

## T Cell-Directed Immunoregulatory Effects of the Sphingosine 1-Phosphate (S1P) – S1P<sub>1</sub> (Edg-1) G Protein-Coupled Receptor (GPCR) Axis

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Mouse spleen and human blood T cells express S1P<sub>1</sub> and S1P<sub>4</sub> (Edg-6) GPCRs, which are downregulated by TCR-dependent stimulation. Occupancy of S1P<sub>1</sub> by S1P, at normal blood and lymph concentrations, suppresses chemotactic responses to chemokines and other stimuli, and to a lesser extent proliferation and cytokine generation. Results of analyses of S1P GPCR selective antagonists and individual transfectants reveal the primacy of S1P<sub>1</sub>, as contrasted with S1P<sub>4</sub>, in transducing S1P signals to T cells. Some immunosuppressive drugs which are structurally-homologous to S1P, such as FTY720 and its phosphorylated derivative, bind to S1P<sub>1</sub> and other S1P GPCRs to release T cells from S1P inhibition of chemotaxis, increase their chemokine-directed influx into lymph nodes, and prevent T cell access to foreign tissue grafts and autoimmune antigens. This hypothesis is confirmed by the alterations of T cell behavior in mice with abnormal expression of S1P<sub>1</sub> GPCR. Physiological concentrations of S1P and T cell S1P<sub>1</sub> GPCRs have unique T cell regulatory effects, which may provide novel targets for immunotherapy.