May 16th, 1:45 PM

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

Jenny Aurielle B. Babon
University of Massachusetts Medical School

Et al.

Let us know how access to this document benefits you.
Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Cell Biology Commons, Immune System Diseases Commons, Immunology and Infectious Disease Commons, and the Translational Medical Research Commons


Creative Commons License

This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.
This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.
BROAD REPERTOIRE OF T CELL AUTOACTIVITY DIRECTLY FROM ISLETS OF DONORS WITH TYPE 1 DIABETES (T1D)

Jenny Aurielle B. Babon\textsuperscript{1}, Megan E. DeNicola\textsuperscript{1}, David M. Blodgett\textsuperscript{1}, Thomas S. Buttrick\textsuperscript{3}, René Maehr\textsuperscript{4}, Rita Bottino\textsuperscript{5,6}, Ali Naji\textsuperscript{7}, John Kaddis\textsuperscript{8}, Wassim Elyaman\textsuperscript{3}, Eddie A. James\textsuperscript{9}, Rachana Haliyur\textsuperscript{10}, Marcela Brissova\textsuperscript{10}, Lut Overbergh\textsuperscript{2}, Chantal Mathieu\textsuperscript{2}, Thomas Delong\textsuperscript{11}, Kathryn Haskins\textsuperscript{11}, Alberto Pugliiese\textsuperscript{12}, Martha Campbell-Thompson\textsuperscript{13}, Clayton Mathews\textsuperscript{13}, Mark A. Atkinson\textsuperscript{13}, Alvin C. Powers\textsuperscript{10,14,15}, David M. Harlan\textsuperscript{1}, Sally C. Kent\textsuperscript{1}

\textsuperscript{1}Division of Diabetes, Diabetes Center of Excellence, Department of Medicine, University of Massachusetts Medical School; \textsuperscript{2}Laboratory for Clinical and Experimental Endocrinology, Department of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium; \textsuperscript{3}Ann Romney Center for Neurologic Diseases, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; \textsuperscript{4}Program in Molecular Medicine, Diabetes Center of Excellence, University of Massachusetts Medical School; \textsuperscript{5}Institute of Cellular Therapeutics, Allegheny-Singer Research Institute, Pittsburgh, PA; \textsuperscript{6}Department of Biological Sciences, Carnegie Mellon University, Pittsburgh, PA; \textsuperscript{7}Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, PA; \textsuperscript{8}Department of Information Sciences, Beckman Research Institute, City of Hope, Duarte, CA; \textsuperscript{9}Benaroya Research Institute at Virginia Mason, Seattle, WA; \textsuperscript{10}Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; \textsuperscript{11}Department of Immunology and Microbiology, University of Colorado School of Medicine, Denver, Anschutz Medical Campus, Aurora, CO; \textsuperscript{12}Diabetes Research Institute, University of Miami, Miami, FL; \textsuperscript{13}Departments of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL; \textsuperscript{14}Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN; \textsuperscript{15}VA Tennessee Valley Healthcare System, Nashville, TN

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\textsubscript{115-127}, GAD\textsubscript{274-286}, GAD\textsubscript{555-567}), proinsulin\textsubscript{76-90}, and to chromogranin A or proinsulin expressed by DR\textsubscript{4}+DQ\textsubscript{8}+ 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 (GRP\textsubscript{78}292-305(Arg-Cit297) and IAPP\textsubscript{65-84}(Arg-Cit 73, 81)), deaminations (IA-2\textsubscript{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\textsubscript{10-18}, IA-2\textsubscript{797-805} and insulin specific glucose-6-phosphatase catalytic subunit related protein, IGRP\textsubscript{265-273}. These results have implications for the development of successful prevention and reversal therapeutic strategies in T1D.

Contact:
Jenny Aurielle B. Babon, Ph.D.
University of Massachusetts Medical School
Jenny.babon@umassmed.edu