The Epigenetics of Autoimmunity

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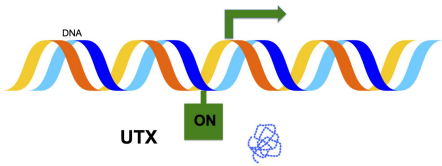
Introduction

Type 1 diabetes is an autoimmune disease that destroys the endocrine function of the pancreas . Onset is typically childhood or early adulthood, with 200,000 pediatric patients in the US. Current therapy focuses on intensive lifelong insulin replacement, and do not address the underlying autoimmunity. Despite life saving insulin therapy, patients continue to have long term morbidity from ischemic heart disease, retinopathy, nephropathy.

The incidence of patients with Type 1 diabetes is increasing over time, a change that may be linked to epigenetic changes. **Epigenetic Modifications** (including histone modification and DNA methylation) influence gene expression without altering the DNA sequence.



There has been conflicting evidence regarding whether dysfunction in UTX protein or decreased UTX levels affect the incidence of Type 1 diabetes. Adults with Turner's Syndrome (XO or X mosaic X) have a 11x increased incidence of T1DM, and patients with Kabuki Syndrome 2 (pathogenic UTX variants) have been associated with neonatal hypoglycemia and hyperinsulinism.

While multiple cell types have been implicating in causing Type 1 diabetes autoimmunity, the T cell is one of the most important cell types in initiating diabetes, Using a Non Obese Diabetic Mouse Model of Human Autoimmune Diabetes, we examined the impact of removing UTX within the T cells to determine the role of UTX in mediating autoimmunity.

Results

Figure 1

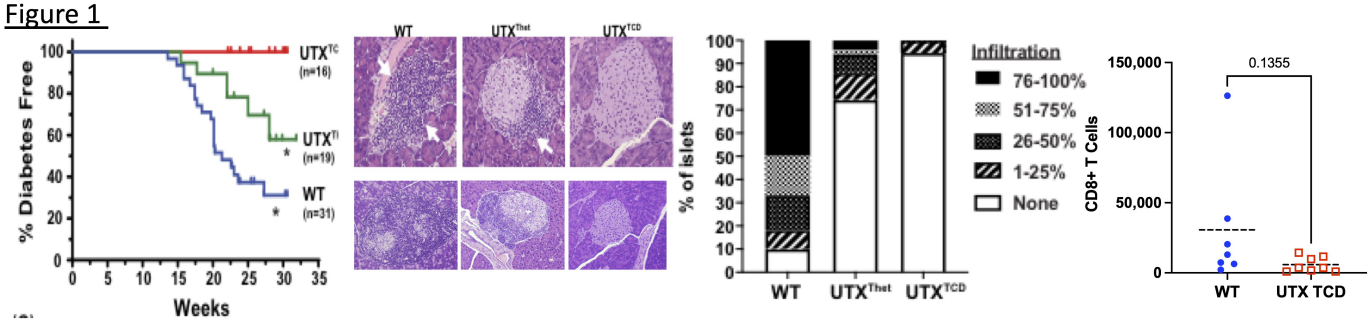
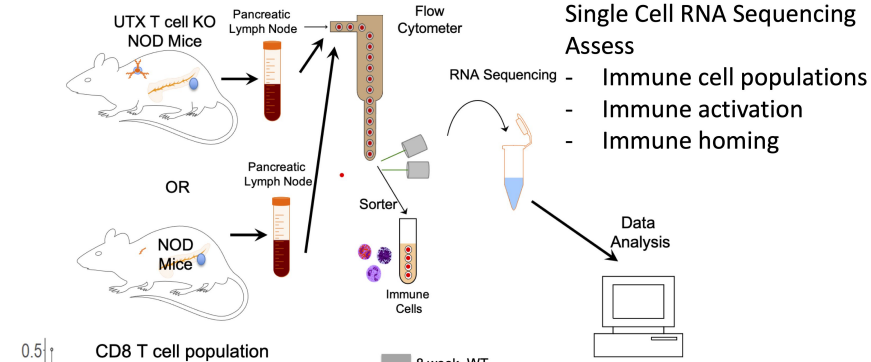
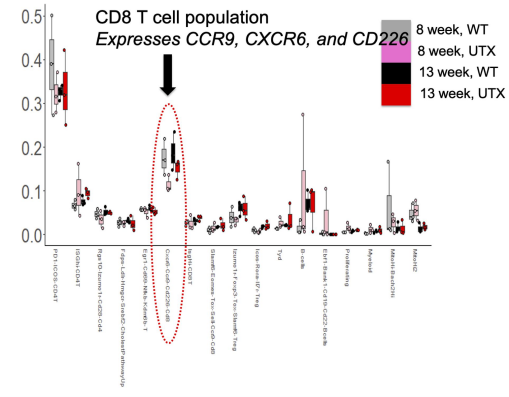


Figure 2



Single Cell RNA Sequencing Assess

- Immune cell populations
- Immune activation
- Immune homing



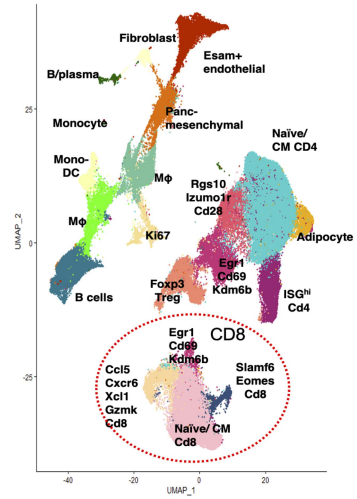


Figure 1:
NOD–UTX TCD mice do not develop diabetes in contrast to NOD-WT mice. NOD–UTX TCD mice have less pancreatic infiltrate (of all immune cells and specifically of CD8+ T cells).

Figure 2:
Single cell sequencing of pancreatic lymph node reveals that the most differential gene expression between NOD-UTX TCD and WT mice exists between the CD8+ T cells.

Discussion

Our results demonstrate that UTX in T cells plays an important role in the process of anti-pancreatic infiltration and resulting diabetes in our autoimmune mice. There is a lower number of CD8+ Tcells within the pancreas. These mice continue to get salivary autoimmune infiltration (data not shown) and continue to have normal numbers of CD8 T cells in secondary lymphoid organs of the spleen, and inguinal nodes but not pancreatic nodes (data not shown).

Our single cell sequencing has f revealed that the cell populations with the most differentiatial gene expression are found with in CD8+ T cells. This cell population has revealed differences in homing molecules, that may be at the root cause as why UTX deficient T cells are unable to initiate diabetes. Our next steps are to examine the the cell surface protein expression of these cells, and then to see if UTX cells perform less well in chemotactic assays, as additional evidence that they are unable to home from the lymph node into the target pancreatic tissue.

References:
Cook et al. T follicular helper cell dependent clearence of persistent virus infection requires T cell expression of Histone demythlase UTX. Immunity
Gangerrault et al . Pancreatic Lymph nodes are required for priming Beta cell reactive T cell in NOD mice. Journal of Experimental Medicine 2002