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Impact of myelin-specific antigen presenting B cells on T cell activation in multiple sclerosis

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Abstract The role of B cells in the pathogenesis of Multiple Sclerosis (MS) is incompletely understood. Here we define a possible role for B cells as myelin-specific antigen presenting cells (B-APCs) in MS. Peripheral blood B cells (PBBC) isolated from both MS patients and healthy controls (HC) were activated *in vitro* with either CD40L/IL-4 or a Class B CpG oligodeoxynucleotide (CpG ODN)/IL-2. Both activation techniques induced PBBCs to upregulate CD80 and HLA-DR, rendering them more efficient APCs than resting B cells. Although the CD40L/IL-4 B-APCs were highly effective in eliciting CNS-antigen specific proliferation by autologous T cells, CpG ODN/IL-2 stimulated B cells were not. Furthermore, CD40L/IL-4 B-APC induced responses by autologous $CD4^+$ T cells were susceptible to blocking with anti-HLA-DR antibody, suggesting that T cell responses were specific for antigen presentation by B-APC. CNS-antigen specific $CD8^+$ T cell proliferation was also blocked by HLA-DR, suggesting that $CD8^+$ proliferation is in part dependent on $CD4^+$ help.
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Introduction

Multiple Sclerosis (MS) is an autoimmune mediated demyelinating disease of the central nervous system (CNS) with unknown etiology. Much of the research investigating the impact of B cells in MS has focused on the role of CNS specific antibodies produced by B cells on the pathogenesis of the disease [1]. For example, myelin-specific antibodies are present in the cerebrospinal fluid of MS patients [2,3], serum [4,5], and at sites of demyelination in MS plaques [6]. Myelin-specific antibodies can enzymatically proteolyze MBP *in vitro*

Abbreviations: ODN, oligodeoxynucleotide; CNS, central nervous system; RRMS, relapsing remitting multiple sclerosis; PPBC, peripheral blood B cells; MBP, myelin basic protein; GA, glatiramer acetate; B-APC, B cell antigen presenting cell.

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[7], or in some models of MS, facilitate remyelination of axons [8]. Antibodies and plasma cells with similar specificity are also present in the cerebrospinal fluid (CSF) of other non-demyelinating inflammatory/infectious diseases of the CNS [3]. In addition, no correlation was found associating serum IgG anti-myelin antibodies with progression to clinically definitive MS [9]. Therefore the presence of anti-myelin antibodies is currently not a conclusive or specific clinical marker for confirming MS, and the role of anti-myelin antibodies in the pathogenesis of the disease process remains elusive.

B cells have several other functions in the immune system quite removed from their traditional role of producing antibodies. These other capabilities include maintaining the organization and morphological functionality of secondary lymphoid organs [10], and functioning as professional antigen presenting cells (APCs) [11–18]. In some murine models, B cells are necessary in the development of a primary T cell mediated immune response [15,19–21], but not in others [22,23]. Secondary immune responses mediated by memory T cells are impaired in the absence of B cells [13,23,24], suggesting that the APC function of B cells is a necessary precondition for the full development of T cell memory. Furthermore, in the non-obese diabetic murine model, B cells are required for the development of T cell mediated destruction of insulin producing β cells, suggesting that at least in this model of autoimmunity, B cells are the required APCs in developing autoimmune T cell responses [25] that result in target tissue destruction. A similar requirement for B cells as APCs in the collagen induced arthritis mouse model corroborates the pivotal role played by B cells in compartment driven responses [17].

