Inducing insulin resistance: Human iPS cell model offers new look at key driver of type 2 diabetes

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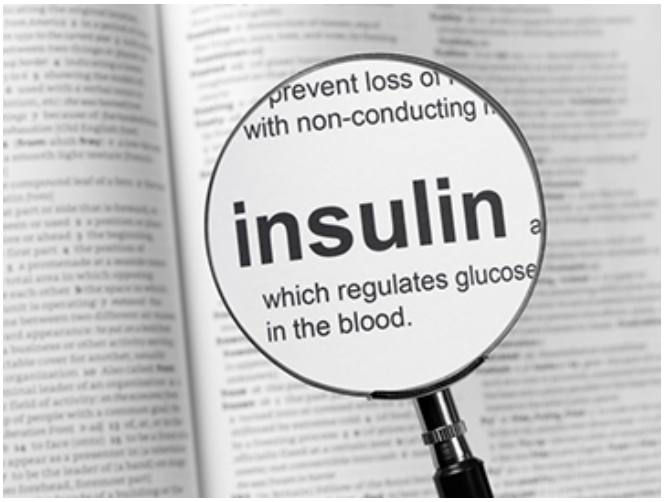

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(Medical Xpress)—Harvard Medical School researchers at Joslin Diabetes Center have created the first induced pluripotent stem cells (iPSCs) that offer a human model of insulin resistance, a key driver of type 2 diabetes.

"This is one of the very first studies of human iPSC models for type 2 diabetes, and it points out the power of this technology to look at the nature of diabetes, which is complex and may be different in different individuals," said C. Ronald Kahn, the HMS Mary K. Iacocca Professor of Medicine and chief academic officer at Joslin.

Until now, scientists examining the causes and effects of insulin resistance have struggled with a general lack of human cell lines from tissues such as muscle, fat and liver that respond significantly to insulin, said Kahn. Studying insulin resistance as it progresses through pre-clinical stages of type 2 diabetes has been particularly challenging.

"There have been no good human cell models to study insulin resistance, but such cells can now be made with iPSCs," said Kahn, co-senior author of a paper about the study published in the journal *Diabetes*.

Japanese biologist Shinya Yamanaka won a Nobel Prize in 2012 for discovering how to create iPSCs, cells derived from normal adult cells that have the ability to differentiate into almost any other kind of cells.

Generation of iPSCs typically starts with connective tissue cells called fibroblasts from skin samples. Kahn and his colleagues used fibroblasts from three patients with severe insulin resistance brought on by mutations in the gene for the insulin receptor (IR), a molecule that crosses the cell membrane and plays a key role in insulin signaling and glucose metabolism.

The Joslin researchers "reprogrammed" the fibroblasts into iPSCs by using viral procedures that activated four genes that together maintain cells in the iPSC state. The scientists then looked at gene activation in insulin signaling pathways for iPSCs and fibroblasts with IR mutations, and for corresponding cells derived from people without those mutations.

Among the study findings was that IR mutations alter expression of many genes both in fibroblasts and iPSCs compared to normal cells, "but the impact is very much dependent on the cell type," said Kahn. "You see one type of expression pattern in the fibroblasts and a different type of pattern in the iPSCs."

Insulin is a key ingredient for the growth and proliferation of normal stem cells. The study demonstrated that insulin resistance also reduces

the ability of the iPSCs to grow and proliferate. That defect may represent a previously unrecognized mechanism that aids in developing diabetes, said Kahn, as well as helping to explain the problems in wound healing, tissue repair and even beta-cell growth that are common among people with diabetes.

"Our next phase of research is to make these iPSCs into liver, muscle and fat cells, and then see if we can use them to model those tissues in people," he said.

In one line of research, Kahn added, the Joslin team will examine how much of insulin resistance in type 2 diabetes is genetic and how much of it is acquired in the environment, because resistance acquired in the environment presumably will disappear in the iPSCs.

More information: Salvatore Iovino, Alison M. Burkart, Kristina Kriauciunas, Laura Warren, Katelyn J. Hughes, Michael Molla, Youn-Kyoung Lee, Mary-Elizabeth Patti, and C. Ronald Kahn. "Genetic Insulin Resistance is a Potent Regulator of Gene Expression and Proliferation in Human iPS Cells." *Diabetes*, published ahead of print July 24, 2014, DOI: 10.2337/db14-0109 1939-327X

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