Effect of HIV-1 on S1PR1 Expression in the Human Thymus

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One of the most significant issues for HIV infected patients is the regeneration of functional T cells in the peripheral blood and lymphoid tissues following onset of infection. T cell reconstitution after the acute phase of HIV-1 infection is incomplete in many individuals in spite of successful antiretroviral therapy and is associated with persistent immune activation. The thymus is essential for the maturation of T cells from bone marrow stem cells. There is only limited information on the mechanisms regulating egress of mature T cells from the thymus to the periphery, and no data exist describing the impact of HIV infection on these processes. Others and we have established that S1P receptor 1 (S1P-R1), one of the five receptors to the signaling molecule Sphingosine-1-phosphate, is required in both mice and humans for T cell egress from the thymus. Our novel preliminary data indicate that HIV increases expression of S1P-R1 in mature human thymocytes; however, thus far no studies have been done to examine the mechanism or implications for egress of this phenomenon.

Our overall goal with these studies is to examine the mechanisms by which HIV infection alters the expression and function of a receptor on T cells that has been shown to be necessary for mature T cell migration throughout the body. We are especially interested in whether the increase we have observed in expression of this receptor also results in increased output of new T cells, as this would be highly beneficial for HIV patients unable to regenerate ideal T cell levels. We propose that this increase in S1P-R1 expression, if functional, contributes to regeneration of competent T cells after the acute phase of HIV-1 infection and may therefore be a target for patients otherwise unresponsive to immunotherapy.

Our hypothesis is that HIV infection upregulates S1P receptor 1 on mature thymocyte subsets and thereby increases egress of new T cells from the human thymus to peripheral blood and lymphoid organs. To examine this novel question, we propose to utilize our well-established humanized mouse model, the Human Immune System (HIS) mouse. Humanized mice offer the distinct advantage of allowing us to study changes in S1P-R1 expression and T cell egress in human tissue. HIS mice are implanted with human fetal thymus and liver tissue, which results in the development of a “human-like” immune system in the mouse. We will infect these mice with HIV and characterize the expression of S1P-R1 in the human thymus, then examine with various assays whether the increase in receptor expression permits egress of thymocytes. We expect to find that the increase in S1P-R1 during HIV allows additional T cell output, which we may be able to modulate as a means to novel therapy for patients. Therefore, this project represents an important and promising prospect for regeneration of T cells in HIV infected individuals and the field of T cell reconstitution.