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Understanding regulatory B cells in autoimmune diseases: the case of multiple sclerosis

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The suppressive function of B cells is mediated mostly through their provision of cytokines with anti-inflammatory properties, in particular interleukin-10. This B cell activity has been convincingly described in mice with autoimmune, infectious, as well as malignant diseases, and evidence is accumulating of its relevance in human. This review provides a personal view of this B cell function using multiple sclerosis and its animal model experimental autoimmune encephalomyelitis as representative examples, in an attempt to bridge observations obtained in mice and human, with the goal of providing a coherent transversal framework to further explore this field, and eventually manipulate this B cell function therapeutically.

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Introduction

B cells are the unique precursors of antibody-secreting cells (ASC), and antibody production has for a long time been regarded as the only function of B cells. However, it is now known that activated B cells also contribute to immunity through the presentation of antigens to T cells and the production of cytokines [1]. B cells achieve multiple effects through the production of cytokines. This article reviews the IL-10-mediated regulatory function of B cells in T cell-mediated autoimmune diseases of the central nervous system (CNS), namely multiple sclerosis (MS) in human, and its pre-clinical model experimental autoimmune encephalomyelitis (EAE) in mice.

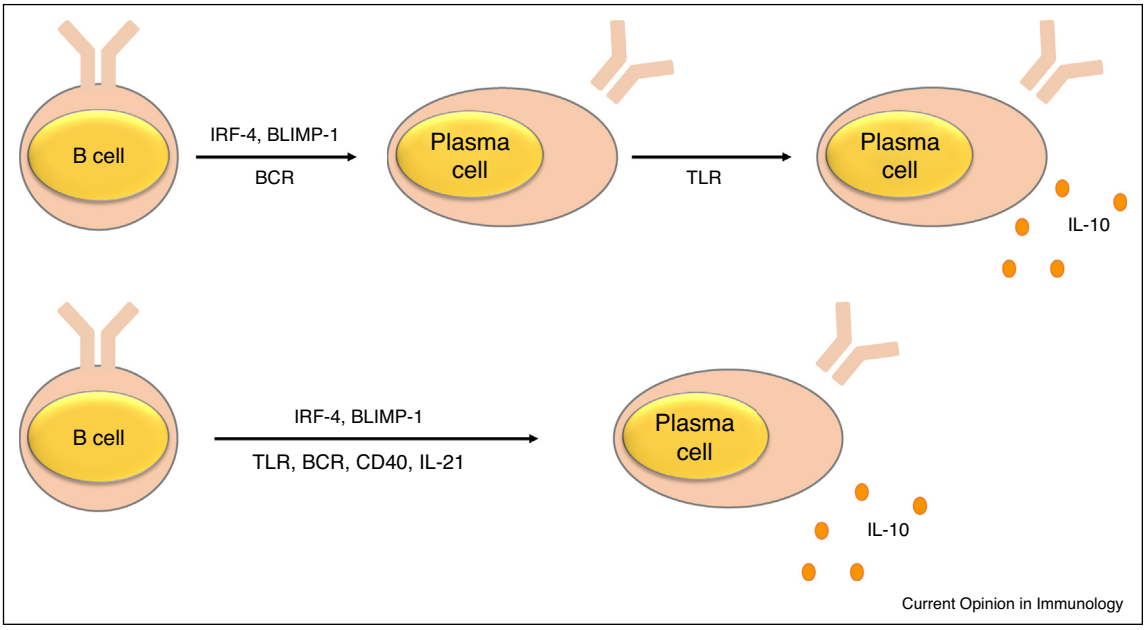
MS is a chronic inflammatory demyelinating disease of the CNS associated with the accumulation of immune cells at lesion sites. Although the aetiology of this disease is not known, genome-wide association studies (GWAS) have shown that human leukocyte antigen (HLA) class II genes had the strongest influence on the risk of developing MS, suggesting an important role for $CD4^+$ T cells in MS [2]. This concept is supported by the recent identification of autoantigens targeted by intralesional $CD4^+$ T cells in subgroups of patients, including the self-antigens RAS guanyl-releasing protein 2 (RASGRP2), and guanosine diphosphate (GDP)-L-fucose synthase [3••,4••]. Furthermore, myelin-reactive $CD4^+$ T cells can induce EAE in non-human primates or rodents upon adoptive transfer, and $CD4^+$ T cells are necessary for the development of EAE induced by immunization with myelin antigens [2].

