HIV-1 infection reduces emigration of mature thymocytes from the human thymus by downregulation of the sphingosine-1-kinase receptor S1PR1

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Background: Sphingosine-1-phosphate (S1P) is a chemotactic sphingolipid molecule present at high levels in blood, but low levels in lymphoid and other tissues. In the mouse it has been shown that S1P plays an important role in the egress of lymphocytes from the lymphoid tissues to peripheral blood. We investigated the dynamics of S1P and its five known receptors, S1PR 1-5, in the context of egress of naive T cells from the human thymus to the periphery, which is thus far not well understood. We hypothesized that thymocytes migrate toward S1P when ligated to S1PR1, and that due to interactions between CD69, Interferon alpha and HIV-1, that HIV infection would downregulate S1PR1.

Methods: To examine the kinetics of migration in response to S1P, we performed migration assays in transwell-membrane plates with various concentrations of S1P in the presence or absence of agonists and antagonists to S1P. To determine which S1P receptors are expressed on developing T cell subsets in the thymus we performed real-time PCR and 9-color flow cytometry on fetal, postnatal and thymic implants from NSG thy/ liv mice to verify the expression of S1PR1-5 on thymocytes. We additionally performed *in vitro* and *in vivo* HIV-1 infection of thymocytes with X4- (NL4-3) and R5- (JR-CSF) tropic virus.

Results: Our results show that S1PR1 is significantly upregulated in mature thymocyte subsets about to exit the thymus to the periphery as naïve T cells. Thymocytes migrate to S1P and FTY720 inhibits migration by functioning as a S1P analogue to downregulate of one or several of the S1P receptors: S1PR1, 3, 4, 5. *In vitro*, S1PR1 expression is decreased in mature naïve thymocytes 2d post infection. This effect is no longer observed at two weeks. *In vivo* infections are currently in progress to confirm this effect.

Conclusion: HIV-1 infection perturbs the natural egress of mature thymocytes from the thymus via downregulation of S1PR1, the primary S1P receptor for thymic egress. As T cell reconstitution is a constant challenge in HIV infection, this discovery could have significant impact on how we approach therapeutics targeting T cell regeneration.