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**INSULIN-MAKING PROTEIN IDENTIFIED
IN BETA CELLS**

JDRF-funded researchers at the University of Massachusetts have identified a protein in beta cells that regulates the production of insulin. The finding suggests that a drug or therapy that increases the activity of this protein could enable people with diabetes to boost their own insulin production and better manage type 1 diabetes.

The protein, IRE1, operates in beta cells within the endoplasmic reticulum (ER), a large, intracellular membrane folded over many times on itself. Most proteins are assembled inside the ER before being transported to other sites within the cell to perform specific tasks. IRE1 helps regulate the process by which the insulin protein is folded into final form so it can function properly.

"We're excited by the therapeutic applications of this finding, which could potentially benefit beta cell regeneration and islet transplantation," said Richard Insel, M.D., JDRF's Executive Vice President for Research.

The finding was made by Fumihiko Urano, M.D., Ph.D., and colleagues at the University of Massachusetts Medical School. It is published in the journal *Cell Metabolism*.

Previous JDRF-funded research led by Dr. Urano found that IRE1 has an essential role in removing abnormal proteins that accumulate in cells as the result of physiological stress, such as high blood glucose. This latest discovery suggests that a drug targeting IRE1 could potentially enhance insulin secretion and protect beta cells.

The researchers dosed mouse islets for short periods with varying concentrations of glucose and measured IRE1 activity in the beta cells. They found that higher glucose concentrations caused higher IRE1 activity, suggesting IRE1's role in secreting insulin in response to hyperglycemia.

When the researchers blocked IRE1's signals, the production of insulin decreased, further establishing the link. The study shows that IRE1 is activated by short-term increases in glucose levels, allowing the body to synthesize more insulin when needed.

The researchers also found, however, that sustained periods of

high glucose make IRE1 overactive. That stalls insulin production and also causes a buildup of abnormal proteins in the ER, resulting in beta cell damage.

The researchers suggest that drugs regulating IRE1 activity for short periods could enhance the body's insulin production. This might delay the development of type 1 diabetes, or reduce the amount of external insulin needed by type 1 patients. Further animal tests will establish whether IRE1 can be activated only to the extent that it provides benefits.

**CELLULAR PATHWAYS IDENTIFIED THAT
CONTROL BETA CELL GROWTH AND FUNCTION**

Scientists at Stanford University have found that two proteins work together to regulate the growth and function of insulin-secreting beta cells. The discovery could help researchers design drugs that regenerate beta cells and make them perform better, reducing insulin needs in people with diabetes.

The two proteins, calcineurin and NFAT, work in tandem to spur beta cells to multiply and produce more insulin to adapt to increased body size, as might happen with pregnancy, aging or obesity. If either protein is impaired, beta cells don't multiply as well, and diabetes may result. On the other hand, therapies that boost the activity of the proteins could restore blood sugar control in people that have diabetes.

"This finding may provide a basis for identifying potential targets for treatments aimed at regenerating beta cells and beta cell function," JDRF Executive Vice President for Research Richard Insel, M.D., said.

The study was led by Jeremy Heit, M.D., Ph.D., in the laboratory of Seung Kim, M.D., Ph.D., a JDRF-funded researcher. It is published in the journal *Nature*.

Dr. Kim's lab was studying calcineurin's possible connection to a well known, but poorly understood, phenomenon: Patients taking immune-suppressing drugs after an organ transplant frequently develop diabetes. Because these drugs are known to interfere with calcineurin function, the scientists suggested that calcineurin played an important role in beta cell function.

To clarify the connection, Drs. Kim and Heit studied mice that lacked calcineurin production in the pancreas after birth. After 12 weeks, the animals were severely diabetic. The researchers found that the absence of calcineurin prevented the beta cells from multiplying as the mice grew in those first weeks. It also reduced the amount of insulin made by the existing beta cells.

To clarify the pathway through which calcineurin acts, the researchers bypassed this protein and instead activated NFAT, which calcineurin regulates. Beta cells lacking calcineurin but with active NFAT behaved normally, multiplying as the mice

aged and producing normal amounts of insulin. This suggests that calcineurin regulates beta cell function via signals passed to NFAT. More importantly, it suggests that drugs targeting either calcineurin or NFAT could be effective at enhancing insulin secretion.

In addition to a role in regenerative medicine, targeting calcineurin might prove useful in stimulating beta cells in the laboratory to multiply for replacement transplants. It might even help guide embryonic stem cells to become insulin secreting cells.

As for NFAT, scientists are finding that its interplay with other proteins affect other cells relevant to type 1 diabetes. The August issue of *Research Frontline* described a study by JDRF-funded researchers published in *Cell* showing that NFAT influences immune tolerance. Depending on which protein it is paired with, NFAT can spur immune cells into attack mode or direct them to stand down.

Combined with the latest finding, it appears NFAT not only helps determine whether beta cells are attacked by immune cells (as occurs in type 1 diabetes) but also whether beta cells are able to multiply and perform properly. This suggests that the NFAT pathway may be an attractive therapeutic intervention point for preventing the disease and for reversing it.

