Differences in cellular signaling offer clues to insulin resistance

15 September 2021, by Max Bingham

Credit: Pixabay/CC0 Public Domain

In what could be a starting point for new therapeutics to tackle insulin resistance, a major driver of type 2 diabetes and metabolic syndrome present in 20–30 percent of the general U.S. population, researchers recently found that insulin resistance in the general population seems likely to be caused by a series of cell-specific signaling defects, some of which appear to be sex specific.

In addition, only a portion of the defects are shared with those seen in diabetes, pointing towards the existence of novel pathways behind insulin resistance in the general population.

The new study by Harvard Medical School researchers at Joslin Diabetes Center was published Sept. 10 in the *Journal of Clinical Investigation*.

"Most people know that insulin is an important hormone for controlling blood glucose, but most people don't realize how important insulin is for all aspects of metabolism—not just sugar, but lipids, amino acids, and proteins," said senior author C. Ronald Kahn, the Mary K. Iacocca Professor of Medicine at HMS and head of the Integrative Physiology and Metabolism Section at Joslin.

"Insulin resistance, that is the failure of the body to respond normally to insulin, is very common in the population, not just in people with diabetes or obesity, and these individuals are at high risk for developing these metabolic disorders. So, that is why we decided to study how insulin signaling is altered in cells from this insulin resistant part of the population," he said.

The research is based on a stem-cell modeling system called iMyos that can be used to investigate cell-specific changes in signaling in combination with a technique called phosphoproteomics.

Specifically, the researchers used stem cells derived from blood cells of individuals without diabetes who were either insulin sensitive or resistant.

The researchers could then investigate differences in cellular signaling, both in the absence and presence of insulin stimulation, to determine how insulin resistance or sensitivity affected signaling in a series of different pathways.

In what emerges as a complex picture, they found large differences in phosphoproteome signatures based on insulin sensitivity status but also based on the sex of the cell donors.

"We identified a comprehensive network of cell signaling defects in non-diabetic individuals and also uncovered critical nodes of signaling changes shared with type 2 diabetic patients" said lead author Nida Haider, HMS research fellow in medicine at Joslin.

"These critical nodes where signaling was altered go well beyond the classical insulin signaling, opening a whole new view of insulin resistance. One of the most striking and surprising findings was that many of the signaling changes were sex specific," Haider said.

"Thus, even in the absence of adding sex hormones, these male and female cells showed differences in their phosphoproteome fingerprint. This was very unexpected."

Importantly, the investigators also found that the differences and changes did reflect on multiple downstream biological processes, implying that therapeutic interventions at specific points in the signaling cascade will likely affect biological outcomes.

"Further investigation will be needed to identify the regulators that are responsible for the phosphoproteome changes associated with insulin resistance, and for the drastic differences by sex," Kahn added. "Unraveling these critical nodes in insulin resistance will be able to serve as novel targets for the development of future therapies."

More information: Nida Haider et al, Signaling defects associated with insulin resistance in non-diabetic and diabetic individuals and modification by sex, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI151818

Provided by Harvard Medical School