B cells also have important roles in MS and EAE, acting both as drivers and regulators of the disease. The most convincing evidence of their pathogenic involvement is the beneficial effect afforded by B cell depletion therapy in this disease. The regulatory function of B cells in T cell-mediated autoimmune disease of the CNS was discovered through the observation that B cells protected mice from chronic EAE through the production of IL-10 [5]. This regulatory effect was particularly noticeable during disease progression since it intercepted ongoing disease, and promoted an almost complete recovery from clinical symptoms [5]. This review provides our personal view of the IL-10-mediated regulatory activities of B cells in MS and EAE, focusing on the similarities observed in these two diseases, with the aim of developing a coherent framework useful to further investigate this B cell function (Figure 1).

Regulatory functions of B cells in MS

Human B cells produce IL-10 upon activation, yet this function is impaired in patients with relapsing-remitting MS (RRMS) or secondary progressive MS [6,7]. This defect is observed across a broad range of B cell activation conditions involving TLR9, or CD40, or both BCR and CD40, while B cells from MS patients do not otherwise show a globally diminished response [6,8,9]. This B cell phenotype is therefore both pervasive and specific. It is reversible because B cells from MS patients infected by helminth parasites show a normal IL-10 production [8], which is associated with a less severe disease course compared to non-infected patients [10].

Figure 1



Possible pathways for the generation of IL-10-producing plasmocytes.
The currently available data indicate that B cells can differentiate into IL-10-producing ASC following different modalities. Top: They can first develop into ASC via a mechanism dependent on BCR but independent of CD40 and TLR, and these ASC can be subsequently be induced to produce IL-10 upon stimulation via TLR, as documented for the case of LAG-3^{+} natural regulatory plasma cells [64••]. Bottom: They can also directly develop into IL-10-expressing ASC upon exposure to appropriate activation signals provided by TLR, BCR, receptors for cytokines such as IL-21, and possibly CD40. It is expected that the transcription factors IRF4 and BLIMP-1 are required in these two pathways considering their mandatory role in ASC differentiation.

B cell-derived IL-10 might already influence MS at the beginning of the disease. Indeed, the occurrence of a radiologically isolated syndrome (RIS) and/or a clinically isolated syndrome (CIS) usually precedes MS, and individuals with a RIS or CIS are more prone to develop MS within the next 6 months if they have a deficit in IL-10-producing B cells [11].

A defect in IL-10 production by B cells might thus facilitate both MS onset as well as progression, and the correction of this abnormality might allow an improvement of the disease course. It is therefore of interest to understand the mechanism controlling IL-10 expression in B cells, and the molecular basis for the impairment of this B cell function in MS.

Molecular mechanisms controlling IL-10 expression in B cells and phenotype of IL-10-producing B cells during CNS autoimmunity

The molecular pathways controlling IL-10 expression in B cells, and the phenotype of the B cells providing IL-10 in a suppressive manner *in vivo* were analysed in EAE. Some of the results obtained in this pre-clinical model coincide with observations realized in MS, underlining the relevance of exploring this B cell function in parallel in the human disease and its experimental model.

