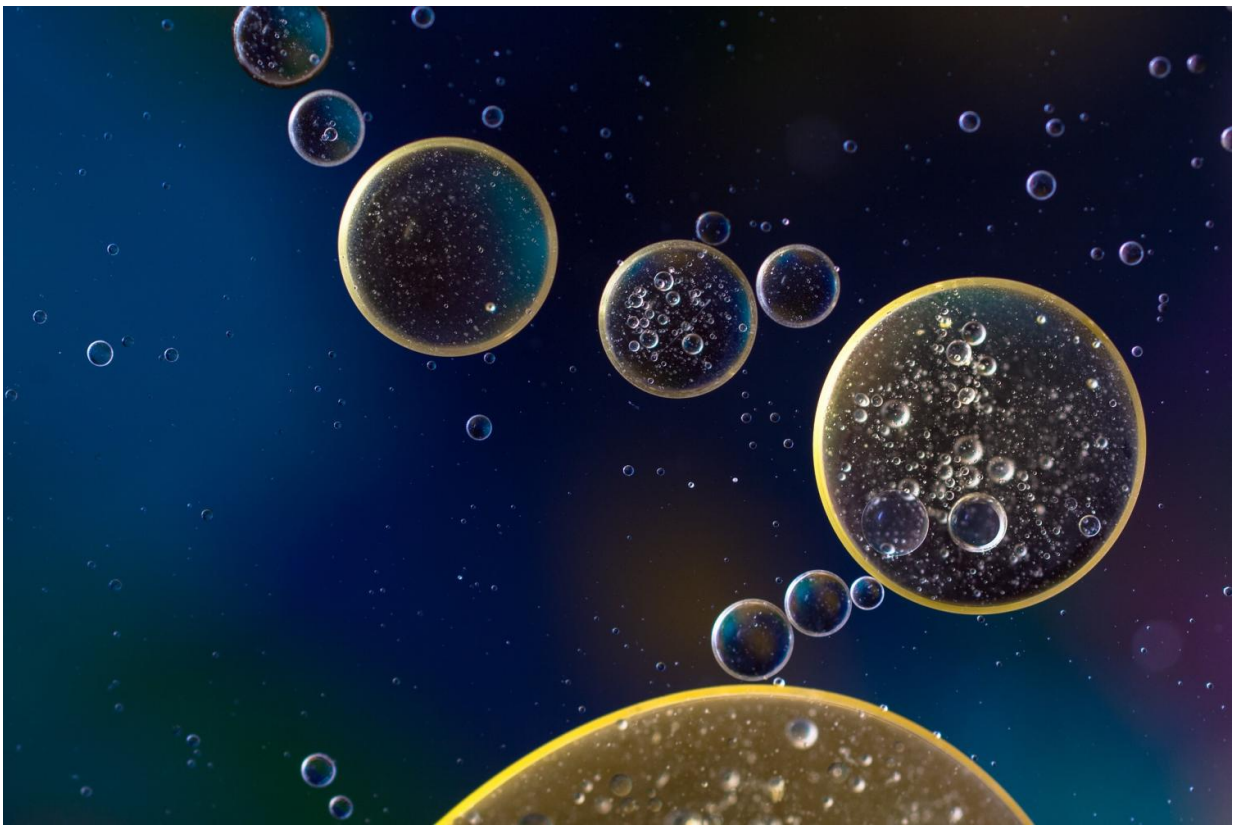
MedicalXpress

Study uncovers how pancreatic cells reprogram themselves to limit the immune response during buildup to type 1 diabetes

February 28 2022



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For the first time, researchers have revealed that during the development of Type 1 Diabetes (T1D), when insulin-producing cells in the pancreas

are under attack from T lymphocytes, the cells lining the pancreatic duct reprogram themselves in an attempt to suppress autoimmune T cell responses. This study is published today in *Nature Metabolism*.

"The first events that occur in a patient heading towards Type 1 Diabetes, the events that trigger autoimmunity, have been difficult for researchers to pin down because of our inability to biopsy the pancreas, and the fact that clinical diagnosis is only made once massive beta cell destruction has occurred," said senior author Golnaz Vahedi, Ph.D., an associate professor of Genetics and member of the Institute for Diabetes, Obesity and Metabolism at the Perelman School of Medicine at the University of Pennsylvania. "That is why it is so important to develop a better understanding of the earliest molecular events in T1D pathogenesis, so we can uncover more about biomarker identification and disease prevention."

Autoimmune diseases, which affect as many as 23.5 million Americans, occur when the body's immune system attacks and destroys healthy organs, tissues and cells. There are more than 80 types of autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and T1D. In T1D, immune cells called T lymphocytes attack and destroy insulin-secreting pancreatic beta cells and the pancreas stops producing insulin, the hormone that controls blood sugar levels.

"Although it might be an ultimately unsuccessful attempt of the pancreas to limit the adaptive T cell response responsible for destroying beta cells, this finding that the ductal cells are capable of playing this suppressive role towards autoimmune T cell responses is unprecedented," said co-senior author Klaus Kaestner, Ph.D., the Thomas and Evelyn Suor Butterworth Professor in Genetics. "Our study shows that these cells, which had never previously been linked to immunity, may change themselves to protect the pancreas."

Established in 2016, the Human Pancreas Analysis Program (HPAP) is supported by a $28 million grant from the National Institutes of Health with major contributions from Penn, the University of Florida and Vanderbilt University. The HPAP, which is co-directed by Kaestner and Ali Naji MD, Ph.D., the J. William White Professor of Surgical Research, started collecting pancreatic tissues from hundreds of deceased organ donors diagnosed with T1D. Because many T1D patients harbor beta cell autoantibodies called Glutamic Acid Decarboxylase (GAD) in their bloodstream years before clinical diagnosis, HPAP also collects samples from autoantibody-positive donors, who are at risk for developing T1D but have not received that diagnosis.

"Our study took those quality tissue samples and created high-resolution measurements of millions of cells from patients at various stages of T1D progression, resulting in a single-cell atlas of pancreatic islets," said co-senior author R. Babak Faryabi, Ph.D., an assistant professor of Pathology and Laboratory Medicine and a core member of Epigenetics Institute at Penn.

Blood tests to check for levels of GAD are common for patients with, or at risk for, T1D, and doctors use it as a diagnostic tool. Another finding of this study is the new understanding of what is happening on a molecular level in the pancreas and how it correlates to the findings of the GAD test.

"Our study is the first to show that even when a person is not clinically considered to have T1D, high levels detected in their GAD test indicate large-scale transcriptional remodeling of their beta cells," said Naji, a study co-senior author. "It solidifies to clinicians to closely monitor patients with increasing levels of GAD, as we now know what cellular and molecular changes are in motion in relation to those levels."

Although researchers do not yet know whether these transcriptional

changes are contributing to or are consequences of disease pathogenesis, the discovery of molecular phenotypic changes in pancreatic cells of autoantibody-positive individuals advances the understanding of early pancreatic changes occurring in T1D, and sets the course for continued research in this area.

More information: Robert Faryabi, Single-cell multi-omics analysis of human pancreatic islets reveals novel cellular states in type 1 diabetes, *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00531-x. www.nature.com/articles/s42255-022-00531-x

Provided by Perelman School of Medicine at the University of Pennsylvania