

Review Article

Potential Impact of B Cells on T Cell Function in Multiple Sclerosis

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Multiple sclerosis is a chronic debilitating autoimmune disease of the central nervous system. The contribution of B cells in the pathoetiology of MS has recently been highlighted by the emergence of rituximab, an anti-CD20 monoclonal antibody that specifically depletes B cells, as a potent immunomodulatory therapy for the treatment of MS. However, a clearer understanding of the impact B cells have on the neuro-inflammatory component of MS pathogenesis is needed in order to develop novel therapeutics whose affects on B cells would be beneficial and not harmful. Since T cells are known mediators of the pathology of MS, the goal of this review is to summarize what is known about the interactions between B cells and T cells, and how current and emerging immunotherapies may impact B-T cell interactions in MS.

1. Introduction

It has long been established that T cells are mediators of the pathology of multiple sclerosis (MS) in both murine models and patient studies [1–6]. Although, the impact of B cells and their antibody products in mediating the pathology of MS has long been considered [7–10], their contributions have been more recently highlighted by the demonstration that Rituximab, an anti-CD20 monoclonal antibody that specifically depletes B cells, was a potent immunomodulatory therapy for the treatment of MS [11, 12]. More importantly, however, the efficacy of Rituximab in the treatment of MS patients is independent of secreted antibody since Rituximab does not affect plasma cell frequencies or serum and cerebrospinal fluid (CSF) antibody levels [13]. Thus, scientists in the field have refocused their attention on the possible roles of B cells in MS that are independent of their antibody secreting function. This paper summarizes the possible “antibody secretion-independent” roles of B cells on T cell activation and regulation, the relative impact of the B cell subpopulations on T cell activation and regulation, evidence that these mechanisms are altered in MS, and how

current and emerging immunotherapies may impact B-T cell interactions in MS.

2. What Is known about the Consequences of B-T Cell Interactions?

It has long been assumed that B cells are unlikely to play a significant role as antigen-presenting cells (APCs) in the induction of effector T cells since human B cells are less potent APCs *in vitro* on a per-cell basis compared to dendritic cells [14]. However, in 1982, investigators published for the first time that human B cells could present antigens [15]. In fact, B cells are potent APCs in humans *in vitro* in the context of both alloantigen [16, 17] and exogenous-foreign-antigen [18] responses. Studies in mouse models in which the B cells cannot secrete antibodies have further highlighted the importance of antibody independent B cell responses [19, 20]. These results demonstrated that B cells are required for generating optimal primary and secondary T cell responses and are implicated as APC in a number of

disease models in the mouse including rheumatoid arthritis and type 1 diabetes [21–23].

More recently, it has been demonstrated that activated B cells are more effective in activating T cells than their resting or naïve counterparts in the mouse [24–26]. This finding has been confirmed with human B cells as well, since human naïve B cell alloantigen presentation can be increased with CpG-ODN stimulation [27]. Antigen-specific B cell APC function can also be increased with CD40L stimulation [27–31].

The most well-studied consequence of B-T cell interactions, however, is the induction of T cell tolerance or expansion of regulatory T cells [32–34]. For example, in mice, antigen specific naïve B cells induce naïve T cells to proliferate and differentiate into regulatory T cells [35]. HEL-specific CD43– (naïve) B cells do not elicit T cell proliferation or IL-2 and interferon-gamma (IFN γ) secretion, suggesting that they induce T cell tolerance [36]. In mouse models, naïve B cells did not participate in T cell priming *in vivo*, implicating naïve B cells as a source of regulatory B cells [25, 37, 38].

However, few have examined the role of memory B cell antigen presentation in humans, which is a crucial consideration since memory B cells are antigen experienced. Our group demonstrated that memory B cells from healthy donors express sufficient levels of CD80 and HLA-DR to operate as antigen presenting cells to induce antigen specific T cell proliferation and IFN γ secretion [39]. Our group has also found that memory B cells from these same healthy donors also produce high concentrations of lymphotoxin-alpha (LT α) in comparison to their naïve counterparts. Another group demonstrated that memory B cells from healthy donors induce T cell proliferation in response to glatiramer acetate (GA), a peptide mimic of the neuroantigen, myelin basic protein (MBP), with some indication that CD80 expression is important for this function [18]. In a separate study [16], it was demonstrated that resting memory B cells from healthy donors elicit robust allogeneic T cell proliferation that was significantly inhibited by anti-CD80 and anti-CD86 antibodies in contrast to naïve B cells, which were unable to stimulate allogeneic T cell proliferation. With the exception of these three studies, memory B cell antigen presentation in healthy donors has not been explicitly examined.

