

Brendan M Ball, Caitlyn Guldenpfennig, Alexis N Cattin-Roy, and Habib Zaghouani. The Influence of IL-4 On T Cell Development And Type One Diabetes

T1D, otherwise known as juvenile diabetes, is a chronic autoimmune disease in which the pancreas produces little to no insulin. This happens with the damaging of the beta-cells, insulin-producing cells, in the islets of Langerhans by the immune system. This immune system attack leads to apoptosis of beta cells, thus establishing insulin deficiency and hyperglycemia which can lead to major health concerns such as ketoacidosis (buildup of acids in the bloodstream), kidney failure, heart disease, stroke, and blindness. Type One Diabetes (T1D) currently affects about 1.6 million people in the United States with about 64,000 new cases diagnosed every year. Although the genetic factors of patients play a huge role in their diabetes susceptibility, there are significant environmental implications that play a role in diabetes susceptibility in patients.

If we inject IL-4 cytokines to act as an environmental factor in the thymus, then that will alter

central tolerance and stop the targeting of beta cells by escaped autoreactive T cells. This led us to test the hypothesis that intra-thymic IL-4 will tighten central tolerance in the NOD and reduce the number of autoreactive cells in turn leading to less disease. To test this, we used the non-obese diabetic (NOD) strain of mouse, which is a model that is able to develop spontaneous autoimmune diabetes that shares a lot of similarities to T1D in human subjects, such as pancreas-specific autoantibodies, autoreactive CD4⁺ and CD8⁺ T cells, and genetic linkage to the disease. We injected IL-4 into the thymus, as well as saline for our control group, to test if this affects T cell development and to see its effects on diabetes. We have multiple experimental readouts including sequencing the variable regions of the T cell receptors to look at the T cell repertoire and also check blood sugar as the mice get older. Early results indicate that we are able to alter the T cell repertoire and have one that is consistent with a healthy immune response (No beta-cell autoantigen specific receptors and good diversity). This study shows that IL-4 aids in the production of thymic cells that perform central tolerance thus tightening T cell selection. Future directions include analyzing how many T cells are actually left in the thymus, if any, that are capable of eliminating insulin producing cells. These findings may have translational implications that can be tried in human studies to provide therapeutic approaches to preserve central tolerance.