IgM are located outside the splenic follicles and proximal to the central arteriole (T cell zone) [24], possibly as product of the strong extrafollicular plasmablast response produced in *T. cruzi* infection [27]. Therefore, as suggested by Mauri and Blair [28], it seems plausible to hypothesize that regulatory plasmablasts are contained within the IgM$^+$ plasmablast pool, and are probably short-lived plasma cells. It would be of great interest to further examine in these regulatory plasmablast populations their degree of somatic hypermutation, their ability to simultaneously release cytokines and antibodies, their expression of inhibitory receptors and how long these cells can persist after the resolution of inflammation.

Finally, there is evidence that B cells would regulate immunity not only through cytokine production but also via surface molecules, such as CD39, CD73 and Programmed death-ligand 1 (PD-L1). Indeed, a novel population of B cells has been shown to regulate colitis in an IL-10-independent manner but dependent on the expression of CD39 and CD73 [29]. CD39 is an ectonucleoside triphosphate diphosphohydrolase-1 and CD73 is an ecto-5′-nucleotidase which hydrolyze exogenous adenosine triphosphate (ATP) to adenosine 5′-monophosphate (AMP) and finally produce immunosuppressive adenosine (ADO) [30–32]. In the dextran sulfate sodium salt-induced colitis murine model, transfer of ADO-producing CD73$^+$ B1 cells conferred resistance to the colitis susceptible CD73$^{-/-}$ mice [29]. In addition, experiments performed by Saze and collaborators [33] demonstrated that upon activation, human B cells increase their expression of CD39 and acquire the capability to downregulate proliferation of autologous CD4$^+$ or CD8$^+$ T cells. They also showed that 5′-AMP and perhaps other components of the ADO pathway (such as inosine and hypoxanthine) produced by activated B cells are potentially responsible for this inhibitory activity. ADO not only suppresses T cell but also B cell proliferation since 2-chloroadenosine, used instead of ADO because of its greater stability, inhibited B cell proliferation. The result suggests an immunosuppressive autocrine mechanism mediated by the CD39/ADO pathway [33].

As regards the role of PD-L1-expresing B cells there are a few reports. Like in PD-L1$^+$ Tregs which can transduce an inhibitory signal into effector T cells through interacting with programmed death-1 (PD-1), PD-L1-expressing B cells also have been proved to exert a suppressive role on PD1-expressing CD8$^+$ T cells, inhibiting their proliferation and effector functions in *Salmonella* infection [34] and cancer [35]. Considering the great impact of PD-1/PD-L1 pathway on cancer and viral infection progression [36–38], more studies about PD-L1-expressing B cells or their products of differentiation are needed.

3. Induction and development of regulatory B cells

The diversity in the phenotypes reported for B regs has led to controversies about their origin and development. Regarding B10 development, several reports suggest that B10 cells are T cell-independent. Indeed, major histocompatibility complex (MHC) class I and class II molecules, and CD1d expression are not required for B10 cell development [39]. Furthermore, naïve B cells produced large amounts of IL-10 upon activation with TLR-2, -4, or -9 ligands in vitro, but not upon stimulation via CD40 or B cell-receptor for antigen (BCR) either alone or combined [40]. The idea that intrinsic TLR signaling induces suppressive B cells was confirmed in vivo in a model of EAE. Mice in which only B cells lacked TLR-2, TLR-4 or the major TLR-signaling adaptor, MyD88, developed a chronic form of the disease, whereas mice with wild-type B cells recovered after a short episode of paralysis [40]. Thus, the suppressive functions of

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B cells appear to be part of a counter-regulatory circuit promoted directly by the signals that stimulate immunity [41]. In addition, TLR-signaling may be important not only for B10 development but also for TGF-β producing B cells that emerge after stimulation with LPS [18].

