

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS), in which CNS myelin becomes the target of an immune attack. MS is characterized by perivascular inflammatory lesions, demyelination, and axonal damage, but its immunopathogenesis is not yet well understood. Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model for MS that serves to explore the pathogenesis of MS, including the involvement and importance of different cell types in induction of EAE. To investigate the role of the different antigen-presenting cells (APCs) in EAE induction and in T cell tolerance a new mouse model was generated in our laboratory (by T. Heinen; termed IiMOG), which allows the cell type-specific presentation of an encephalitogenic self-peptide of myelin oligodendrocyte glycoprotein (MOG_{p35-55}) on MHC class II of B cells, macrophages, or dendritic cells (DCs). DCs are believed to induce both tolerance and immunity, depending on their maturation status as immature or mature, respectively. The role of B cells in induction or tolerization of immune responses has not been an area of intensive study to date. In this work we demonstrate that constitutive presentation of MOG_{p35-55} specifically by B cells leads to tolerance to EAE. Furthermore, transferred MOG-specific T cells are tolerized *in vivo* by naïve as well as by activated B cells. These T cells do not express classical early activation markers such as CD69 or CD44, but show an upregulation of the coinhibitory molecules CTLA-4, PD-1, BTLA, and CD5, which are involved in tolerance and negative regulation of T cells. B cell-tolerized MOG-specific T cells appear unresponsive, dysfunctional, and become highly susceptible to activation-induced cell death (AICD) – a process that is not prevented by blocking of the upregulated inhibitory receptors. Proliferation of T cells after interaction with MOG-presenting B cells was slightly increased upon blockade of CTLA-4, but not PD-1 or CD5.

Inducible presentation of MOG_{p35-55} by resting DCs also induces tolerance to EAE. In transfer experiments, however, total DCs presenting MOG_{p35-55} induce proliferation and activation of CD4⁺ MOG-specific T cells. Previously, immature DCs have been shown to induce the generation of regulatory T cells (Tregs). The B cell-tolerized T cells showed increased or decreased expression levels of the inhibitory cytokine TGF- β and its inhibitor Smad7, respectively, yet no suppressive activity was detectable *in vitro* after reaching the tolerant state. The increase in TGF- β expression, a hallmark of the induced Treg lineage, was therefore not a result of the tolerized cells differentiating into Tregs. Nevertheless, we were able to demonstrate a role for B cells in the homeostasis of Treg cells and provide evidence for Tregs being less sensitive to apoptosis than MOG-specific conventional CD4⁺ T cells.