

In this issue:**Researchers Find Protein that Spurs Beta Cell Growth****Possible Mechanism Found for Type 1 Diabetes Trigger****Researchers Clarify How Type 1 Affects Beta Cell Function****RESEARCHERS IDENTIFY PROTEIN THAT SPURS BETA CELL GROWTH**

JDRF-funded researchers at Rockefeller University have identified a protein that regulates cell growth in pancreatic islets. The discovery, in mice, represents a critical step in regeneration, whose aim is to stimulate beta cell growth and restore insulin secretion in people with type 1 diabetes.

The protein, Tmem27, appears to have its stimulatory effects only in beta cells and not other cell types. This finding provides the opportunity for drug hunters to develop therapies that boost functional beta cell mass without causing harmful side-effects in other tissues. The research was led by Markus Stoffel, Ph.D., and was published in the journal *Cell Metabolism*.

"This is a breakthrough discovery in the field of beta cell regeneration," said JDRF Senior Vice President of Research & Development Paul Burn, Ph.D. "Identifying this protein gives researchers an entry point to study the underlying biochemical pathways involved in beta cell growth. This, in turn, will produce drug targets and eventually lead to the development of therapies that can stimulate that growth." Dr. Burn added that the therapy's potential to treat diabetes is likely to draw interest from biotechnology and large pharmaceutical companies seeking to create drugs that might address both types of diabetes. Partnering with industry, he noted, will put the research on the fast-track to achieving practical results.

Dr. Stoffel is a member of JDRF's Regeneration of Beta Cell Function team, which focuses on human beta cell regeneration and its potential as a cure therapeutic. The program's goal is to develop novel strategies that restore lasting glucose regulation in patients with type 1 diabetes by activating functional beta cell regeneration, without interventions such as islet transplantation. According to Dr. Burn, "This discovery demonstrates that directed exploratory research can result in exciting discoveries, and at the same time help bring novel drug targets closer to market."

POSSIBLE MECHANISM FOUND FOR TYPE 1 DIABETES TRIGGER

A direct pathway through which a virus or dietary factor could disrupt the body's normal immune function and trigger type 1 diabetes has been uncovered by researchers at the JDRF/Beverly Berry Center for Immunological Tolerance in Type 1 Diabetes at Harvard Medical School. The study suggests that the immune system goes awry by overreacting to foreign matter entering the pancreatic lymph nodes. In response, T cells within the pancreatic lymph nodes increase ranks and destroy everything, including the body's own insulin cells.

"This finding is another an important step in identifying the triggers of type 1 diabetes," said JDRF Executive Vice President for Research Richard Insel, M.D. "Researchers will now increase focus on this intersection of "self" and "non-self" antigens as they develop strategies to block the disease."

When it is functioning normally, the immune system is able to distinguish between self (the body's own cells) and non-self (foreign material) to defend the body against toxins or bacteria (antigens) without inflicting damage through "friendly fire." In people with type 1 diabetes and other autoimmune diseases, the immune system mistakenly responds to the body's own molecules, or "self antigens," and launches an attack on the body's cells.

Previous research had shown that lymph nodes draining the pancreas, rather than the pancreas itself, make up ground zero for the autoimmune response. At that site, T cells first become incited into action and go on the attack against insulin-producing beta cells. But scientists do not know what triggers the destruction, or which route whatever prompted the attack may take to get to the lymph nodes.

The Joslin research, conducted in mice, shows that the T cells in the pancreatic lymph nodes encounter antigens deriving from the intestinal tract, which may contain foreign material. This event instructs the T cells to recognize and destroy cells bearing the foreign substance.

In most people, this does not cause problems, since T cells are not sufficiently activated to destroy anything beyond the foreign material. But in people genetically at risk for type 1 diabetes, certain viral or dietary elements may profoundly affect the T cell response, triggering a cascade that destroys the beta cells. Dr. Insel noted that it's as if the mixture of self and non-self throws the normally precise immune response into disarray and causes it to demolish cells indiscriminately.

The study was published in the December 6 issue of the

Proceedings of the National Academy of Sciences by Diane Mathis, Ph.D., Christophe Benoist, M.D., and and fellow researchers at the Joslin Diabetes Center at Harvard.

If additional research confirms that the same convergence of self and non-self antigens occurs in human pancreatic lymph nodes, scientists will have a clearer target for intervening in the encounter between the T cells and foreign antigens and possibly blocking the first stage of the disease.

RESEARCHERS CLARIFY HOW TYPE 1 DIABETES AFFECTS BETA CELL FUNCTION

Despite extensive research on the immune mechanisms causing type 1 diabetes, insulin secretion before and after diagnosis remains a less studied aspect of the disease. In the latest issue of the journal *Diabetes*, JDRF-funded researcher Kevan Herold, M.D., and colleagues at Columbia University assessed recent findings about insulin production and the potential impact on treatment strategies.

Until recently, scientists believed that by the time a person was diagnosed with type 1 diabetes, the ability to secrete insulin was long gone. Destruction of the insulin-producing beta cells was thought to be so thorough that any treatment would have little effect.

As Herold and his colleagues explain, however, recent findings have shown that prompt clinical intervention can be effective. Research by Dr. Herold in 2004 found that average total insulin secretion of newly diagnosed patients was 52 percent of that in a person without diabetes, much higher than previously thought. The conclusions from the study were important: If significant insulin-producing capability exists at the time of diagnosis, researchers have a much better chance at restoring glucose regulation by expanding or replacing the mass of beta cells

The *Diabetes* article points out that this possibility is significant in the context of other recent scientific findings—some of them surprising—regarding insulin-secretion during the course of type 1 diabetes:

- Even people who have had type 1 diabetes for many years still retain some beta cell function. This finding was unexpected; researchers don't understand exactly why the autoimmune attack does not continue until all beta cell function is

destroyed. But the presence of beta cells in patients with established type 1 diabetes—some for decades—is the basis for targeted therapies in all type 1 patients, especially efforts to stimulate regeneration of beta cells.

- Type 1 diabetes appears to progress more quickly in children than in adults. Younger-aged children have less residual insulin production when type 1 diabetes is diagnosed compared with adults. In adults, it seems to take longer for the autoimmune attack to reduce insulin secretion to a point that causes the disease. This suggests that in younger patients, a more aggressive approach to intervention may be needed because of the limited reserve present at the time of diagnosis. Older patients, on the other hand, might benefit from restorative therapies even months after they are diagnosed.
- There is evidence that insulin resistance may help cause type 1 diabetes. Insulin resistance, the inability of the body to effectively use insulin to metabolize food, has traditionally been associated with type 2 diabetes. But a new theory suggests that insulin resistance may produce or aggravate conditions that in turn cause type 1 diabetes. Under this theory, type 1 and type 2 diabetes are primarily the same disorder, with one or more of three “accelerators” at play in a given person: 1) insulin resistance, 2) increased beta cell apoptosis (cell death) and 3) autoimmune attacks on beta cells. If insulin resistance is present in a type 1 patient, then increasing beta cell mass may need to be combined with other therapies in order for the body to metabolize properly
- Even partial insulin-secreting capacity can make a big difference in preventing complications. Although a diagnosis of type 1 diabetes means a person must immediately start taking insulin to stay alive, those who retain some residual insulin-secreting capacity will fare better at avoiding complications such as damage to eyes, kidneys and nerves down the road. Researchers still lack a full understanding of everything islets do to regulate the body's systems, so even intensive insulin therapy in a type 1 patient cannot lower complications risk to the level found in someone without the disease. In light of this, increasing beta cell mass would be worth pursuing even if it does not completely free the patient