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Researchers find beta cell stress could trigger the development of type 1 diabetes

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In type 1 diabetes (T1D), pancreatic beta cells die from a misguided autoimmune attack, but how and why that happens is still unclear. Now, JDRF-funded scientists from the Indiana University School of Medicine have found that a specific type of cellular stress takes place in pancreatic beta cells before the onset of T1D, and that this stress response in the beta cell may in fact help ignite the autoimmune attack. These findings shed an entirely new light into the mystery behind how changes in the beta cell may play a role in the earliest stages of T1D, and adds a new perspective to our understanding how T1D progresses, and how to prevent and treat the disease.

In the study, published in the March 22 issue of the journal *Diabetes*, the researchers, led by Sarah Tersey, Ph.D., assistant research professor of pediatrics, and Raghavendra Mirmira, M.D., Ph.D., professor of pediatrics and medicine at the Indiana University School of Medicine, show for the first time in a mouse model of T1D that beta cells become stressed early in the disease process, before the animal develops diabetes. In response to the stress, beta cells activate a cell death pathway leading to the loss of beta cell mass in the animal.

In all cells, there is a vital compartment known as the endoplasmic reticulum (ER) where secreted proteins, like insulin, are produced and processed before being released by the cell. Pancreatic beta cells are highly specialized for the production and secretion of insulin and therefore, the ER plays a critical role in their function, making them particularly sensitive to ER stress. The study by Tersey and colleagues

show that an alteration of the beta cell ER stress response occurs early in the disease, and if the ER stress is not resolved properly, it can result in defects in insulin secretion, and ultimately death of the beta cell.

"The ER stress in the beta cell has been implicated in type 2 diabetes, but its role in triggering beta cell dysfunction in type 1 diabetes has not been clear until now, which is why these findings are exciting, " said Dr. Mirmira. "Although the paper does not directly address a potential role for ER stress in the development of human T1D, what we observed in the mice is consistent with clinical observations of type 1 diabetes in people where defects in insulin secretion precede overt diabetes."

"We need to look more closely at beta cells and their role in type 1 diabetes because they may be participating in their own demise," said Andrew Rakeman, Ph.D. Senior Scientist of Regeneration for JDRF. "This study shows that beta cell stress is occurring at the earliest stages of the disease process, raising the intriguing possibility that beta cell stress could be part of the trigger for the autoimmune process that leads to type 1 diabetes. This is exciting because it not only teaches us something about the early events in T1D progression, but suggests that drugs or therapeutic strategies that alleviate ER stress might be used to delay progress of the disease, either preventing insulin dependence or preserving beta cell function, improving glucose control and reducing the risk of complications."

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