B-cell activation influences T-cell polarization and outcome of anti-CD20 B-cell depletion in central nervous system autoimmunity.

Abstract: Clinical studies indicate that anti-CD20 B-cell depletion may be an effective multiple sclerosis (MS) therapy. We investigated mechanisms of anti-CD20-mediated immune modulation using 2 paradigms of experimental autoimmune encephalomyelitis (EAE). Murine EAE was induced by recombinant myelin oligodendrocyte glycoprotein (rMOG), a model in which B cells are considered to contribute pathogenically, or MOG peptide (p)35-55, which does not require B cells. In EAE induced by rMOG, B cells became activated and, when serving as antigen-presenting cells (APCs), promoted differentiation of proinflammatory MOG-specific Th1 and Th17 cells. B-cell depletion prevented or reversed established rMOG-induced EAE, which was associated with less central nervous system (CNS) inflammation, elimination of meningeal B cells, and reduction of MOG-specific Th1 and Th17 cells. In contrast, in MOG p35-55-induced EAE, B cells did not become activated or efficiently polarize proinflammatory MOG-specific T cells, similar to naive B cells. In this setting, anti-CD20 treatment exacerbated EAE, and did not impede development of Th1 or Th17 cells. Irrespective of the EAE model used, B-cell depletion reduced
the frequency of CD4(+)CD25(+)Foxp3(+) regulatory T cells (Treg), and increased the proinflammatory polarizing capacity of remaining myeloid APCs. Our study highlights distinct roles for B cells in CNS autoimmunity. Clinical benefit from anti-CD20 treatment may relate to inhibition of proinflammatory B cell APC function. In certain clinical settings, however, elimination of unactivated B cells, which participate in regulation of T cells and other APC, may be undesirable. Differences in immune responses to MOG protein and peptide may be important considerations when choosing an EAE model for testing novel B cell-targeting agents for MS.