Memory B cells from treatment naïve RRMS patients, however, have the unique ability to present neuroantigens to autologous T cells and generate a proliferative response and IFN γ production [39]. Memory B cells from healthy donors are unable to support T cell proliferation and IFN γ production in response to neuroantigens. Taken together it appears that memory B cells might directly contribute to T cell activation by presenting neuro-antigens and secreting cytokines that enhance the Th1/IFN γ producing T cell subset. We are currently testing whether memory B cells from treatment-exposed RRMS patients maintain their capacity to incite T cell activation in a neuroantigen specific manner.

These findings have generated considerable interest in dissecting the mechanism of B-T cell interactions, especially as they relate to the antigen experience of B cells. The

two primary antibody secretion independent ways that B cells potentially impact T cell activation or regulation are by (1) providing costimulatory signals through direct B-T cell interactions and (2) cytokine secretion. The following sections detail the primary surface molecules and secreted factors that are thought to contribute to T cell activation or regulation by B cells.

3. What Types of Surface Molecules Expressed by B Cells Could Be Influencing T Cell Function?

Figure 1 depicts aspects of the currently accepted model of important B-T cell interactions [40, 41]. Interactions between B7.1/B7.2 (CD80/CD86) expressed on B cells and their ligands and CD28 and CTLA4 expressed on T cells have long been studied in MS [42, 43], and much is understood regarding the influence of these interactions on T cell responses [44–46]. In fact, circulating CD80+ B cells are increased during active relapse phases of MS, compared to patients in remission or controls [47], suggesting that this population may be involved during the active phase of the disease. Importantly, others have demonstrated that a subset of memory B cells, but not naïve B cells, express CD80 [16, 18] CD86 [16], and CD25, although this expression is not necessarily concurrent [18, 48]. The impact of CD80 expression on B cells and their ability to activate T cells is certainly of interest since the stimulation of memory T cells is CD28 independent [49].

Interactions between MHCII, peptide, and the TCR are certainly central to effective B-T cell costimulation, especially in the context of MS, in which HLA-DR haplotypes have a strong association [50–52]. T cell proliferation in the presence of CD19+ B cells (containing both naïve and memory B cells) activated with CD40L and antigen is reduced by ~60% in the presence of anti-HLA-DR antibodies [28].

Interactions between CD40 expressed on B cells and CD40 ligand (CD40L) expressed on T cells are also critical to mount an effective T cell response [53]. This consistent observation led to the development of anti-CD40L biologics to dampen T cell responses but became problematic due to the increase in thromboembolic events associated with these biologics, and the discovery that activated platelets express CD40L [54, 55]. Anti-CD40 agonists, however, are being developed for applications in tumor immunotherapy to mobilize T cells in patients with cancer [56]. Yet it is unclear what *types* of T cells are mobilized by CD40-activated B cells. This is a critical point to consider since purified B cells stimulated with one of these new CD40 agonists in combination with CpG (a TLR9 agonist) secreted high levels of both IL-6 and IL-10 [57, 58].

Interactions between OX40L expressed on APCs and OX40 expressed on T cells have profound effects on T cell responses. For example, Wang et al. have reported that coculturing IFN γ -activated microglia from mouse brain tissue with murine CD4+ T cells significantly increased T cell proliferation, which was readily blocked by the addition of anti-OX40L in the cultures [59]. In humans, exposure of human T

