

Immunoregulatory Lysophospholipids and Their G Protein-Coupled Receptors: Major T Cell Trophic Factors and Functional Inhibitors

Edward J. Goetzl, Wengang Wang, Mei-Chuan Huang, Christine McGiffert and Markus H. Graeler

The lysophospholipid (LPL) growth factors sphingosine 1-phosphate (S1P) and lysophosphatidic acid (LPA) are generated by macrophages, dendritic cells, mast cells and platelets, which contributes to tissue levels of 1 to 100 nM, and lymph and plasma concentrations of 0.1 to 1 uM. Distinctive profiles of G protein-coupled receptors (GPCRs) for S1P and LPA are expressed by each type of immune cell, and are regulated by cellular activation. At 1 to 100 nM, S1P signals T cells through their principal S1P₁ GPCRs with consequent protection from apoptosis, enhancement of chemotaxis to chemokines, and facilitation of optimal suppressive activity of CD4⁺25⁺ (T_{reg}) T cells. At 0.3 to 3 uM, S1P inhibits T cell chemotaxis and to a lesser extent other functions. Tonic S1P-S1P₁ GPCR inhibitory signals suppress homing of blood and spleen T cells to chemokines in secondary lymphoid tissues. S1P₁ GPCR antagonists evoke lymphopenia by permitting blood T cells to enter lymph nodes in response to chemokines and blocking S1P₁ GPCR-dependent T cell efflux from lymph nodes. Inversely, there is an increase in blood level of T cells in transgenic mice, which overexpress lymphocyte S1P₁ GPCRs. The immunotherapeutic activity of S1P₁ GPCR antagonists, which limit T cell access to organ grafts and autoimmune antigens, does not reduce other functional capabilities of T cells. LPLs and their GPCRs thus constitute an immunoregulatory system of sufficient prominence for pharmacological targeting in transplantation, autoimmunity and immunodeficiency. (Supported by NIH grant HL-31809.)