Scientists discover key pathway for development of insulin-producing cells

July 17 2012, BY KRISTA CONGER

(Medical Xpress) -- Researchers at the Stanford University School of Medicine have identified a molecular signaling pathway that drives the growth and maturation of young human beta cells — the insulin-producing cell type in the pancreas that malfunctions in diabetes — in mice and humans.

The pathway, called the Cn/NFAT pathway, has been shown to be important in the growth and development of many cell types, including immune cells and neurons. But this is the first time it's been shown to be involved in the development of human beta cells.

"This is likely a major step forward in our understanding of how human beta cells become functional," said Seung Kim, MD, PhD, professor of developmental biology and a Howard Hughes Medical Institute investigator. "We are beginning to apply what we've learned about the normal maturation process of the pancreas to create substitute or replacement cell types for therapy in diabetes."

Kim is the senior author of the research, published July 17 in *Developmental Cell*. Graduate student William Goodyer is the first author of the study.

The study comes on the heels of a previous study, published last October in Nature, in which Kim and other researchers in his lab described the involvement of a molecule called PDGF in beta cell development. Now, the new findings from Kim's team bring scientists still closer to being

able to generate functional beta cells in a laboratory dish for transplant into a human patient, or to coax a diabetic's non-functioning beta cells to begin dividing and producing insulin.

The new research also solves a mystery as to why many adults taking a certain class of immunosuppressive drugs develop transient type-2 diabetes. In addition, the findings suggest a possible path for treating a subcategory of pancreatic cancer.

Beta cells are found in the islets of the pancreas. They are the only cells in the body that produce insulin, a hormone that signals the body to absorb sugar from the blood after a meal and store it in a variety of cells. Without adequate insulin production, blood sugar levels can become dangerously high — a condition called hyperglycemia — and cause organ damage or even coma and death. Type-1 diabetes is caused by a failure to produce insulin; type-2 diabetes is caused by combined deficits in the body to respond to and make insulin.

In the current study, the researchers learned that the Cn/NFAT pathway (an abbreviation for calcineurin/nuclear factor of activated T cells) drives the growth and maturation of beta cells after birth in mice and humans. They had suspected that the pathway might be involved because 10 to 30 percent of people receiving calcineurin inhibitors (drugs used to suppress the immune system after organ transplant, for example) develop temporary diabetes during their treatment.

"We knew this pathway was a good one to consider, because development of cells like beta cells requires a specific message to sense the need to change and mature," said Kim. They wondered if the Cn/NFAT pathway could be that message for beta cells. In addition, they knew that calcineurin is activated by calcium, which also signals beta cells to release insulin.

The researchers found that mice in which the pathway was genetically inactivated secreted less insulin, had fewer beta cells and died within about 12 weeks of birth from severe diabetes; in contrast, stimulating a protein called glucokinase increased the expression of genes required for insulin storage and secretion in islet cells from young mice.

The investigations of this pathway in humans had been hampered by the fact that beta cell proliferation in the pancreas is robust in newborns and young children, but declines with age. The problem for researchers who want to study beta cells has been that very young human organ donors are rare and that obtaining islet cell samples from young, deceased children is complicated.

Kim has overcome this hurdle by, over the past several years, developing a network of organ donation professionals who know to call him when a child's pancreas becomes available. He then extracts the islet cells from the tissue sample and uses them for research. This enabled the researchers to see whether their findings in mice are mirrored in young humans, in whom the beta cells in the pancreas undergo most of their maturation and growth from birth until about age 10.

"We know that certain cellular signals, such as calcium signaling, increase in the pancreas in mice after birth," said Kim. "If we inactivate that calcium signaling, the beta cells don't grow or develop. The key to our research was obtaining these pancreatic islets from young people, when all these things were still happening, so we could assess the significance of this pathway in humans."

The researchers found that, as in mice, the levels of genes known to be important to beta cell proliferation were higher in human islet cells from donors aged 1 to 5 years than in islets from human adults. They also found that exposing these young human islet cells to a calcineurin inhibitor significantly reduced their proliferation.

The discovery of the involvement of the Cn/NFAT pathway in beta cell development has many implications.

“Through our long-standing partnership with my Stanford colleague Jerry Crabtree, we are trying to develop new drugs to treat diabetes based on these findings,” said Kim. “For example, we could activate the pathway with glucokinase, and also use compounds that block the natural inhibition of beta cell proliferation that occurs with age. It’s also possible that we could enhance the function and relevant properties of this pathway to generate replacement beta cells.”

Finally, understanding how to switch islet cell growth on and off may lead to new therapies for rare pancreatic islet cancers called neuroendocrine tumors.

“We think our findings are highly relevant for these types of cancers,” said Kim.

In addition to Goodyer and Kim, other Stanford researchers involved in the study include research assistant Xueying Gu, lab manager Yinghua Liu, and professor of pathology and of developmental biology Gerald Crabtree, MD.

Provided by Stanford University Medical Center