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Novel mechanism of insulin resistance in type 2 diabetes

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Insensitivity to insulin, also called insulin resistance, is associated with type 2 diabetes and affects several cell types and organs in the body. Now, scientists from Sweden's Karolinska Institutet have discovered a mechanism that explains how insulin-producing cells can be insulin resistant and insulin sensitive at the same time.

The findings are being published in the journal *Cell Reports*, and may lead to future novel treatment strategies for type 2 diabetes.

Insulin is critical in lowering blood glucose concentration. Individuals with type 2 diabetes suffer from insulin resistance and this means that their cells/organs are insensitive to insulin. In type 2 diabetes the body tries to compensate by producing more insulin, and also by increasing the number of insulin-producing cells. Finding new treatment strategies is only possible by gaining a greater understanding of what happens in the body of a diabetic patient. One scientific challenge is to explain how a cell/organ at the same time can be insulin resistant in one biological function and insulin sensitive in another.

Drs Barbara Leibiger and Ingo Leibiger, both members of Professor Per-Olof Berggren's research group at the Department of Molecular Medicine and Surgery, Karolinska Institutet, are particularly interested in the insulin-producing beta cells.

"The beta cell must have insulin to work properly", says Barbara Leibiger, PhD, Associate Professor, and lead author of the current study.

"In a person with diabetes, the beta cells become insensitive to insulin."

The researchers have previously shown that the beta cell has two receptors with different biological functions, insulin receptor A and insulin receptor B. In the current study, they found that under diabetic conditions, even though insulin receptor B is insulin insensitive for one signalling pathway, insulin can under these conditions instead activate a different signalling pathway, leading to beta cell proliferation. The researchers also identified the factor, PI3K-C2α, that caused the switch from one signalling pathway to another.

"The results are important since it explains how the beta cell can go from a differentiated state to a proliferative state", says Ingo Leibiger, PhD, Associate Professor, who co-supervised the current study with Professor Berggren. "This means that the cells change from being glucose-responsive to instead increase in number."

According to the study authors, also including researchers from the Pohang University of Science and Technology, Republic of Korea, factors involved in the re-routing of the insulin signal represent tentative therapeutic targets in the treatment of diabetes.

More information: 'PI3K-C2α Knockdown Results in Rerouting of Insulin Signaling and Pancreatic Beta Cell Proliferation', Barbara Leibiger, Tilo Moede, Meike Paschen, Na-Oh Yunn, Jong Hoon Lim, Sung Ho Ryu, Teresa Pereira, Per-Olof Berggren, and Ingo B. Leibiger, *Cell Reports*, October 06, 2015 paper issue, online first September 17, 2015.

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