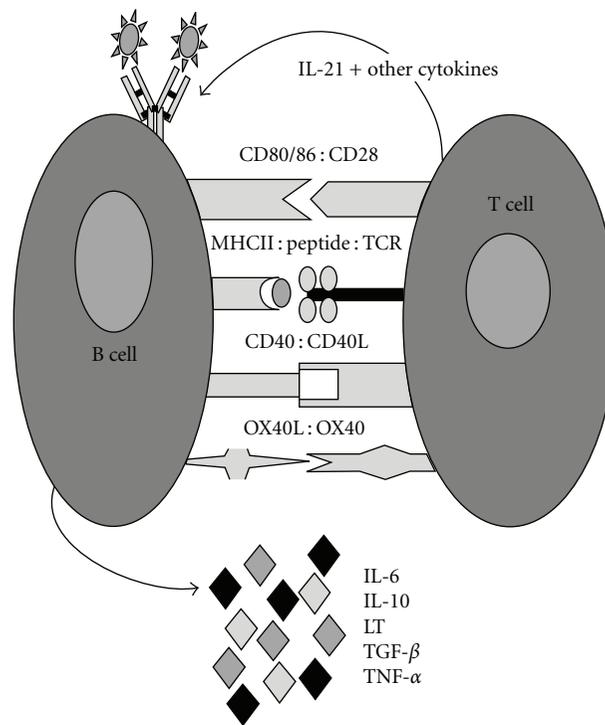


FIGURE 1: Important co-stimulatory molecules in B-T cell interactions.

cells to OX40L prevents the development of IL-10-producing T cells [60] and IL-17 producing T cells [61]. Thus, biologics that block or enhance these interactions may be useful therapeutics for autoimmunity and infection, respectively, and are currently being considered for development in these arenas. However, the impact of OX40-OX40L ligation on B-T cell interactions has not been formally investigated.

4. What Types of Secreted Factors Produced by B Cells Could Be Influencing T Cell Function?

The influence of T cell derived cytokines in health and disease has dominated scientific literature for at least 2 decades. However, it has become apparent that activated B cells have a high capacity to produce both inflammatory and regulatory cytokines [92] (Table 1). For example, recent investigations have demonstrated that IL-10-producing B cells have an immunomodulatory role in experimental allergic encephalomyelitis (EAE), which is the mouse model of MS [93, 94]. However, CD19+ B cell pools from MS patients have a diminished capacity to produce IL-10 [95, 96], suggesting that the inflammatory responses in MS patients may be partially attributable to a defect in IL-10 production by B cells. *In vitro* activation of purified naïve and memory B cells from the RRMS patient cohort used in our studies using CD40L (as was done by [96]), demonstrates that naïve B cells produced similar amounts of IL-10 reported by [66, 95, 97], but memory B cells did not produce appreciable amounts of IL-10 [39]. Interestingly, when we cultured naïve B cells with T cells in our B-T

cell culture system, we did not observe appreciable T cell proliferation in response to neuro-antigens, suggesting that the amount of IL-10 produced by naïve B cells from RRMS patients may regulate T cell responses. In support of this concept, IL-10 treatment of CD4 T cells from patients with rheumatoid arthritis significantly decreased the numbers of Th17 cells *in vitro* [98].

So what *pro*-inflammatory cytokines do B cells generate that have a high likelihood of effecting T cell function in response to neuro-antigens? $LT\alpha$ and tumor necrosis factor alpha ($TNF-\alpha$) are classic candidates of the TNF superfamily with similar structure [99, 100]. Their expression by B cells is required for germinal center formation [101] and the migration of antigen-loaded myeloid dendritic cells (mDCs) to follicles [102]. $LT\alpha$ is also required for the generation of memory B cells and isotype switch [103]. $LT\alpha$ and $TNF-\alpha$ are readily produced by activated memory B cells from healthy donors [104], and T cells express receptors for these cytokines [105]. Furthermore, $TNF\alpha$ and $LT\alpha$ levels are increased in MS lesions and mediate oligodendrocyte toxicity *in vitro* [106]. B cells from RRMS patients showed increased $LT\alpha$ and $TNF\alpha$ and decreased IL-10 production in response to polyclonal stimuli (CD40L and BCR crosslinking) in the presence of a TLR9 agonist or $IFN\gamma$ [107]. In fact, when CD19+ cells are removed *in vitro* from peripheral blood mononuclear (PBMC) cultures, CD4+ and CD8+ T cell proliferation is decreased and may be due to a lack of B cells secreting $LT\alpha$ and $TNF\alpha$ [107], which would support T cell proliferation.

