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Researchers show some cells in pancreas can spontaneously change into insulin-producing cells

April 5 2010

Alpha cells in the pancreas, which do not produce insulin, can convert into insulin-producing beta cells, advancing the prospect of regenerating beta cells as a cure for type 1 diabetes. The findings come from a study at the University of Geneva, co-funded by the Juvenile Diabetes Research Foundation, that is published today in the online edition of the scientific journal *Nature*.

The researchers, led by Dr. Pedro L. Herrera, demonstrated that beta cells will spontaneously regenerate after near-total beta cell destruction in mice and the majority of the regenerated beta cells are derived from alpha cells that had been reprogrammed, or converted, into beta cells. Using a unique model of diabetes in mice, in which nearly all of the beta cells are rapidly destroyed, the researchers found that if the mice were maintained on insulin therapy, beta cells were slowly and spontaneously restored, eventually eliminating the need for insulin replacement. Alpha cells normally reside alongside beta cells in the pancreas and secrete a hormone called glucagon, which works opposite to insulin to regulate the levels of sugar in the blood. Alpha cells are not attacked by the autoimmune processes that destroy beta cells and causes type 1 diabetes.

Type 1 diabetes is a chronic, autoimmune disease that affects children, adolescents and adults, in which the immune system attacks the beta cells in the pancreas that produce insulin, a hormone that enables people to convert food into energy. People with type 1 diabetes are dependent

on insulin treatment for the rest of their life.

Dr. Herrera's results are the first to show that beta cell reprogramming can occur spontaneously, without genetic alterations. Previous efforts to reprogram non-beta cells into beta cells relied on genetic manipulations - processes that can not be easily translated into therapies.

According to Dr. Andrew Rakeman, JDRF Program Manager in Beta Cell Therapies, the breakthrough in Dr. Herrera's work is the demonstration that alpha- to-beta-cell reprogramming can be a natural, spontaneous process., "If we can understand the signals that are triggering this conversion, it will open a whole new potential strategy for regenerating beta cells in people with type 1 diabetes," he said. "It appears that the body can restore beta cell function either through reprogramming alpha cells to become beta cells or, as previously shown by others, by increasing growth of existing beta cells. This path may be particularly useful in individuals who have had the disease for a long time and have no, or very few, remaining beta cells."

Role of Removing Beta Cells

Dr. Herrera's team genetically engineered the animals to be susceptible to a toxin that would destroy only their beta cells. When the mice were exposed to the toxin, the beta cells were rapidly and efficiently destroyed - greater than 99% just 15 days after treatment. Then, to track the source of newly regenerated beta cells, Dr. Herrera's team used another genetic manipulation to permanently label mature alpha cells and all their descendents with a fluorescent protein. This "genetic lineage tracing" approach allowed the scientists to track the fate of the alpha cells and their progeny; the presence of fluorescently labeled beta cells in the recovered animals gave conclusive evidence that alpha cells had reprogrammed into beta cells.

The Geneva researchers pointed out that the critical factor in sparking the alpha-to- beta-cell reprogramming was removing (or ablating) nearly all the original insulin-producing cells in the mice. In mice where the loss of beta cells was more modest, the researchers either found no evidence of beta cell regeneration (when only half the cells were destroyed) or less alpha cell reprogramming (when less than 95% of cells were destroyed).

"The amount of beta-cell destruction thus appears to determine whether regeneration occurs. Moreover, it influences the degree of cell plasticity and regenerative resources of the pancreas in adult organisms," said Dr. Herrera.

Regeneration Research

In type 1 diabetes, the immune system attacks beta cells, stopping a person's pancreas from producing insulin, the hormone that enables people to get energy from sugar. JDRF has been at the forefront of diabetes research looking to develop therapeutics to drive the regeneration of insulin-producing cells within a person's body (as an alternative to transplanting insulin-producing cells from other sources). Beta cell regeneration involves triggering the body to grow its own new insulin producing cells, either by copying existing ones - some are usually still active, even in people who have had diabetes for decades - or causing the pancreas to create new ones.

This study is another step forward for JDRF's research focus on Regeneration as a potential pathway to restore insulin production - and normal blood sugar in people with type 1 diabetes. JDRF has become a leader in this new and exciting research field, funding a wide range of research projects, including studies like Dr. Herrera's, and an innovative diabetes drug discovery and development partnership with the Genomics Institute of the Novartis Foundation (GNF), focused on regeneration

approaches.

In addition to regenerating or replacing insulin producing cells, a cure for type 1 diabetes will also require stopping the autoimmune attack that causes diabetes, and reestablishing excellent glucose control.

Provided by Juvenile Diabetes Research Foundation International