To achieve a suppressive effect in EAE B cells need to be activated via multiple pathways including intrinsic signalling via the BCR for antigen, CD40, TLR, and the IL-21 cytokine receptor [5,12,13]. B cells must thus be highly activated to control disease progression. At the intracellular level, the expression of IL-10 in B cells involves the endoplasmic reticulum calcium sensor stromal interaction 1 as well as 2 (STIM-1 and STIM-2), and mice with B cells lacking both STIM proteins develop an exacerbated EAE compared to controls [14]. The lack of STIM proteins leads to the impaired activation of the transcription factor Nuclear Factor of Activated T-cells (NFAT) [14], which can directly induce *Il10* transcription [15,16]. NFAT also stimulates *Il10* expression in B cells indirectly by inducing the transcription factor interferon regulatory factor 4 (IRF4) [17]. Mice with a *Irf4* deficiency restricted to B cells develop a more severe EAE than controls [18]. However, NFATs have complex roles in *Il10* expression in B cells, because NFATc1α/A, a short isoform of NFATc1 with a distinct N-terminal domain [19] inhibits *Il10* transcription by binding to an intronic site of the *Il10* gene in cooperation with the histone deacetylase 1 (HDAC1) [20]. Accordingly, mice with *Nfatc1*-deficient B cells developed a milder EAE than controls [20]. Further work is required to reach an integrated view of the role of NFATs in IL-10 production by B cells.

Another transcription factor necessary for the suppressive function of B cells in EAE is BLIMP-1 encoded by the *Prdm1* gene [18]. Remarkably, IRF4 and BLIMP-1 are both indispensable for the differentiation of B cells into ASC [21]. No B cell has been described yet that expresses both IRF4 and BLIMP-1 besides ASC. The notion that B cells acquire suppressive functions via a molecular mechanism interrelated with the processes driving antibody-producing cells differentiation is further indicated by the fact that IL-21 is needed both for the regulatory function of B cells and their differentiation into ASC *in vivo* [13,22]. In keeping with this, ASC were identified as the main source of B cell-derived IL-10 in lymph nodes, spleen, and brain in EAE [18,23,24••]. Remarkably, plasma cells (but not B cells) were also the major source of IL-10 together with astrocytes in the CNS lesions of MS patients [25••]. This plasma cell-derived IL-10 might be protective because MS patients treated with atacicept, a drug that neutralizes the plasmocyte survival factors APRIL and BAFF, displayed a severe exacerbation of the disease leading to the interruption of the clinical trial [26]. Although the neutralization of BAFF can also affect the survival of B cells, including transitional B cells that are considered as a source of IL-10-producing regulatory B cells, this is unlikely to explain the disease exacerbation observed upon atacicept treatment because B cell depletion therapy with anti-CD20 such as rituximab, which depletes B cells but does not affect plasmocytes directly, led to the improvement of MS [27–29]. Further precision on the distinctive roles of APRIL and BAFF in MS shall be obtained via clinical trials assessing specifically how targeting BAFF or BAFF receptor affects MS.

B cell subsets might differ by their capacity to generate IL-10-producing ASC. Transitional B cells, $CD1d^{hi}$ marginal zone B cells, and B1 cells were the B cell subsets able to achieve IL-10-dependent suppressive functions upon adoptive transfer in recipient mice [30–32]. These subsets also share a distinctively high propensity to differentiate into ASC upon activation compared to other B cells [33–36]. Human peripheral blood B cells can be differentiated into IL-10-producing ASC *in vitro* upon culture with the TLR9 agonist CpG in the presence of IL-2, IL-6, and IFN-α [18]. The IL-10-secreting plasmablasts obtained in these cultures originate principally from the $CD24^{hi}CD27\text{-}CD38^{lo}$ immature B cells present in the initial B cell preparation [18]. Such an *in vitro* culture system might be highly valuable to dissect the molecular mechanisms implicated in the generation of human IL-10-producing regulatory plasmocytes.

