Autoantigens, T Cells and TCRs: Human Disease-specific Therapeutic Targets

In-situ Detection of Islet Antigen-specific CD8 T Cells in Insulitic Lesions of New-onset and Long-term Type 1 Diabetes Patients

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Purpose: The definition of type 1 diabetes (T1D) as an autoimmune disease has historically been inferred from the HLA associated genetic risk, islet autoantibodies and circulating beta cell-reactive T cells. However, a direct association of islet autoreactive T cells with beta-cell destruction in human pancreatic islets has never been demonstrated, while little is known about disease progression after diagnosis.

Methods: Frozen pancreas samples were obtained from eleven cadaveric T1D donors with disease durations ranging from one week to eight years. Sections were analyzed for the presence of insulin-sufficient beta cells, CD8+ insulitic lesions and HLA class I hyperexpression. Finally, consecutive sections were probed by *in situ* tetramer staining for CD8 T cell reactivity against six defined islet autoantigens associated with T1D.

Summary of Results: Pathological features such as HLA class I hyperexpression and insulitis, reported in recent-onset T1D, were found to persist in patients with longstanding disease. Insulitic lesions were present in a multifocal pattern, with varying degrees of infiltration and beta-cell loss across affected organs. Both single and multiple CD8 T cell auto-reactivities were detected within individual islets, implying that autoreactive CD8 T cells detectable in peripheral blood act locally in inflamed islets.

Conclusions: Our observations reveal a heterogeneous disease course with protracted, heterogeneous autoimmune responses in clinical T1D and provide the first direct evidence for beta cell specific CD8 T cell autoreactivity within islets. The persistence of substantial beta-cell mass and insulitis many years after clinical manifestation offers novel opportunities for therapeutic intervention, even in case of long-lasting disease.