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Early research reveals new clues to origin of diabetes

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University of Michigan scientists have identified events inside insulin-producing pancreatic cells that set the stage for a neonatal form of non-autoimmune type 1 diabetes, and may play a role in type 2 diabetes as well. The results point to a potential target for drugs to protect normally functioning proteins essential for producing insulin.

A study published online today in the journal PLoS One shows that certain insulin gene mutations involved in neonatal diabetes cause a portion of the proinsulin proteins in the pancreas' beta cells to misfold. Proinsulin proteins are the precursors of insulin, which the body needs to regulate blood sugar levels. Crucially, the misfolded mutant proteins cause normal proinsulin proteins in beta cells to misfold as well, the scientists found in studies of mouse and rat beta cells.

"Once the 'good' proinsulin turns 'bad,' it cannot be made into insulin and so the beta cells, and then the whole animal, become insulin deficient. The insulin deficiency causes diabetes and from there, things get worse and worse," says Peter Arvan, M.D., Ph.D., the study's senior author. He directs the Michigan Comprehensive Diabetes Center and is William and Delores Brehm Professor and chief of Metabolism, Endocrinology and Diabetes at the U-M Medical School.

"We want to see how the mechanism we found in this rare form of neonatal diabetes applies to other forms of diabetes," says Ming Liu, M.D., Ph.D., the study's first author and a research assistant professor of internal medicine at the U-M Medical School.

Diabetes researchers know that protein misfolding in beta cells also occurs on a smaller scale in mice and people without diabetes, and at higher levels in type 2 diabetes, Arvan says. In type 2 diabetes, people develop reduced sensitivity to insulin, causing beta cells to work overtime and eventually fail. In non-autoimmune type 1, diabetes results when genetic mutations cause insufficient production of insulin from pancreatic beta cells.

"In all diabetes, beta cells don't perform to the level needed," says Arvan. "It's possible that the beta cell failure of type 2 diabetes also has a critical protein folding component," he says. "The question is, can you reach a point in ordinary diabetes where misfolding causes the problem we have identified?"

In lab dish cultures of normal rat and mice beta cells, the scientists introduced single gene mutations known to be involved in various types of neonatal diabetes. They consistently found that misfolding occurred in normal proinsulin protein when mutant proinsulin protein was present. They also observed the same aberrant events in the pancreatic beta cells of Akita mice, a mouse model with the same mutation that occurs in a human family with neonatal diabetes.

Proteins, which are molecules made of amino acids arranged in a certain order determined by genes, normally fold into specific shapes. But sometimes misfolding occurs. Protein folding is a phenomenon that has drawn a lot of recent attention from scientists who believe it plays a role in several common diseases.

Diabetes researchers currently lack a clear picture of why beta cells in the pancreas fail in diabetes. Many researchers look at stress and the stress response from the beta cells' endoplasmic reticulum or ER, a structure that transports materials within the cell. Stress in this structure occurs in diabetes, along with reduced beta cell mass.

Arvan and Liu found in the study that each of the mutations they examined led to ER stress and the ER stress response in beta cells, but that these ER events alone could not block insulin production in normal beta cells and do not appear to be the origin of the insulin deficiency. They hypothesize that protein misfolding events first block insulin production and cause insulin deficiency, leading to diabetes.

Uncovering the earliest events in the molecular mechanism of the disease may help diabetes researchers discover new therapies, the authors say. New drugs that could emerge would be at least several years away.

"It may be possible to find a way to modulate the environment in the endoplasmic reticulum to let the normal protein fold quickly, before the abnormal protein can act," says Liu.

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