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Study Uncovers Detail About Development of Diabetes

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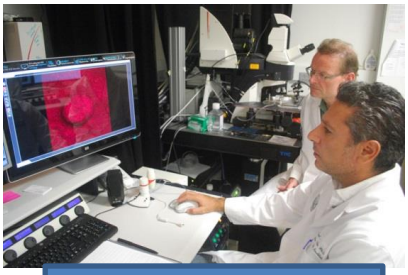
A research team led by Professor Per-Olof Berggren, Ph.D., an adjunct Professor and Mary Lou Held Chair at the Diabetes Research Institute at the University of Miami Miller School of Medicine and director of the Rolf Luft Research Center for Diabetes and Endocrinology at Karolinska Institutet in Stockholm, and visiting Professor at the Lee Kong Chian School of Medicine, Nanyang Technological University in Singapore, has revealed new evidence in mice on a mechanism that contributes to failure and death of the insulin-producing beta cells during development of diabetes.



At rear, Per-Olof Berggren, Ph.D., and Midhat H. Abdulreda, Ph.D.

The study is published in the *Proceedings of the National Academy of Science (PNAS)*.

Ten years ago, the same team discovered that apolipoprotein CIII (apoCIII) is elevated in the blood of type 1 diabetes patients which produces excessive activation of certain calcium channels in the beta cells, causing their failure to release insulin and eventual death. In this recent study, the team in collaboration with Midhat H. Abdulreda, Ph.D., assistant professor of surgery at the Miller School's Diabetes Research Institute, now shows that apoCIII is also involved in type 2 diabetes and that the effect of apoCIII can be prevented by blocking the affected calcium channels. This may guide new therapeutic interventions to prevent beta cell deterioration during disease progression in both type 1 and type 2 diabetes.

"This adds another piece to the puzzle of this multifaceted disease, diabetes," said Abdulreda. "We hope to leverage this new information to help preserve beta cell mass in type 1 and type 2 diabetes."

In this study, the researchers used insulin-resistant mice with type 2 diabetes. Because of the disease, the mice had elevated levels of apoCIII in their blood. This apoCIII was mainly

produced in the liver, although the islets themselves in the pancreas also produce apoCIII as a consequence of local islet insulin resistance. To isolate the effects of the liver-produced apoCIII on the pancreatic islets from those of apoCIII produced locally by the islet cells, the researchers used the "living window" model which was developed by the same team and previously used to uncover novel aspects of islet biology and immunology. The "living window" model, consists of transplanting isolated pancreatic islets into the anterior eye chamber – a technique that makes it possible to study beta cell function and survival in real time.

In this study, normal islets capable of producing apoCIII were transplanted into one eye of type 2 diabetic mice while genetically modified islets, incapable of producing apoCIII, were transplanted to the other eye of the same mice. This simultaneous transplant helped reveal that islets in each eye reacted differently despite the fact that they were exposed to the same elevated levels of apoCIII in the blood. Only the apoCIII-producing islets showed inflammation and cell death, whereas, the non-apoCIII-producing islets thrived.

"This shows that local production of apoCIII has damaging effects on beta cells," said Lisa Juntti-Berggren, M.D., chief physician and professor at the Rolf Luft Research Center for Diabetes and Endocrinology at Karolinska Institutet. "Circulating apoCIII had no direct damaging effect on the beta cell under type 2 diabetic conditions."

The researchers are currently proceeding with animal studies to investigate the possibilities of blocking the production of apoCIII locally in islets of Langerhans cells.

"Our goal is to develop a treatment strategy where you can prevent type 2 diabetes from developing in individuals with a high risk of the disease; people with insulin resistance, for example," said Per-Olof Berggren.

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