

**Maintaining Tolerance in Myelin Basic Protein-Specific T Cells:
The Short and the Long Story**

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A loss of tolerance in myelin-specific T cells is believed to contribute to the pathogenesis of multiple sclerosis. We investigated how the immune system normally maintains tolerance to myelin basic protein (MBP) in order to define how a break down in these mechanisms could result in autoimmune disease. CD4⁺ T cells specific for MBP121-140, a highly immunogenic MBP epitope in B10.PL mice, are largely tolerized by clonal deletion in the thymus. The efficiency of central tolerance is age-dependent, however, reflecting the developmental regulation of MBP expression. MBP121-140-specific T cells escape central tolerance in young mice when little MBP is synthesized. These T cells will encounter MBP in the periphery later in life when more MBP is available, indicating that peripheral tolerance may be required to prevent MBP121-140-specific autoimmune responses. To define the peripheral tolerance mechanisms, the fate of MBP121-140-specific T cells injected into the periphery of either wild-type or T cell-deficient mice was analyzed. T cell-deficient recipients succumbed rapidly to widespread autoimmunity, while wild-type recipients were protected by regulatory T cell activity. These endogenous regulatory T cells did not prevent the proliferation, expansion or trafficking of MBP-specific T cells. Instead, Th1 cytokine production by MBP-specific T cells transferred into wild-type mice was strongly suppressed. The ability of Tregs to cause suppression of Th1 cytokines and prevent autoimmunity during the first week after transfer of MBP-specific T cells was abrogated by activation of APCs in vivo. Interestingly, in vivo activation of APCs thirty days after transfer of the MBP-specific T cells no longer triggered autoimmunity. Instead, activation of the APCs caused the MBP-specific T cells that persisted in the periphery of wild-type mice to further suppress their Th1 cytokine responses. The tolerant phenotype of MBP-specific T cells persisting in wild-type mice was dependent on both T cell intrinsic and extrinsic factors and did not represent a terminally differentiated state as re-transfer of these T cells into T cell-deficient recipients caused autoimmune disease.

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2. Seamons, A., Perchellet, A. and **J. Goverman**. 2003 Immune Tolerance to Myelin Proteins. *Immunological Research* 28(3):201-221.