

## **S1P and lymphocyte egress from lymphoid organs**

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Lymphocyte egress from lymphoid organs is essential for the emergence of T cells from the thymus, for recirculation of naïve lymphocytes during immune surveillance and for newly generated effector T and B cells to travel to sites of infection. Sphingosine-1-phosphate receptor-1 (S1P1) has been identified as having a key role in promoting lymphocyte exit from lymphoid organs. Lymphocytes that are genetically deficient in S1P1 are defective in egress from the thymus and secondary lymphoid organs. Sphingosine-1-phosphate (S1P) is abundant in plasma and lymph and evidence in support of a model where lymphocytes exit in response to S1P came from the finding that interference with S1P lyase activity led to marked elevations in S1P concentrations within lymphoid organs and disrupted egress. Upon activation, lymphocytes are transiently retained within the lymphoid organ, and we find that activated lymphocytes markedly downregulate expression of S1P1. Restoration of S1P1 in activated lymphocytes using retroviral gene transduction can promote premature egress of the cells. Innate immune stimuli can also downregulate lymphocyte egress from lymphoid organs, a process known as lymphoid organ shutdown, and we are examining whether shutdown-inducing stimuli lead to alterations in lymphocyte S1P1 function. Our on-going work in these areas will be presented and the lymphocyte intrinsic and extrinsic roles of S1P1 will be discussed.

Schwab, S., Pereira, J.P., Matloubian, M., Xu, Y., Huang, Y. and Cyster, J.G. (2005) Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. *Science* 309, 1735-1739.

Lo, C.G., Ying, X., Proia, R.L. and Cyster, J.G. (2005) Cyclical modulation of sphingosine-1-phosphate receptor 1 surface expression during lymphocyte recirculation and relationship to lymphoid organ transit. *J Exp Med* 201(2): 291-301.

Cinamon G, Matloubian M, Lesneski MJ, Xu Y, Low C, Lu T, Proia RL, Cyster, JG. (2004) Sphingosine 1-phosphate receptor 1 promotes B cell localization in the splenic marginal zone. *Nat Immunol.* 5(7):713-20.

Matloubian, M., Lo, C.G., Cinamon, G., Lesneski, M.J., Xu, Y., Brinkmann, V., Allende, M.L., Proia, R.L. and Cyster, J.G. (2004) Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* 427:355-360.