Contrary to results reported in vitro, BCR signaling may also be an important stimulus for B10 development in vivo. It has been reported that transgenic mice with a fixed BCR have a decrease of approximately 90% in the frequency of B10 cells [39], and mice deficient/transgenic for receptors that influence BCR signaling showed altered numbers of B10 [5]. For instance, a deficiency in CD19, a molecule that promotes BCR signaling, resulted in a decreased B10 development whereas overexpression of CD19 in mice expressing transgenic human-CD19 caused an increase in B10 numbers [5]. In a similar manner, deficiency in CD22, a negative regulator in BCR signaling, boosts the numbers of B10 [42] [43]. Then, this may be an antigen-specific mediated induction of B10 in vivo since, as we have previously mentioned, Fab_2 anti-IgM Ab did not induce IL-10 expression [39].

Unexpectedly, B cell-activating factor (BAFF), a member of TNF family cytokines that is a key regulator for B cell maturation and function and whose increase is associated to autoimmunity [44], induced IL-10 production by B cells mainly derived from marginal zone (MZ). Notably, BAFF treatment in vivo increased the number of IL-10-producing B cells in marginal zone regions, and the transfer of BAFF-induced $CD5^+CD1d^{hi}$ IL-10-producing B cells partially prevented the development of collagen-induced arthritis (CIA) [45].

On the other hand, an interaction between B10 cells and T cells has also been described. This interaction may be necessary to explain how IL-10 production by B10 cells and the negative regulation of antigen-specific autoimmune inflammation occur in vivo, without inducing systemic immunosuppression. Using a mouse model for multiple sclerosis, Yoshizaki and collaborators [46] demonstrated that B10 cell maturation into functional IL-10-secreting effector cells in vivo requires IL-21 and CD40-dependent cognate interactions with T cells. Moreover, ex vivo stimulation of B cells via CD40 and IL-21 receptor favored B10 cell development and expansion, and the generated IL-10-producing B10 effector cells could inhibit disease symptoms once the autoimmune disease was established. Then, these data may indicate that while B10 cells do not require exclusively T cells to acquire IL-10 competence, they do need cognate interactions with IL-21-producing T cells to become functional regulatory $IL\text{-}10^+$ B cells in vivo.

Concerning the origin of B regs beyond B10 cells, it has been reported that TIM-1 (T cell Ig domain and mucin domain protein 1) expressing regulatory B cells can be induced through TIM-1 ligation [6]. TIM-1 is a co-stimulatory molecule that regulates immune responses by modulating $CD4^+$ T cell effector differentiation. Rothstein's group showed, in a transplant murine model in vivo [6], that B cells rather than T cells, and in particular IL10-producing among all B cell populations, expressed TIM-1. $TIM\text{-}1^+$ B cells, that included transitional, MZ and follicular B cells as well as the B cell population characterized as $CD1d^{hi}CD5^+$, express not only IL-10 but also IL-4, promote Th2 responses, and are able to transfer allograft tolerance. In conclusion, this work proposes TIM-1 as a novel therapeutic target for modulating the immune response and provides insight into the signals involved in the generation and induction of B regs.

Another population of B regs induced in T cell-independent manner is the IL-17-producing B cells. Its program operates independently of key candidate receptors on the B cell surface, such as BCR, CD40, and MyD88-dependent innate receptors. Furthermore, this process is also independent of IL-6, IL-23, AhR, RORγt, and RORα [24], which are usual signals required for IL-17 production by T cells or innate lymphoid cells [47–51]. B cell expression of IL-17 can be induced directly in vitro by live *T. cruzi* trypomastigotes. We found that the parasite-derived trans-sialidase was responsible for B cell activation and IL-17 production via a mechanism that modifies the glycosylation of B cell surface molecules [24]. Our observations suggest that the generation of $IL\text{-}17^+$ B cells may be an unappreciated feature of the B cell innate immune response to *T. cruzi* infection that may condition the further T cell