Transforming growth factor-beta ($TGF-\beta$) and IL-6 are readily secreted by activated B cells as well [108], and there

TABLE 1: Cytokines produced by B cells.

Cytokine effects		Demonstration
IL-10	Inhibits T cell proliferation, IFN- γ and IL-2 production while enhancing Th2 responses [62–64]	Purified CD19+ peripheral human B cells produce IL-10 protein after dual stimulation with CpG and CD40L [65]. Maximal IL-10 production was noted with CD40L alone, compared to dual stimulation of BCR cross-link and CD40L [66]. IL-10 was secreted primarily by naïve CD19+CD27– B cells [39].
TGF- β	Induces tolerance and inflammation-dependent additional cytokine signals; IgA class switch and dampening NK activity [67–69]; development of Th17 and Treg cells [70]	Human total CD19+ B cells produce TGF- β mRNA in response to BCR cross-linking [71]. Anti-immunoglobulin treatment of murine B cell lymphomas induces active TGF- β [71].
LT- α	Required for the formation of germinal centers and follicles, upregulation of adhesion molecules [72, 73]	Purified human CD19+ B cells produce significant amounts of LT- α after dual stimulation with CpG and CD40L [65]. Maximal production was observed after dual stimulation of BCR cross-link and CD40L [66]. LT- α was secreted primarily by memory CD19+CD27+ B cells [39].
TNF- α	Increases IL-2 receptor and HLA-DR expression; induces T cell proliferation and IFN- γ production [74, 75]	Human CD19+ B cells produce TNF- α in response to CpG stimulation alone or in combination with CD40L [65, 76], or dual stimulation of BCR cross-link and CD40L [66]. TNF- α was secreted primarily by memory CD19+CD27+ B cells [39, 77].
IL-12	Critical for Th1 development, induces IFN γ production, enhances NK and CTL activity, inhibits Th2 development, and inhibits IgE class switching [78]	Human total CD19+ B cells produce IL-12p70 in response to dual stimulation with CpG and CD40L, but not in response to CpG (or CD40L) alone [65].
IL-6	Mediates early inflammation; activates endothelium and acts as growth and recruitment factor for lymphocytes [79–82]	Mediates early inflammation, activates endothelium, and acts as growth and recruitment factor for lymphocytes [79–81].
IFN- γ	Amplifies IFN- γ production; activates CTL and NK; critical for Th1 response [83, 84]	EBV-transformed B cell lines constitutively express IFN- γ as measured by qPCR [85]. PMA or IL-2 stimulation of EBV or B cell tumor lines induces IFN- γ [86].
IFN- α	Upregulates inflammatory cytokines [87]; implicated in the pathogenesis of several inflammatory autoimmune diseases including RA and IBD [88–90]	Purified human CD19+ B cells produce IFN- α transcripts in response to TLR8 agonist, but only in the first 24 hours post-stimulation [91]. Interestingly IFN- β , another type 1 interferon, is used as a treatment for RRMS.

is certainly much excitement regarding the ability of TGF β and IL-6 in combination to mediate Th17 cell activity since Th17 cells are central to the inflammation associated with EAE [1, 109–114]. However, the classic role of TGF β has been to induce tolerance in the immune system, and indeed, anti-TGF β treatment of mice led to worsening of EAE disease and more severe clinical pathology in these mice [115]. TGF β has been attempted ineffectively as a treatment for progressive MS [116]. *In vitro* recombinant TGF β decreased neuroantigen-specific T cell frequency and IFN γ and IL-4 producing T cells from MS patients [117].

More recently, others have demonstrated that murine Th17 cells can be generated by either IL-6 alone or IL-6 in combination with TGF β , but only those Th17 cells that had been generated with IL-6 alone are encephalitogenic [1]. IL-6 is increased in the CSF of other inflammatory neurological disorders including transverse myelitis (TM) and neuromyelitis optica (NMO) [118, 119], in the lesions of MS patients [120], and in some cases, correlates with relapse or general neurodegeneration in the progressive phase [121]. However, IL-6 is not increased in the CSF of MS patients and IL-6 levels do not correlate with other CSF parameters including oligoclonal bands, pleocytosis or IgG index [118,

122, 123]. Whether IL-6 is central to the generation of human Th17 cells remains under investigation [124, 125].

