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Detection of CD8+ T cell responses in individuals with long-term type 1 diabetes and generation of human CD8+ T cell lines specific to islet-associated autoantigens

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Abstract:
Type 1 diabetes (T1D) is an autoimmune disease characterized by the activation of lymphocytes against insulin-producing β-cells in the pancreas. In humans, CD8+ T cells are predominantly found in sites of insulitis and are considered to be one of the main drivers of β-cell destruction, thus indicating the need to analyze the frequency and function of these autoreactive CD8+ T cells. Peripheral blood mononuclear cells (PBMC) from individuals with long-term T1D were stained *ex vivo* for T cell surface markers and HLA-A2 pentamers containing known islet-associated epitopes to determine if there are autoreactive CD8+ T cells circulating in the periphery. All T1D donors tested had at least one detectable autoreactive CD8 T cell population and the frequencies of these autoantigen-specific T cells were comparable to previously published data from T1D individuals. We then developed a method of establishing CD8 T cell lines by co-culturing negatively isolated CD8 T cells and peptide-pulsed monocyte-derived dendritic cells from the PBMC of one T1D donor (A*02:01, A*33:01, B*14:02, B*40:01, DRB1*01:02, DRB1*04:04). We expanded a CD8 T cell line specific to the preproinsulin peptide PPI_{15-24}. This cell line produced IFN-γ and expressed CD107a in the presence of PPI_{15-24}-pulsed target cells, but not to an unrelated peptide or media alone. Using a similar approach, we were able to generate CD8 T cell lines from the same T1D donor that were cytotoxic to target cells pulsed with the autoantigens glutamic acid decarboxylase peptide ($GAD65_{114-123}$) and islet-specific glucose-6-phosphatase catalytic subunit-related protein peptide ($IGRP_{265-273}$). These autoreactive T cell lines can be utilized in *in vivo* assays using humanized mouse models to further understand the mechanism of β-cell destruction and disease progression. Studying the functionalities of these autoreactive T cells will also provide insights into identifying immune correlates to better assess both novel and existing immunotherapeutic strategies for T1D.

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