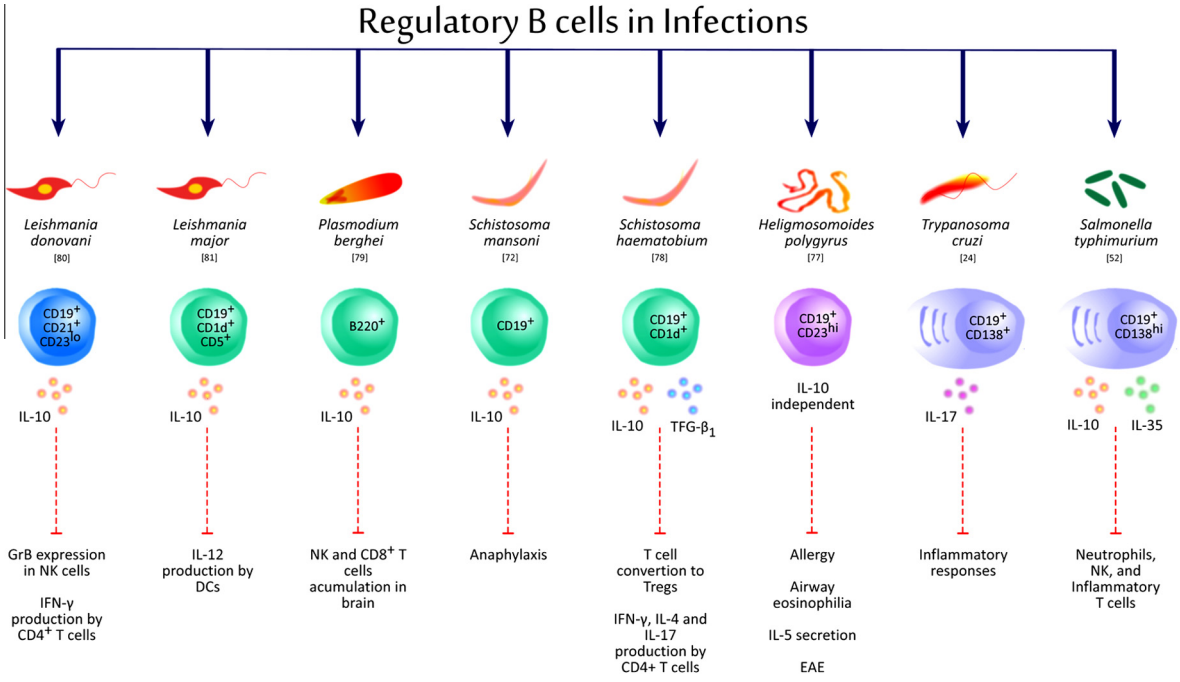

Fig. 1. Detection and characteristic of B regs in different infections. Different microorganisms (parasites and bacteria) induce B regs with different phenotype and cytokine profiles that control microorganism-induced inflammation.

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Table 1
Stimuli reported to induce B regs in vivo and in vitro.

Stimuli	Type of B regs induced
TLR-2, 4 and 9 ligands	B10 [40]
LPS	TGF-β-producing B cells [18]
BCR signaling in vivo	B10 [39,42,43]
BAFF	IL-10-producing MZ B cells [45]
CD40 and IL-21 receptor stimulation	B10 [46]
TIM-1 ligation	IL-10- and IL-4-producing B cells [6]
Trypanosoma cruzi trans-sialidase	IL-17-producing B cells [24]
IL-1β and IL-6	IL-10-producing B regs [53]
IL-33	IL-10-producing B regs [54]
IL-35	IL-35- and IL-10-producing B regs [55]

response. Interestingly, also *Salmonella* induced extrafollicular cytokine-producing plasma cells, although in this case the cytokines produced are IL-10 and IL-35 [22,52]. Therefore, it can be inferred that, in several infectious diseases and in response to the direct effect of microbial-derived compounds, T cell independent-B cell responses are able to adopt biologically relevant Ab-independent functions.

