Measuring gene expression changes over time may help predict T1D diabetes progression

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Type 1 diabetes (T1D) is an autoimmune disease in which a misdirected immune system gradually destroys healthy pancreatic islet β cells, resulting in a lack of insulin. The exact cause of T1D remains unknown.

However, β cell-reactive autoantibodies can be detected in circulating blood months to years before diagnosis, raising the possibility of intervening to stop or delay T1D before children develop the disease.

Monitoring the number, type, and concentration of autoantibodies appearing in the blood can help predict the long-term risk of progression from autoimmunity to symptomatic T1D.

Now new findings suggest that measuring how patterns of gene expression in white blood cells change in children starting in infancy—before autoantibodies appear indicating an autoimmune reaction against the β cells—can predict earlier and more robustly which genetically-susceptible individuals will progress to T1D. The comprehensive international study included co-investigators from the University of South Florida Health Informatics Institute (HII).

The research was published on March 31 in *Science Translational Medicine*.

HII Director Jeffrey Krischer, Ph.D., a professor in the USF Health Morsani College of Medicine's Department of Internal Medicine, and Hemang M. Parikh, Ph.D., an assistant professor of bioinformatics in the USF Health Morsani College of Medicine's Department of Pediatrics, were co-investigators of the study led by the UK researchers at the University of Cambridge.

"Our identification of specific changes in the blood related to natural killer cells provides evidence for the potential involvement of these immune cells in the onset or progression of type 1 diabetes in asymptomatic children," Dr. Parikh said. "This creates a possible new target for early therapeutic intervention using immune modulation."

This study was based on blood samples longitudinally collected from 400

children in The Environmental Determinants of Diabetes in the Young (TEDDY) consortium as they grew older, from birth to age 6. (TEDDY follows children at risk of developing T1D, collecting blood and other samples long before disease symptoms emerge.)

Using genomic approaches and bioinformatics analytical methods, the blood samples were processed to measure the expression of thousands of genes simultaneously. This allowed researchers to identify which genes were switched on and off in each child at varying points in time.

Among the study's key findings:

- Discovered dynamic, early changes in white blood cell gene expression: Whether or not they progressed to autoimmunity or T1D as they matured, all children in the study showed marked changes in patterns of gene expression in their blood within the first few years of life. This observation highlights the dynamic context in which healthy infants develop early autoimmune disease.When the researchers adjusted for the large changes in gene expression patterns with age, very specific patterns correlating with the rate of progression toward T1D diagnosis became apparent. They identified changes in blood gene expression not seen in healthy children, and these changes began before any other evidence of autoimmunity. Furthermore, the faster the changes occurred, the quicker the children progressed toward T1D onset.

- Linked NK cell signature with T1D progression: By comparing a specific pattern of gene expression associated with T1D progression to groups of genes expressed by many different cell types, the researchers found that this pattern came from a distinct immune cell population known as natural killer (NK) cells. Although NK cells have been observed in the pancreas of

children with recent-onset T1D, the role of these immune cells does not figure prominently in current theories explaining how the immunopathology of T1D develops. A more detailed study is needed to determine whether NK cells actively contribute to the T1D-related autoimmune process destroying β-cells in the pancreas, reflecting a pathophysiological response.

- Created a robust predictive model, independently confirmed: The researchers used their new knowledge about longitudinal changes in gene expression patterns to build a model to predict which infants would get T1D and when disease onset was likely to happen. The predictive model incorporates the latest evidence about how the seroconversion of autoantibodies influences progression to T1D. Its accuracy was validated using a second, independent group of prediabetic children from the Type 1 Diabetes Prediction and Prevention Study.

"This type of large-scale research is only possible through the collaboration of many people, including healthy children at risk for T1D, patients with T1D, their families, and countless others," Dr. Parikh added. "USF is fortunate to play a part in such huge international efforts to tackle this complex autoimmune disease."

More information: Louis-Pascal Xhonneux et al, Transcriptional networks in at-risk individuals identify signatures of type 1 diabetes progression, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abd5666

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