Whether B cells are required as APCs in the development or perturbation of MS is unknown. However, Rituximab, a monoclonal antibody used to deplete B cells, significantly reduced new and pre-existing T1 gadolinium-enhancing lesions compared to placebo in patients with relapsing remitting MS (RRMS) [26]. Since this drug does not directly deplete long-lived antibody producing CD138^{+} plasma cells, the beneficial effect of this drug in RRMS is unlikely related to antibody titer. In addition, it was observed that overall, T cell numbers were reduced in the CSF of MS patients undergoing Rituximab treatment [27], suggesting a requirement for B:T cell interactions in T cell activation/entry into the CNS. Furthermore, it has been reported that peripheral B cells with high CD80 expression are enriched in RRMS patients undergoing a relapse, but not present in RRMS patients in remission [28]. Since the high expression of CD80 is considered necessary for the full potency of B cell APC function, these data provide further evidence that B–T cell interactions are important in the exacerbation of MS.

The focus of this study was to evaluate the ability of B cells from MS patients to be competent APCs in a myelin antigen specific manner. Compared to activated DCs and/or monocytes, *ex vivo*, human peripheral blood B cells (PBBC) do not constitutively express the costimulatory molecules necessary to be efficient APCs and do not survive in culture for long periods of time without stimulation. Therefore we chose to activate B cells from MS patients and healthy controls using a classic antigen independent *in vitro* stimulation approach with CD40L and IL-4 to study their ability to be efficient myelin-specific APCs to autologous T cells. Our results demonstrate that B cells from some but not all MS patients can present MBP to autologous T cells, a finding that likely parallels diversity of myelin antigens in the promotion of this disease.

Results

Both CD40L/IL-4 and CpG ODN/IL-2 stimulation sufficiently activate human B cells to express costimulatory molecules and upregulate MHC II

PBBC were stimulated with CD40L/IL-4, to mimic T-dependent B cell activation, then evaluated for upregulation of CD80 and MHC II (HLA-DR) which are classical markers of B cell activation and are required to instigate potential B:T cell interactions. We found that 8 days of stimulation were required for maximum expression of CD80 and HLA-DR, which was maintained for the duration of *in vitro* stimulation using this approach. For some patient samples, the number of B cells that were required to perform the experiment could not be obtained on day 8 of stimulation because of the low starting number of B cells obtained from the *ex vivo* samples. This required us to increase the time of stimulation for some patients up to 16 days, with negligible change in the

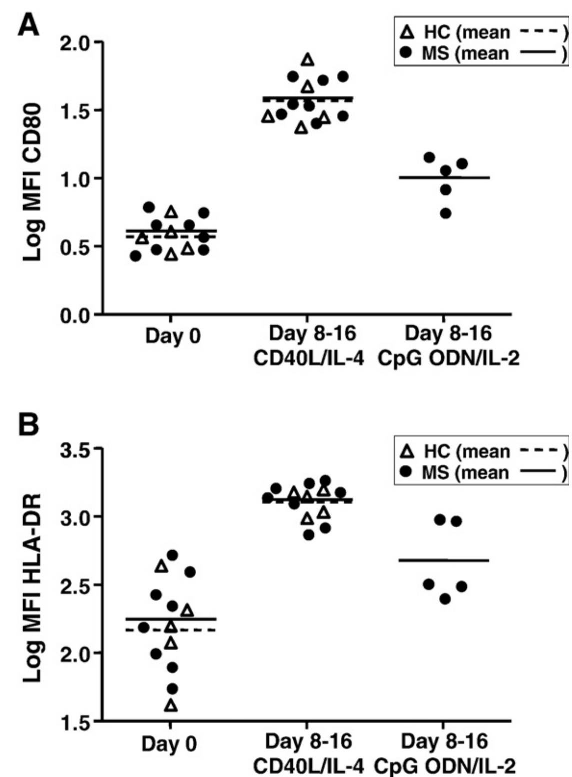

Figure 1 Costimulatory molecule expression following *in vitro* stimulation of PBBC. *In vitro* expression of CD80 (A) and HLA-DR (B) were evaluated by flow cytometry prior to activation at day zero, and after PBBCs were stimulated for 8–16 days of culture in either the CD40L/IL-4 or CpG ODN/IL-2 culture systems. Closed circles and open triangles represent expression from MS patients (MS1–9) and HCs (HC1–5) respectively. The solid and dotted lines represent the MS and HC averages respectively.

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