B regs can also emerge in inflammatory microenvironments via cytokine stimulation. Recently, it has been demonstrated that a B reg cell population arose in response to the pro-inflammatory cytokines IL-1β and IL-6, which are produced after the induction of antigen-induced arthritis [53]. Moreover, B regs also appeared in response to IL-33 (a recently identified IL-1 family member) protecting mice from inflammatory bowel disease [54]. Finally, a novel B reg subset (i35Breg) was induced by IL-35. This i35 B regs can also produce IL-35, orchestrating a positive feedback loop that increases the amounts of B regs [55].

In summary, the available information (summarized in Table 1) indicates that B regs emerge in response to the same inflammatory signals that drive the immune system activation, and can limit the developing inflammation avoiding an exacerbated response. Accordingly, and based on the idea that B regs are not lineage specific, Rosser and Mauri [17] suggested that B regs are short-lived effector cells that are expanded in response to inflammation or, alternatively, that B regs are an inflammation-inducible subset that enters in a further differentiation pathway after the resolution of an inflammatory response, such as the maturation of immature B cells into plasmablasts.

However, it may also be conceivable that B regs are a particular/specialized B cell subset expressing a particular transcription factor that is amplified in response to different inflammatory stimuli or specific-antigens and acquires different phenotypes, including different sets of effector regulatory molecules, depending on the characteristics of the inducing stimuli.

4. Regulatory B cells in autoimmunity

B10 cells and their IL-10-dependent regulatory function have been extensively described in the autoimmune model of EAE. How B or B10 cells contribute to the initiation, development or regulation of this disease has been studied by Matsushita and collaborators [56]. Their report showed that CD20-mediated B cell depletion exacerbated the disease symptoms if performed before the induction of EAE due to the depletion of the B10 cell population. However, if the depletion was performed during EAE progression, the disease symptoms were suppressed, mainly because B cells promoted the generation of pathogenic antigen-specific $CD4^+$ T cells and their influx into the Central Nervous system [56]. This report provided insights about how important it would be to consider the timing of the autoimmune disease and the roles of the different B cell populations when establishing therapeutic treatments involving depletion or an autologous adoptive transference. Furthermore, PD-$L1^+IL\text{-}10^+$ B cells were shown to be the key players in estrogen (E2)-mediated protection against EAE [57–59]. E2 has been proved to protect mice from EAE, while this protection was abrogated in B cell-deficient (muMT) mice [60]. E2 treatment upregulated the expression of PD-L1 on B cells and increased the numbers of IL-10-producing $CD1d^{hi}CD5^+$ B cells [60]. In addition, E2 treatment in PD-$L1^{-/-}$ mice was also ineffective, and transfer of PD-$L1^{-/-}$ B cells to muMT mice could not restore the protection observed in WT mice [57]. In particular, in PD-$L1^{-/-}$ mice, a decrease in the percentage of $CD1d^{hi}CD5^+$ B cells was observed together with a decrease in splenocyte production of IL-10 [57]. When IL-10-producing B cells (PD-$L1^+$) were transferred into muMT [59] or PD-$L1^{-/-}$ [58] mice, there was a partial recovery of the E2-mediated protection mechanism. In a different model of EAE, regulatory B cells were demonstrated to exert their suppressive function also through PD-L1 [61]. PD-$L1^{hi}$ B cell-transfer before EAE induction delayed the onset and ameliorated the disease symptoms. This correlated with a decrease in $CD4^+$ T follicular helper (Tfh) cell percentages and numbers as well as in Central Nervous system infiltration, together with a decrease in myelin oligodendrocyte glycoprotein (p35–55) (MOG_{35-55})-specific IgG, IFN-γ and IL-17. Tfh regulation may be independent of IL-10 since PD-$L1^{hi}$ B cells do not quite produce this cytokine and transfer of PD-$L1^{hi}IL\text{-}10^{-/-}$ B cells suppressed Tfh proportion and numbers when immunized with KLH. Recipients receiving PD-$L1^{hi}$ B cells showed a downregulation of the proportion and number of T-bet^+, $Gata3^+$ and $ROR\gamma t^+$ $CD4^+$ T cells [61].

