Scientist discover important new player in diabetes onset

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If you think of diabetes onset like an elaborate molecular drama, then a research team led by a La Jolla Institute scientist has unmasked a previously unknown cellular player, which is critical to proper insulin secretion. "Defective insulin secretion is a hallmark of both type 1 and type 2 diabetes," said Catherine Hedrick, Ph.D., a scientist at the La Jolla Institute for Allergy & Immunology, who led the team, which included researchers from the University of Virginia.

Working in mouse models, the team discovered that the ABCG1 protein is essential for the beta cells of the pancreas to produce sufficient amounts of insulin. Insulin is needed by the body to convert glucose from food into energy. Problems with insulin production underlie both type 1 and type 2 diabetes. "Based on our studies in mice, we think that some diabetes patients may have reduced expression of ABCG1 which impairs their insulin secretion," said Dr. Hedrick, who has previously published findings showing that type 2 diabetics have lower levels of ABCG1 than non-diabetics.

The research team also showed that proper expression of the ABCG1 protein in beta cells could be restored in the mice by treatment with some existing antidiabetic drugs. "Our study suggests that certain existing antidiabetic drugs may also provide therapeutic benefit related to restoring normal levels of ABCG1 protein in beta cells and improving insulin secretion in people with type 2 diabetes," said Dr. Hedrick. "Our research points to the need to investigate this possibility further as well as to explore the potential development of new therapies that boost

ABCG1 protein levels and insulin secretion," she said.

The finding was published online today in the *Journal of Clinical Investigation* in a paper titled "An intracellular role for ABCG1-mediated cholesterol transport in the regulated secretory pathway of mouse pancreatic beta cells." Jeff Sturek, Ph.D., from the University of Virginia, was lead author on the paper and Dr. Hedrick, who was a faculty member at the University of Virginia before joining the La Jolla Institute in late 2009, was senior author.

Ann Marie Schmidt, Ph.D., the Gerald & Janet Carrus Professor of Surgical Science at Columbia University, who specializes in research on the mechanisms of diabetic complications, called the finding a "very novel and extremely important" discovery illuminating the ABCG1 protein's role in optimizing insulin secretion. "This mechanism may be very helpful for people with type 2 diabetes, but also type 1 because it may extend the period of time before all insulin-producing potential is gone," she said. "While delaying disease onset is important in both types of diabetes, it is particularly critical for type 1 diabetics who tend to manifest diabetes as children and who can suffer more severe disease consequences because of the lifelong nature of their illness and their eventual complete loss of the ability to produce insulin."

Matthias von Herrath, M.D., director of the La Jolla Institute's Type 1 Diabetes Research Center, agreed and praised the ABCG1 finding as an important step in understanding the cellular mechanisms of insulin secretion. "Dr. Hedrick's discovery offers important insights on possible ways to increase insulin production, which is key to controlling both types of diabetes," said Dr. von Herrath, who is among the world's leading type 1 diabetes researchers. "We are pleased that she recently joined our Institute and will be contributing to our Center's efforts to combat this terrible disease."

Dr. Hedrick, who primarily researches the high correlation between diabetes and heart disease, began studying the ABCG1 protein several years ago as she looked at cholesterol buildup and coronary plaque formation in diabetes sufferers. "The primary, known function of ABCG1 is to remove excess cholesterol from the body. But with this study, we have discovered a new function for the ABCG1 protein. We now know that it is also very important for transport of cholesterol to various membranes within beta cells and, most likely, within other cells," she said. "Everybody thinks cholesterol is bad. But actually, scientists have long known it is an essential component of all cell membranes."

Dr. Hedrick and her team at the University of Virginia had heard of studies in diabetes mouse models showing that islet beta cells contained excessive cholesterol. "We wondered if this was somehow related to ABCG1, since its function is to remove excess cholesterol from the cells of the body," she said. "So we decided to investigate."

It was a novel idea, since ABCG1 was only known to sit on the plasma membrane of cells and no one had studied ABCG1 function within cells. "One surprising finding from our work is that ABCG1 action in beta cells is actually intracellular," said Dr. Sturek of the University of Virginia. "We found that the majority of ABCG1 actually sits inside the beta cell and that it's really important for delivering cholesterol intracellularly to the insulin granule membranes. Without delivery of cholesterol to these membranes by ABCG1, the insulin granules do not develop or function properly and, as a result, release significantly less insulin. This is particularly interesting because it suggests that we look at intracellular roles for ABCG1 in other cell types."

In previous studies, Dr Hedrick and her team had also made the finding that people with type 2 diabetes have relatively low levels of ABCG1. "We theorized that this contributed to higher rates of heart disease among type 2 diabetics since failure to successfully remove cholesterol

from arteries can lead to arterial plaque buildup, a key contributor to heart disease."

Based on this latest research, Dr. Hedrick believes that boosting the levels of ABCG1 in diabetes patients may benefit sufferers in two ways - by aiding in reducing arterial plaque buildup and in improving insulin production.

Provided by La Jolla Institute for Allergy and Immunology