Possible new view of diabetes

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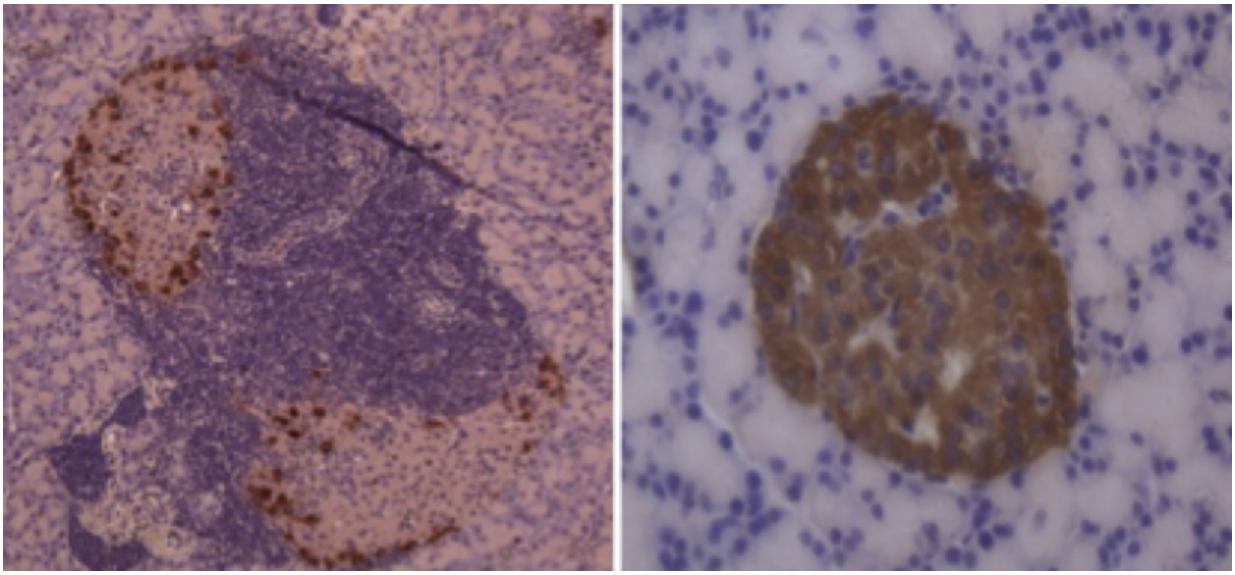

The islet on the left shows the disrupted and depleted beta cells of T1D.

It's hard to change entrenched ideas in science.

Protein is the genetic material.

Genes are continuous and immobile.

The genome consists of 120,000 genes; no, 80,000; no, 60,000; no, 20,325.

What we know about the natural world changes as we learn more. That's

why there's no such thing as scientific "proof," just evidence, hypotheses, and, rarely, enough findings to support a theory. Science is evidence-based, from observations and experiments. We don't "believe" in evolution or climate change as if it is a religion. Yet presenting evidence that challenges a long-held idea can be difficult for a researcher.

Bryon Petersen, PhD, director of the Pediatric Stem Cell Research and Hepatic Disorders Child Health Research Institute at the University of Florida is in the uncomfortable position of challenging dogma, knows that well. His findings suggest that type 1 diabetes (T1D) might not directly be autoimmune in origin, and that tracking blood glucose might not be the only way to manage the disease.

His team has just published a paper in the journal Laboratory Investigation, "Suppression of islet homeostasis protein thwarts diabetes mellitus progression," that puts a little-known molecule on the radar: islet homeostasis protein, aka IHoP.

People with type 1 diabetes make too much IHoP. Plus, experiments in mice and humans show that decreasing IHoP restores blood glucose control and increases the number of insulin-producing beta cells in the pancreas. Perhaps most importantly, excess IHoP is in the blood of patients, making it a possible new biomarker for T1D.