Studies suggested that B regs have also protective effects in different spontaneous models of lupus. For instance, adoptive transfer of splenic $CD1d^{hi}CD5^+$ B cells from wild type NZB/W mice prolongs survival of the highly susceptible $CD19^{-/-}$ NZB/W recipients [62]. Moreover, in a MRL/lpr mice model, transfer of unmanipulated T2 B cells isolated from mice with established lupus failed to confer protection, whereas transfer of in vitro anti-CD40-activated T2 B cells control the progression of lupus and survival through an IL-10-dependent mechanism. B cells isolated from donor MRL/lpr mice stimulated with anti-CD40 converted autologous effector T cells into regulatory IL-10-producing T cells. Interestingly, in vivo administration of agonistic anti-CD40 mAb in MRL/lpr mice promoted the generation of B regs and delayed the progression of the lupus-like disease [63]. A study with systemic lupus erythematosus (SLE) patients suggested that their B regs had a significant impairment in their ability to regulate T-cell cytokine responses. $CD19^+CD24^{hi}CD38^{hi}$ B cells isolated from SLE patients, but not healthy patients, failed to produce IL-10 in response to CD40 stimulation, and were unable to inhibit Th1 responses [64].

Suppressive functions for IL-10-producing B cells were reported for alternative autoimmune models. For instance, chimeric mice with an IL-10 deficiency in B cells presented an increase in IFN-γ- and IL-17-producing $CD4^+$ T cells, and a decrease in IL-10-producing $CD4^+$ T cells during a model of CIA which correlated with an exacerbated clinical score [65]. In addition, BAFF-induced IL-10-producing B regs also protected mice from this autoimmune disease [45]. Furthermore, IL-33-induced IL-10-producing B regs prevented upon transfer the development of spontaneous colitis in IL-10KO mice [54]. Last year Wang and collaborators [55] described the IL-35-dependent induction of IL-35- and IL-10-producing B regs which were capable of conferring protection against murine uveitis through inhibition of the Th17/Th1 response and the expansion of T regs. Notably, these B regs could also be induced ex-vivo from human B cells [55], providing new prospects for autologous adoptive B cell therapies.

Accordingly, regarding B regs as a therapeutic strategy for autoimmunity, it has been shown that treatment of arthritis patients with Tocilizumab (an anti-IL-6R antibody with antagonis-

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tic function) induced changes in B cells that are compatible with the promotion of their regulatory function. After treatment, the shift in B cell properties lied in an increase of TGF-β expression in the $CD25^{hi}$ B cells, and a reduction in the B cell activation status (evaluated through CD69 and MHC-II expression), suggesting that the induction/expansion of B regs may be one of the mechanisms by which anti-IL-6R may produce beneficial effects in rheumatoid arthritis [66]. The precise mechanism by which a dissociation of IL-6/IL-6R complex and/or the neutralization of IL-6 signaling could possibly lead to the expansion of B cells with regulatory characteristics requires better understanding. Another report demonstrated that Laquinimod, an experimental immune modulator for multiple sclerosis, was able to expand IL-10- and TGF-β-producing B and T cells [67].