Even with confounding and often negative results of other studies in MS, it has been suggested to use the IL-6 receptor blocking antibody, Tocilizumab, as a therapeutic agent. Interestingly, IL-6 is increased after treatment of MS patients with IFN β , suggesting that this pleiotropic cytokine might not play an inflammatory pathogenic role in MS as IL-6 can have both systemic and local effects [126]. Because this cytokine differs in its necessity for EAE, it might represent an insurmountable task to go to trial due to the uncertain/unpredictable nature of the outcome without predictive animal models.

5. What Is the Effect of Immunotherapy on B Cell APC Function in MS?

As discussed earlier in this paper, T cells from RRMS patients treated with Rituximab had a poor response to antigen stimulation, suggesting that the lack of B cells in the periphery of these patients has a profound impact on T cell activation. Interestingly, circulating memory B cells are

TABLE 2: Possible impact of established and emerging therapies for MS on B cell function.

Therapeutic agent	Description	Impact on B-T interactions
Tysabri	Blocking antibody to $\alpha 4\beta 1$ integrin (VLA4)	VLA4 is required for extravasation of lymphocytes across the blood brain barrier (BBB). A blockade of this adhesion molecule prevents autoreactive B and T cells from entering the CNS, thus limiting immune-mediated damage. CNS antigens are less available for antigen presentation without migration of antigen presenting cells (such as B cells) across the BBB.
MLN1202	CCR2 blocking antibody	Both B and T cells express CCR2, the receptor for MCP-1 [127]. Mouse studies show that MCP-1 is expressed in the microvessels [128] and that it is increased in MS [129]. This blocking antibody may abrogate leukocyte entrance into the CNS.
BAF312 and Fingolimod	blocking antibodies for the S1P receptor	These agents block egress of lymphocytes from secondary lymphoid organs. This therapy should decrease lymphocytes entry into the CNS. This mechanism is presumed to be similar to Tysabri.
Vitamin D3	Nutritional and environmental nutrient	The vitamin D3 receptor is expressed on GC and naïve and memory B cells [130]. Furthermore, Vitamin D3 reduces proliferative responses of B cells, reduces antibody secretion and class switching, inhibits maturation into memory and plasma phenotypes and induces apoptosis, but does not modulate the expression of HLA-DR or coreceptors [131]. Given these results, this therapy may have a profound effect on B cell activity in the context of MS.
CGP77116	Altered peptide ligand/mimotope for a dominant antigenic determinant of MBP (83–99)	CGP7716 will dampen the MBP-specific response by competing with native MBP. MBP-specific B cells could take up the APL and present it to T cells.
Glatiramer acetate (GA, Cop1, Copaxone)	Random polymer comprised of amino acids in a similar ratio as MBP	GA is known to skew the cytokine milieu toward a Th2 phenotype [132]. The effect of GA on B cell function is unknown.

also reduced in RRMS patients during mitoxantrone therapy [96] and IFN β therapy [133]. IFN β treatment decreases MBP-elicited IFN γ and TNF α , but also decreases IL-10 and increases IL-6 [134]. Another study demonstrated that IFN β increases the expression of a phosphatase (SHP-1) that negatively regulates inflammatory T cell signaling from TNF α , IFN γ , IL-4, and IL-13 [135]. From these results, one may speculate that the effects of IFN β on T cells modulate their responsiveness to cytokine signals, some provided by B cells. On the other hand, *in vitro* studies show that Th17 cells and associated cytokines (IL-23, TGF β and IL-1 β) were reduced, while anti-inflammatory cytokines produced by B cells and dendritic cells were increased. Reemerging B cells from RRMS patients treated with mitoxantrone therapy recovered the ability to produce IL-10 [107], but again, the impact of these IL-10-secreting B cells on neuroantigen-specific T cell responses was not tested. Table 2 lists other current and emerging therapies and their possible impact on B cell function and emphasizes the urgent need to investigate how these drugs may affect B-T cell interactions in the patients receiving them.

In summary, the influence of B cells on T cell function is only beginning to be realized. Further investigations are required in order to fully comprehend the impact of current and emerging therapeutics on B cell responses, which in turn, may have profound impact on T cell function in autoimmune diseases such as MS.

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