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Cell intrinisc immunopathology of type 1 diabetes in a humanized mouse model

In Type 1 diabetes (T1DM) multiple genetic determinants encoding HLA and immunomodulatory molecules create an environment predisposed to immune cell-mediated attack of pancreatic beta cells. Faulty induction and maintenance of self-tolerance is critical to disease evolution, as shown by observed abnormalities in immunoregulatory populations and autoimmune pathogenesis of T1DM in patients and the NOD mouse model. Since these observations are made after T1DM onset, the direct relevance of these abnormalities to disease initiation and progression is unclear. It is clear that T1DM susceptibility is transferred in hematopoietic stem cells (HSCs) in both mouse and man, suggesting that intrinsic defects in HSCs contribute to development of autoimmunity.

We hypothesize that the genetic predisposition to T1DM is associated with hematopoietic-intrinsic abnormalities affecting induction and maintenance of self-tolerance. We will use a humanized mouse model transplanted with allogeneic human thymus and $CD34^+$ HSCs from control and Type 1 diabetic subjects to analyze the evolution of three tolerogenic cell types implicated in the pathogenesis of T1DM. In addition to monitoring development and peripheral reconstitution, we will assess (1) suppressive function of regulatory T cells, (2) presentation/stimulation function of primary dendritic cells and (3) expansion/cytokine production of NKT cells that develop from control and T1DM HSCs. The objective of these studies is to gain insights into functional defects in regulatory T, dendritic, and/or NKT cells that differentiate from T1DM HSCs. Identification of defects in one or all immunoregulatory populations analyzed here will potentially guide treatment strategies in T1DM patients.