5. Regulatory B cells in infections

Helminths are the most remarkable pathogens for their ability to down-regulate host immunity to protect themselves from elimination, minimizing immune-inflammatory disorders in the host. Ten years ago, the Th1–Th2 dichotomy was invoked to explain the regulation of immunopathologic diseases. Thus, reduced Th1 associated autoimmune pathologies were observed following Th2-inducing helminth infections [68–70]. Later, it was also shown that during these type of infections, the T reg population is expanded and that transfer of the parasite-induced $CD4^+CD25^+$ T regs suppressed inflammation following airway allergen challenge [71]. Interestingly, B regs are also expanded in the context of helminth infections and exert regulation in different inflammatory models in mice [72–75] as well as in humans [76]. B cells from *Heligmosomoides polygyrus* infected, but not naïve, mice are able to transfer a downmodulatory effect on allergy, significantly suppressing airway eosinophilia, IL-5 secretion and pathology following allergen challenge (See Fig. 1). The same cell population can also alleviate autoimmune-mediated inflammatory events in the Central Nervous system when transferred to uninfected mice undergoing MOG_{35-55}-induced EAE. In both allergic and autoimmune models, reduction of disease was achieved with B cells from helminth-infected IL-10-deficient donors, indicating that the suppression mechanism was independent of IL-10, and the phenotype of these B cells suggested that they were follicular B regs [77]. Schistosomes can also induce functional B regs in humans that may contribute to the regulatory microenvironment found in schistosomiasis. Compared with uninfected donors, a greater percentage of B cells from *Schistosoma haematobium*-infected donors expressed cytoplasmic IL-10 and membrane-bound latency-associated peptide/TGF-β1. T cells produced less IFN-γ, IL-4, and IL-17 when co-cultured with B cells from Schistosome-infected individuals, and their conversion to $CD25^{hi}Foxp3^+$ and their percentage of $IL\text{-}10^+$ T cells were enhanced. Interestingly, depletion of the $CD1d^{hi}$ IL-10-producing B cell subset resulted in less $IL\text{-}10^+$ T cells in the *S. haematobium*-infected group, with no changes in the levels of $Foxp3^+$ T regs [78] (See Fig. 1). Notably, B regs may regulate not only Th1 or Th17 inflammatory responses, but also Th2-associated pathologies [72,74,77] and cytokines related to a Th2 profile such as IL-4 [73,78].

Not only helminths but also protozoan parasites can trigger B reg development. Blood-stage *Plasmodium berghei* induced expansion of IL-10-producing B reg cells in C57BL/6 mice. Adoptive transfer of $IL\text{-}10^+$ B regs to *P. berghei* infected mice significantly reduced the accumulation of NK and $CD8^+$ T cells and hemorrhage in brain tissue, and improved the survival of the mice compared with control groups without altering parasitemia. Treatment of B reg-cell recipient mice with anti-IL-10 receptor mAb blocked the protective effect of B reg cells [79]. As B regs can contribute to regulation of inflammation and prevent immunopathology, they may also suppress protective host responses and increase susceptibility for infections. For instance, it was reported that muMT mice were more resistant to *Leishmania donovani* infection than control WT mice due to the fact that IL-10 production by MZ B cells suppressed the expression of Granzime B (GrB) in NK cells and of IFN-γ by $CD4^+$ T cells [80]. B cells stimulated following in vitro or in vivo encounter with *Leishmania major* expressed CD1d and CD5 and secreted IL-10 that down-regulated IL-12 production by *L. major*-stimulated dendritic cells. In addition, it was reported that IL-10 produced by regulatory $CD1d^{hi}CD5^+$ B cells in response to *L. major* is critical for Th2 cell development in BALB/c mice [81] (See Fig. 1).

Results from our group have shown the critical role of $IL\text{-}17^+$ producing B cells to control the inflammatory response and favor host resistance during *T. cruzi* infection [24] (See Fig. 1). The mechanisms underlying this protective effect involved, at least in part, the IL-17-mediated recruitment of IL-10-producing regulatory neutrophils [23].

Finally, in case of bacterial infection, during *Salmonella typhimurium* infection, MyD88-dependent IL-10 secretion by $CD138^+$ B cells suppressed neutrophils, NK cells, and inflammatory T cells, which compose the protective immune response in this infection [52] (See Fig. 1). Respect to surface inhibitory molecules, PD-L1-expressing B cells alone or together with PD-L1-expressing monocytes suppressed the expansion of $CD8^+$ OTI cells favoring the persistence of the OVA-carrying-bacteria and *Salmonella* chronic infection [34].

6. Regulatory B cells in cancer

Despite the fact that the immunosuppressive function of B regs could help achieve beneficial effects moderating autoimmune disorders and controlling exacerbated inflammatory responses in infections, its role in cancer can be deleterious. In this line, B cells recruited by the chemokine CXCL13 into prostate cancer tumors promote the progression of castrate-resistant prostate cancer by producing lymphotoxin, which activates a signaling cascade that favors prostate cancer survival [82].