MAKING ISLETS BIGGER AND BOLDER

JDRF-funded researchers have developed a way to protect islets after a transplant so they survive longer and perform better, reducing the amount needed to restore blood sugar control. The new method could help alleviate the severe islet shortage that makes islet replacement problematic and could also eventually offer a way for newly diagnosed type 1 patients to retain some insulin-secreting function.

The researchers used gene therapy to trigger the release of glucagon-like peptide 1 (GLP-1), a hormone in islets that strengthens beta cells and stimulates them to secrete insulin.

“Improving islet survival and performance is important to increase the potential of islet replacement therapies,” said Richard Insel, M.D., JDRF’s Executive Vice President for Research. “Just as important, insights from this research may also prove applicable to preserving residual beta cell function in new-onset diabetes, and in pre-diabetes.”

The study, led by Timothy Kieffer, Ph.D., at the University of British Columbia, is reported in the *Proceedings of the National Academy of Sciences*.

One of the issues facing islet replacement therapies includes the small number of donors and islet attrition. A significant number of islets fail to survive the transplant or stop working soon after, destroyed by the drugs used to prevent the patient from rejecting the islets or induced to self-destruct in a form of cellular suicide called apoptosis. For those reasons, transplants usually require multiple donors for each recipient. A therapy that both protects islets and improves their performance could have a big impact on the procedure’s initial success.

GLP-1 has recently drawn significant attention, and a drug mimicking its action (Byetta) was recently approved for use in type 2 patients. While GLP-1 is normally secreted from cells lining the intestine, Dr. Kieffer and his colleagues found that the hormone can also be produced by a molecule in alpha cells, which reside inside islets. The alpha cells will release GLP-1 if they receive a signal from a natural enzyme, PC1/3, also made by alpha cells.

Researchers had noticed that under certain conditions—such as damage to the pancreas—alpha cells increase PC1/3 production, apparently to compensate for the loss of beta cells. The scientists thought that by exploiting this natural capacity of the body, they could increase GLP-1 secretion and, in turn, increase beta cell mass and insulin secretion.

The researchers used a harmless virus to deliver a gene to alpha cells in cultured mouse islets, instructing the cells to make more PC1/3. When these altered islets were exposed to glucose, the beta cells inside them secreted more insulin than the control islets. The beta cells also proved more resistant to apoptosis when exposed to a molecule that induces the programmed cell death.

The true test came when altered islets and control islets were transplanted into diabetic mice. While the control islets were slow to restore blood sugar control, the modified islets brought a prompt return to normal blood sugar levels.

The researchers said it remains an intriguing possibility that this strategy could also be used to prevent the loss of beta cells in the early stages of diabetes. Because scientists recently developed ways to deliver genes to islets inside a living organism, the means already exist to test this strategy in animals.

ISLET TRANSPLANTATION: A PROMISING WORK IN PROGRESS

A study conducted by an international network of scientists shows that islet cell transplantation remains a promising, though far from perfected, treatment for a small percentage of patients with type 1 diabetes.

The study, conducted by the Immune Tolerance Network and published in the *New England Journal of Medicine*, reports that islet cell transplantation can stabilize blood sugar in type 1 diabetes patients with very poor metabolic control, and often relieve them of the need for, or reduce, insulin injections for up to two years. However, the study of 36 patients also showed that the effectiveness of the islets usually fades after the first year or two, indicating that the procedure needs further refinement before it can become a more available treatment for type 1 diabetes.

To date, the most significant benefit of the procedure, which requires the use of powerful immunosuppressive drugs and is not appropriate for children, appears to be a reduction in severe episodes of low blood sugar, or hypoglycemia, which can strike without warning and cause confusion, unconsciousness, and even death. For diabetes patients who suffer from such episodes, islet transplantation showed that it greatly improved their quality of life, even though the transplanted cells only partially restore insulin

levels and needed to be supplemented with insulin injections.

“This isn’t an all-or-nothing procedure: It’s not an issue of getting patients off insulin altogether and keeping them that way,” said James Shapiro, a researcher at the University of Alberta, who developed the transplant method now in use. “As we’ve shown, even partial survival of the transplanted islets can lead to significantly improved health in these patients.”

Going forward, researchers are seeking to develop better ways of preventing rejection of the transplanted islets using treatments that reprogram the immune system to prevent harmful immune responses while leaving the body’s disease-fighting capabilities intact. Such “immune tolerance therapies” also will need to be improved so they do not damage the islets and reduce their insulin-secreting capacity. The issue of islet supply also remains a significant hurdle for islet replacement therapies to overcome before they can become more generally utilized.

The Immune Tolerance Network is an international research collaboration funded by NIH and JDRF that aims to accelerate the clinical development of tolerance therapies through novel clinical trials and integrated mechanistic studies.

For additional information, see [JDRF’s press release](#) and [NIH’s press release](#).

SCIENTIFIC PAPER RETRACTED

A research paper on the genetics of diabetes described in the [July 2006 issue of *Research Frontline*](#) (“Researchers Find Malfunctioning Gene May Be Linked to Type 1 Diabetes”) has been retracted by the journal in which it appeared. That publication, *Nature Medicine*, said it was retracting the paper because the results could not be reproduced. Aire, the gene described in the story, is still considered to play an important role in immune function—a finding that has been established and validated by previous research. The recent finding—that Aire controls the development of immune cells protecting against autoimmune attack—is the only aspect of the gene that has come into question.