Several studies reported the expression of IL-10 in B cells that did not display a plasmocyte phenotype, in particular using B cell cultures stimulated with potent pharmacological agents such as phorbol 12-myristate 13-acetate (PMA) and ionomycin, which strongly activate protein kinase C (PKC) signalling and raise intracellular Ca^{2+} levels, respectively. Although these pharmacological agents do not mimic any physiologic stimuli B cells may receive (for instance TLR signalling in B cells does not trigger intracellular Ca^{2+} influx [37•]), and thus are not indicative of whether a cell will make IL-10 under physiological conditions, they nonetheless highlight a competence of the identified cells. A pertinent question is therefore: can B cells exert IL-10-mediated suppressive functions before becoming ASC? Activated B cells can secrete IL-10 before their full ASC differentiation *in vitro*, as shown using *Prdm1*-deficient B cells [18]. However, *Prdm1*-deficient B cells are unable to regulate EAE progression *in vivo* [18]. A possible explanation for this discrepancy might be that *Prdm1*-deficient B cells could not produce enough IL-10 to have an effect *in vivo*, unlike ASC uniquely specialized for protein synthesis and secretion. ASC might thus be the most efficient B cell differentiation stage for IL-10 production and IL-10-mediated immunoregulation due to their cellular properties. In the absence of a perfect *in vitro* assay for identifying IL-10-producing B cells with regulatory functions *in vivo*, it is presently necessary to combine complementary approaches including functional and phenotypic *in vivo* readouts. This shall shed light on the capacity of distinct IL-10-producing B cell activation stages to exert a suppressive effect *in vivo*, which likely depends on the number of these cells, their localization, and the sensitivity of their microenvironment to the suppressive effect of IL-10.

MS treatments increasing IL-10 expression in B cells

The initial view that MS was a T cell-mediated disease focused MS drug development towards T cells as therapeutic targets. Most drugs nowadays used to treat MS patients were initially developed based on their capacity to target the encephalitogenic function of T cells in EAE. Meanwhile, B cells emerged as major players in MS. This led to the evaluation of the effect of MS treatments on B cells, and the finding that several commonly used MS drugs significantly altered B cell functions, and increased their IL-10 secretion.

MS patients are usually treated with IFN-β-1b or glatiramer acetate (GA) as first-line immunotherapies to reduce the frequency of acute relapses and slow disease progression [38,39]. Both treatments increase IL-10 expression in B cells [40,41]. We focus here on GA, a synthetic mixture of peptides composed from the amino acids predominant in myelin basic protein (glutamic acid, lysine, alanine, and tyrosine), which has beneficial effects in EAE [42] and RRMS [43]. GA improves EAE in a B cell-dependent manner, ameliorating disease in control but not in B cell-deficient mice [44]. In line with this, B cells from GA-treated mice produced increased IL-10 amounts and suppressed EAE in recipient mice upon adoptive transfer, whereas control B cells had no effect [44]. B cells from GA-treated RRMS patients also displayed an increased

IL-10 expression compared to controls [41]. This effect might be direct because GA bound to human B cells, and stimulated their IL-10 production *in vitro* [45]. As a result, GA-treated B cells inhibited T cell proliferation and T_H1 differentiation *in vitro* [45]. GA affected most particularly human $CD19^+CD27^+IgD^+CD38^-$ memory B cells, which bound GA most efficiently and displayed a uniquely increased IL-10 production as well as capacity to inhibit T cells, compared to other B cell subsets similarly exposed to GA [45]. GA also increased the expression of CD5 and the IL-21 receptor on memory B cells [45]; the IL-21 receptor was key to the suppressive function of mouse B cells in EAE [13]. GA also stimulated antibody-production by B cells *in vitro* [41], which altogether suggests that it might induce IL-10-expressing ASC. Several receptors have been identified for GA including paired Ig-like receptor B (PIR-B) in mice, its orthologs leukocyte Ig-like receptor B (LILRB)-2 and LILRB-3 [46] in human, and mouse MHC-I as well as MHC-II [47]. PIR-B expression is restricted to B cells and myeloid cells [48]. The specific effect of GA on memory B cells is interesting given the emerging role of these cells as drivers of autoreactive $CD4^+$ T cells activation and MS progression [3••,49,50].

Fingolimod (FTY720) is an antagonist of the sphingosine 1-phosphate (S1P) receptor and the first oral drug to be approved for RRMS [51,52]. It prevents T cells from exiting secondary lymphoid organs, which depends on the S1P receptor 1 [53], leading to the reduction of peripheral T cell number in treated patients [54]. FTY720 also affects the B cell compartment, causing a reduction of the number of B cells in blood and CSF with a particularly marked impact on memory and naïve B cells, resulting in a relative increase in blood and CSF of the proportion among B cells of $CD38^+CD27\text{-}CD24^+$ cells [55,56], which can exert regulatory activities [57]. Accordingly, FTY720 increases the frequency of B cells competent to express IL-10 upon stimulation [55,56]. The beneficial effect of fingolimod might thus involve a reduction of memory B cells, and a relative enrichment of B cell subsets prone to exert IL-10-mediated regulatory functions.