In the context of a skin cancer model induced by 7, 12-dimethyl benz[a]anthracene/terephthalic acid (DMBA/TPA), $CD19^+$ cells are responsible for producing the pro-inflammatory cytokine TNF, well recognized as a critical tumor promoter. Besides, $TNF^{-/-}$ mice, normally resistant to this model of chemical induced skin cancer, become susceptible upon transfer of $CD19^+$ cells from WT DMBA/TPA treated mice. Hence, Jh (B cell-deficient) and $Rag2^{-/-}$ (T and B cell deficient) mice were partially and totally resistant to papilloma development, respectively. The protection of tumor growth seen in $TNF^{-/-}$ mice was associated with increased skin levels of IFN-γ and $CD8^+$ T cells and a decrease in macrophages and IL-10-producing B regs [83].

Horikawa and colleagues demonstrated that B10 cells could negatively affect the phagocytic capacity of macrophages. Adoptively-transferred B10 cells dramatically suppressed anti-CD20 mAb-mediated lymphoma depletion by inhibiting mAb-mediated monocyte activation and effector function through IL-10-dependent mechanisms [84]. Furthermore, B regs have been reported infiltrating lung metastases of breast cancer whose primary role is to induce TGF-β-dependent conversion of resting $CD4^+$ T cells to $Foxp3^+$ T regs. These B cells phenotypically resemble activated but poorly proliferative mature B2 cells ($CD19^+CD25^{hi}CD69^{hi}$) that constitutively express active Stat3 and $B7\text{-}H1^{hi}CD81^{hi}CD86^{hi}CD62L^{lo}IgM^{int}$. In the absence of B regs, 4T1 tumors cannot metastasize into the lungs efficiently due to poor T reg conversion [85].

B cells are also able to suppress protective immune responses against tumors through cytokine-independent mechanisms. IL-21

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produced by T regs induced a high expression of GrB in human B cells and an outgrowth of this population, which thereby limited T-cell proliferation by a GrB-dependent degradation of the T-cell receptor ζ-chain [86].

A very elegant work from Shalapour et al. [35] showed that mouse B cells modulate the response to low-dose oxaliplatin which promotes tumor-directed CTL activation by inducing immunogenic cell death. Three different mouse prostate cancer models were refractory to oxaliplatin unless mice were genetically or pharmacologically depleted of B cells. In this model, the crucial immunosuppressive B cells are IgA-expressing plasmocytes that exert their regulatory function through IL-10 and PD-L1. Elimination of these cells, which also infiltrate human-therapy-resistant prostate cancer, allows CTL-dependent eradication of oxaliplatin-treated tumors [35].

7. Concluding remarks

There is a growing body of evidence that shows that B regs are key players in different situations where the immune system is hyperactivated. B regs have been shown to exhibit phenotypes corresponding to MZB1 and follicular B cells as well as plasmablasts. Given their diverse phenotype, it remains unclear whether they emerge from a particular unique B cell subset, or if every B cell subset could acquire a regulatory function upon stimulation in the appropriate condition. It also remains unclear if the regulatory function is exclusive, or if a B reg can also exert other B cell functions like antibody secretion. An unanswered relevant issue is if there is any surface molecule or transcription factor that is commonly and specifically expressed by all B regs.

Altogether, the current literature supports the conclusion that B regs can regulate distinct profiles of inflammation, including Th1, Th17, and Th2. Furthermore, despite the fact that the majority of these regulatory mechanisms involve IL-10 expression, many B reg-mediated regulatory mechanisms comprise different cytokines, cell-to-cell contact, and even adenosine. This evidence may encourage further investigation beyond IL-10 and the well-known regulatory pathways.

Targeting B regs for immune therapeutic strategies may have relevant prospects and development of B reg-induction protocols may be a significant advance in this area. In this regard, reports showing that infection-induced B regs can ameliorate allergic or autoimmune diseases provide insights for novel screening induction protocols and applications for each induced B reg.

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