Anatomy of a pancreas

The pancreas is a dual gland. The exocrine part makes and sends enzymes into digestive juice in the small intestine. That's not the part important in diabetes.

The endocrine (hormone) component consists of cell clusters called islets. An islet harbors four types of cells. About 15 to 20% of the islet

cells are the alpha type, which release glucagon. This hormone raises the level of blood glucose by stimulating the liver to break down the stored form (glycogen) and converts noncarbs, such as amino acids, into even more glucose.

The more abundant beta cells in the islets produce a different hormone, insulin. It counters glucagon, stimulating the liver to instead string glucose molecules into glycogen, and keeps other nutrients from being changed into glucose. Insulin also stimulates cells with receptors for it to take up glucose from the bloodstream. This is why exercise stimulates skeletal muscle to suck up glucose, lowering its level in the circulation. People with diabetes are well aware of this effect.

IHoP promotes glucagon synthesis, so the action opposes that of insulin. Using RNA interference to knock down expression of the IHoP gene in diabetic mice normalizes glucose levels, the new study shows.

The pancreas in a person with T1D comes to harbor many more than 15 to 20% alpha cells as the beta cells die, which is thought to be the trigger for the autoimmune attack widely recognized as the primary cause of the disease. But Dr. Petersen's work suggests that the autoimmunity may be a secondary effect – and that could have clinical implications in diagnosing, monitoring, and treating the disease.

Is autoimmunity indirect?

The view of type 1 diabetes as an autoimmune condition is widely accepted. And that's why Dr. Petersen thinks it took five years to get his study accepted for publication, following rejection from a long list of top journals. He and his co-workers are challenging the paradigm that autoantibodies that attack beta cells trigger T1D. The autoantibodies do so, but secondarily.

"Our research strikes fear in the hearts of diabetes researchers because IHoP explains a lot of things they haven't been able to explain. T1D is not an autoimmune disease!" Dr. Petersen says.

The link between the surge in IHoP and the autoimmune destruction of the insulin-producing beta cells could lie in the resemblance of IHoP to plastin, which is a protein well known to bind to the cytoskeleton of activated T cells, enabling them to move. Perhaps IHoP does the same, giving the appearance of autoimmunity in that activating T cells is part of an immune response. (I'm skipping a few steps here of the cell-to-cell blow-by-blow.)

Silencing IHoP kept the damaging immune cells out of the islets of mice for more than 35 weeks. Dr. Petersen's paper depicts what happens with an illustration of an old-fashioned seesaw. An increase in IHoP tips the balance so glucagon is up, insulin down, and diabetes results. Silencing IHoP balances the seesaw. But the IHoP block must occur early in the disease process to stop the islet destruction in time for the pancreas to heal and begin making insulin again.

The finding is more than a shift in the time-honored view of T1D as an autoimmune disease; it has potential clinical import.

"IHoP does 3 things: first and foremost is that it opens a new corridor of research in understanding the disease. Second is that we have a new target in developing a potential drug/treatment for newly diagnosed patients. Lastly, it gives the field a new biomarker that could provide an earlier diagnosis, which means a better chance in treating," Dr. Petersen explains.

He concedes, though, that there's much we simply do not know about autoimmunity, which he calls "an unfortunate constellation of aberrant immune responses whereby an organism turns against its own healthy

cells and tissues, often resulting in disease." It's an immune response gone off course, but maybe not in a random fashion. "Perhaps these responses are not so much an attack on 'self' but a secondary reaction to an event causing the antigen presenting cells to become activated, thereby resulting in a T-cell response and the impression of autoimmunity," Dr. Petersen suggests.

Diabetes is a major chapter in the history of medicine, from the experiments that revealed the hormone originally named "isletin" in beagles by Frederick Banting and his medical student Charles Best at the University of Toronto in the early 1920s, to insulin pumps and islet transplants forty years later, to the first drug produced using recombinant DNA technology sixty years later.

Maybe IHoP will be the next chapter in the history of type 1 diabetes.

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