Glucocorticoids are the standard therapy for acute MS relapses because they can reduce the severity of clinical impairment and hasten the recovery of acute MS flares [58]. The first treatment of choice to curb MS flares is often intravenous methylprednisolone [58]. Glucocorticoids are also the most widely used class of anti-inflammatory and immunosuppressive drugs. They act mainly by binding to the glucorticoid receptor in the cytosol, leading to its translocation into the nucleus where it modulates gene expression by binding to glucocorticoid response elements [59]. The modulation of gene expression by glucocorticoids differs across cell types [60]. Glucocorticoid treatment is followed by a reduction in antibody serum titters, indicating an effect on B cells [61]. Indeed, methylprednisolone upregulated the expression of *IL-10* and *PRDM1* in cultured B cells, and similar changes in *IL-10* and *PRDM1* expression were observed in B cells isolated from the blood of healthy individuals at 2 hour and 4 hour post-treatment with a single dose of methylprednisolone [62••]. Glucocorticoids might thus facilitate the differentiation of B cells with a unique phenotype associating increased IL-10 expression, engagement towards plasmocyte differentiation, but limiting antibody production [62••].

In sum, the cytokine-mediated suppressive functions of the B cell compartment might take part in the mode of action of drugs currently used to treat MS patients. It will be of interest to examine how prednisolone, and other current MS treatments, impact on IL-10-producing ASC in tissues of patients.

Conclusions

The fact that B cells can exert regulatory function in various diseases through the production of cytokines with immunosuppressive properties such as IL-10 or IL-35 is now well accepted. Here, we used the case of autoimmune diseases of the CNS in mouse and man to review the current knowledge in this field. A coherent framework starts emerging integrating the B cell subsets having a distinctively elevated competence to exert such regulatory activity, the signals controlling the suppressive function of B cells *in vivo*, the transcription factors implicated in this activity, and the implication of plasmocytes as important providers of immunosuppressive IL-10 in mouse and man. The data obtained in EAE and MS suggest similarities between B cell regulatory functions in mouse and man, which might be a precious asset regarding the possibility of translating suppressive B cell-based therapeutic concepts from the bench to the bedside. The fact that some drugs used to treat MS patients were incidentally found to increase IL-10 production in human B cells, and to drive the differentiation of IL-10-expressing B cells with protective function in EAE, provides examples of transfer from the bedside to the bench that are encouraging in terms of translational possibilities. Several strategies might thus be envisioned to harness the regulatory function of B cells therapeutically, including the adoptive transfer of suppressive B cells produced using our knowledge of this B cell differentiation process, or the administration of molecules promoting the differentiation of B cells with regulatory functions *in vivo*. Considering this, it would be useful to identify the mechanisms underlying the defective production of IL-10 by B cells from MS patients. It has been suggested to reflect the reduced serum levels of thymosin-α1, a peptide produced by the thymus, in these patients because the addition of thymosin-α1 to cultures of MS patient B cells increased their IL-10 expression *in vitro* [63]. The thymus might thus contribute to peripheral tolerance by modulating the regulatory functions of B cells. The intestine might be another organ implicated in

systemic B cell-mediated immune regulation. IgA-expressing ASC from the small intestine lamina propria accumulated in the inflamed CNS during EAE and possibly limited disease progression locally through the production of IL-10 in the target organ, suggesting that manipulating the microbiota might be a suitable approach to improve B cell-mediated regulation [24••]. Finally, understanding the pathways driving the generation of natural regulatory plasma cells, which were recently identified in mice [64••], might provide other means to manipulate B cell-mediated regulatory activities for therapeutic purposes. The better understanding of regulatory B cell functions is opening novel possibilities for therapeutic strategies.

Conflict of interest statement

The authors declare no conflict of interest.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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