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Broad Repertoire of T Cell Autoreactivity Directly from Islets of Donors with Type 1 Diabetes (T1D)

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Et al.

BROAD REPERTOIRE OF T CELL AUTOREACTIVITY DIRECTLY FROM ISLETS OF DONORS WITH TYPE 1 DIABETES (T1D)

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Type 1 diabetes (T1D) is an autoimmune disease characterized by the infiltration of lymphocytes into the insulin-producing β-cells in the pancreas. We have isolated live T cells sorted or grown directly from the isolated, handpicked islets of human donors with T1D. We received ~500 islet equivalent EQ of variable purity (10-90%) from 12 donors with T1D (disease duration 0.42-20 years) and from seven control donors and two donors with type 2 diabetes (T2D). A total of 321 T cell lines and clones were derived from the islets of donors with T1D (3 lines from the 9 control donors). These are 131 CD4+ lines and clones, 47 CD8+ lines and 143 lines that contain both CD4+ and CD8+ T cells. From 50 lines and clones examined to date, we have determined the autoreactivity of 19 and have seen a broad repertoire of T cell autoreactivity in the islets, including characterized targets and post-translationally modified targets. Autoreactivity of CD4+ T cell lines was to three different peptides from glutamic acid decarboxylase 65 (GAD; $GAD_{115-127}$, $GAD_{274-286}$, $GAD_{555-567}$), $proinsulin_{76-90}$, and to chromogranin A or proinsulin expressed by DR4+DQ8+ B cells transduced with lentivirus containing constructs with the open reading frames corresponding to whole autoantigens. Reactivity to modified peptides included the glucose-regulated protein 78 and islet amyloid polypeptide with arginine to citrulline modifications ($GRP78_{292-305(Arg-Cit297)}$ and $IAPP_{65-84(Arg-Cit\ 73,\ 81)}$), deaminations ($IA\text{-}2_{545-562(Gln-Glu\ 548,\ 551,\ 556)}$, and to several insulin hybrid peptides. These autoreactive CD4+ T cell lines and clones secreted only pro-inflammatory cytokines (IFN-γ, TNFα) upon peptide stimulation. For CD8+ T cells from islets, from one donor with T1D, we saw binding of a pool of HLA-A2 pentamers loaded with insulin B_{10-18}, $IA\text{-}2_{797-805}$ and insulin specific glucose-6-phosphatase catalytic subunit related protein, $IGRP_{265-273}$. These results have implications for the development of successful prevention and reversal therapeutic strategies in T1D.

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