Biological 'atlas' shows dual personality for immune cells that cause Type 1 diabetes

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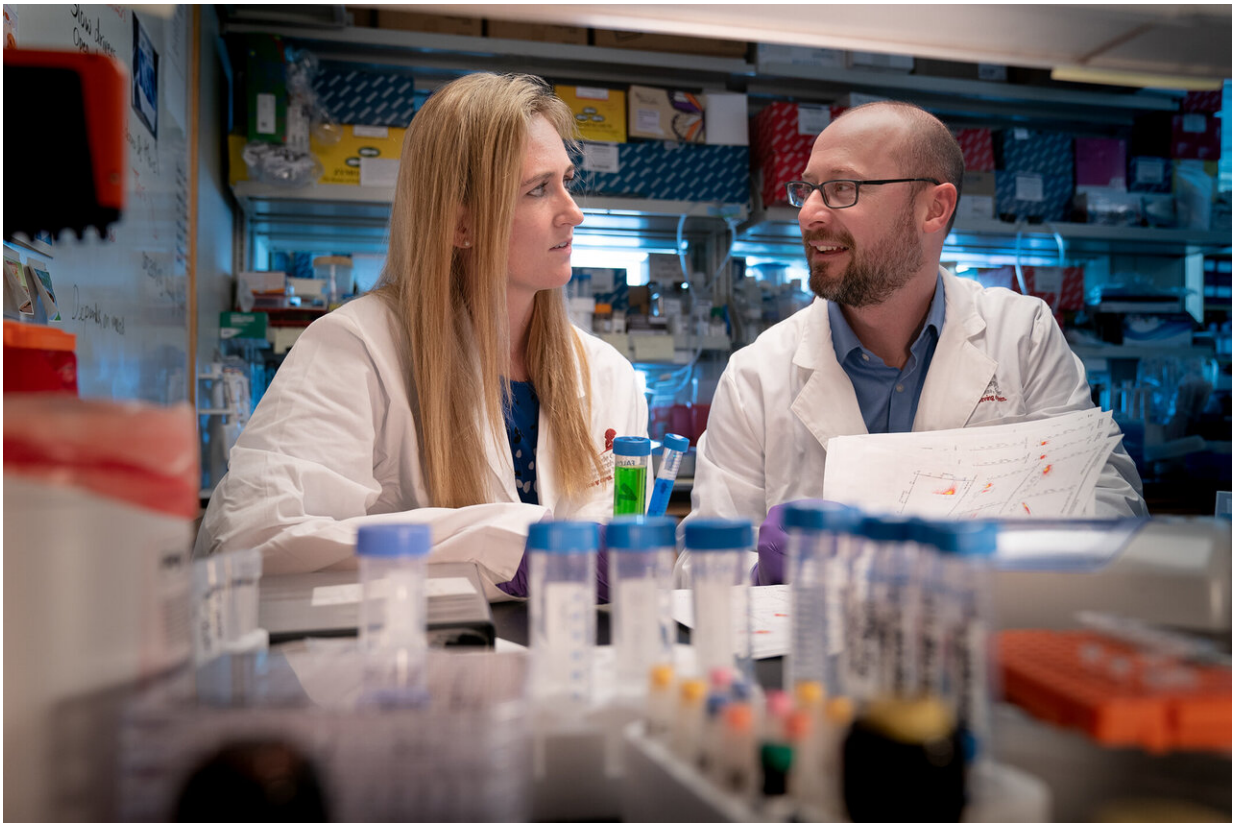

Senior author Ben Youngblood, PhD, and co-author Caitlin Zebley, MD, both of Immunology at St. Jude, discover how T cells have a dual biological personality. Credit: St. Jude Children's Research Hospital

Immunologists at St. Jude Children's Research Hospital have created a

database that identifies gene-regulatory mechanisms in immune cells that facilitate Type 1 diabetes. The findings were published today in *Nature Immunology*.

Type 1 diabetes is an autoimmune disease in which the immune system attacks the body's own cells. In Type 1 diabetes, immune cells called CD8 T cells kill insulin-producing islet cells in the pancreas. By creating an epigenetic "atlas," the researchers revealed that these T cells have a dual biological personality. That dual personality enables the T cells to retain the ability to attack insulin-producing cells across successive generations of T cells.

"A major question has been why these T cells remain functional over long periods of time," said senior author Ben Youngblood, Ph.D., of the St. Jude Department of Immunology. "Our research provides important insights into the stability of that response by establishing the central role of epigenetic programming in human T cell differentiation."

Regulation through epigenetics

The activity of cells is governed by genetic and epigenetic regulation, control switches that give instructions to a cell. The epigenetic regulation mechanisms include a process called methylation in which methyl molecules can be plugged into DNA molecules at key points to suppress their genetic activity.

Youngblood and his team charted the pattern of methylation across the genome of CD8 T cells to understand the epigenetic programming that governs their development, or "differentiation," from immature cells called stem-memory T cells. The researchers collected data on methylation patterns of a variety of T cells, ranging from naïve— not yet possessing the ability to attack—to active effector cells.

From the atlas, investigators discovered that the diabetes-causing T cells possessed a dual personality of both naïve and effector-associated epigenetic programs, revealing for the first time that the cells were epigenetic hybrids, possessing both programs.

The researchers also performed the same analysis on mouse CD8 T cells, revealing they also showed such a dual personality.

Understanding a dual personality

A key to understanding both the human and mouse atlas was a multipotency index developed by co-authors Yiping Fan, Ph.D., of the St. Jude Center for Applied Bioinformatics, and Caitlin Zebley, M.D., a clinical fellow in the Department of Immunology. Through cutting-edge, machine-learning approaches, Fan and Zebley interrogated this data to understand the differentiation status of the autoreactive T cells. Using this novel index, they were able show that methylation sites across the T cells' genome can be used to predict a T cell's differentiation.

The autoreactive CD8 T cells scored high on the index, revealing their preservation of the less-differentiated hybrid state. The atlas and the multipotency index offer important new tools for developing treatments and diagnosis of Type 1 diabetes.

"We now have an epigenetic signature for these cells that we can use to explore treatments for Type 1 diabetes that induce immunological tolerance of these T cells to prevent their attack on islet cells," Youngblood said.

The index could be used as the basis for a diagnostic tool to predict which patients would respond to therapies that encourage that tolerance. To advance this work, Youngblood and his colleagues are collaborating with the Immune Tolerance Network to examine data from past clinical

trials to see whether the index could predict which patients would respond to such therapies and which would not. The ITN, funded by the National Institute of Allergy and Infectious Diseases, is a collaboration of researchers aimed at developing immune tolerance therapies.

The insights from the epigenetic atlas can also be applied to cancer immunotherapies, in which T cells are engineered to recognize and selectively attack tumor cells. Using the multipotency index, researchers could measure how effective such engineered T cells would be in attacking cancer cells. The atlas can also be used to understand the nature of T cell activity in chronic viral infections.

More information: Hossam A. Abdelsamed et al, Beta cell-specific CD8+ T cells maintain stem cell memory-associated epigenetic programs during type 1 diabetes, *Nature Immunology* (2020). DOI: 10.1038/s41590-020-0633-5

Provided by St. Jude Children's Research Hospital

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