Evaluating Environmental Influence On T-Cell Development In Type One Diabetes

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BACKGROUND

- Type One Diabetes (T1D), sometimes 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 attack occurs due to the activation of T cells, specifically CD4 and CD8 T cells, that recognize the islet autoantigens, which leads to apoptosis of beta cells
- Through central tolerance our immune system can eliminate developing T cells that are made to attack self-peptides
- Peripheral tolerance is the second line of defense behind central tolerance because it makes sure that the T cells that escaped from central tolerance don't create autoimmune diseases.
- In the case of T1D, there is a loss of tolerance to tissue autoantigens which is attributed by defects in both central and peripheral tolerance.
- Factors in the environment, such as parasitic infections, induce chemical mediators called cytokines.

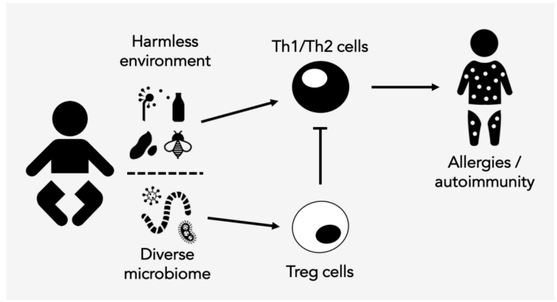

Figure 1: This image depicts the hygiene hypothesis that suggests that there is a benefit to infectious agents and their composites on immunological diseases

HYPOTHESES

If we enter IL-4 cytokines to act as an environmental factor in the thymus, then that will alter the central tolerance and stop the targeting of beta cells by T cells.

METHODS

NOD Mouse Model: We will be using the nonobese 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.

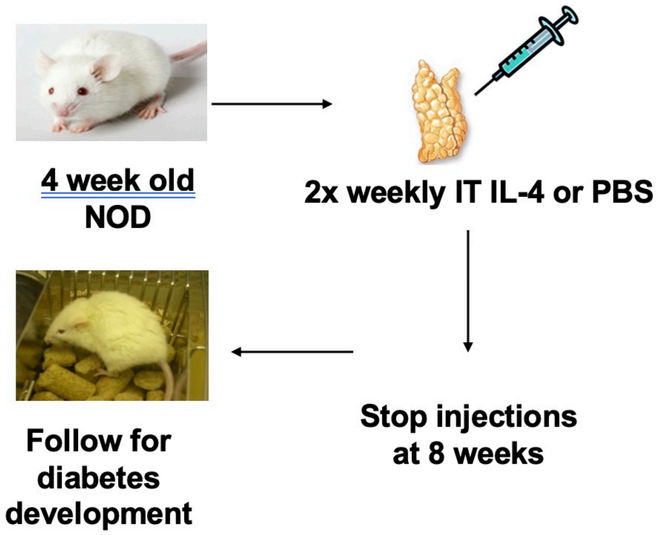

Figure 2: This image depicts the carrying out of our procedure with the NOD mouse and their IL-4 treatments and their saline treatments for our control group

- Peripheral tolerance and environmental factors have been looked at and it is shown IL-4 to be an anti-inflammatory in this since and delay disease.

METHODS

- We want to know if environmental factors (IL-4 is considered an environmental cytokine because it is induced during parasitic infection of the host) can also impact central tolerance.
- To do this we will have IL-4 treatment in 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 will have multiple experimental readouts including sequencing the variable regions of the T cell receptors to look at the T cell repertoire and we will also check blood sugar as the mice get older.

RESULTS

- From our research we are expected to be 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).
- Previous research in our lab has shown that IL-4 aids in the production of thymic cells that preform central tolerance thus tightening T cell selection.
- This leads to 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.

SIGNIFICANCE

If the expected findings are met, they could then be translated into human research to provide therapeutic approaches to preserve central tolerance.

ACKNOWLEDGEMENTS

Funding: University of Missouri Maximizing Access to Research Careers Program (T34)