A new strategy normalizes blood sugars in diabetes

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Researchers at Children's Hospital Boston have identified a new strategy for treating type 2 diabetes, identifying a cellular pathway that fails when people become obese. By activating this pathway artificially, they were able to normalize blood glucose levels in severely obese and diabetic mice. Their findings will be published online by *Nature Medicine* on March 28.

Epidemiologists have long known that obesity contributes to type 2 diabetes. In previous work, researcher Umut Ozcan, MD, in Division of Endocrinology at Children's, showed that the brain, liver and fat cells of obese mice have increased stress in the endoplasmic reticulum (ER), a structure in the cell where proteins are assembled, folded into their proper shapes, and dispatched to do jobs for the cell. In the presence of obesity, the ER is overwhelmed and its operations break down. This so-called "ER stress" activates a cascade of events that suppress the body's response to insulin, and is a key link between obesity and type 2 diabetes.

Until now, however, researchers haven't known precisely why obesity causes ER stress to develop. Ozcan and colleagues now show that a transcription factor that normally helps relieve ER stress, called X-box binding protein 1 (XBP-1), is unable to function in obese mice. Instead of traveling to the cell nucleus and turning on genes called chaperones, necessary for proper ER function, XBP-1 becomes stranded.

Probing further, the researchers found the reason: XBP-1 fails to interact

with a protein fragment called p85, part of an important protein that mediates insulin's effect of lowering blood glucose levels (phosphotidyl inositol 3 kinase or PI3K). Ozcan's group identified a new complex of p85 proteins in the cell, and showed that normally, when stimulated by insulin, p85 breaks off and binds to XBP-1, helping it get to the nucleus.

"What we found is, in conditions of obesity, XBP1 cannot go to the nucleus and there is a severe defect in the up-regulation of chaperones," says Ozcan. "But when we increase levels of free p85 in the liver of obese, severely diabetic mice, we see a significant increase in XBP1 activity and chaperone response and, consequently, improved glucose tolerance and reduced blood glucose levels."

When people are obese, the insulin signaling that normally increases free p85 is impaired, leading to more ER stress and more insulin resistance, ultimately leading to type 2 diabetes. But Ozcan thinks this vicious cycle can be circumvented through strategies that increase levels of free p85. His group is taking further steps to activate this novel pathway to create new treatment strategies for type 2 diabetes.

More information: Sang Won Park, Yingjiang Zhou, Justin Lee, Allen Lu, Cheng Sun, Jason Chung, Kohijiro Ukei and Umut Ozcan. The regulatory subunits of PI3K, p85α and p85β, interact with XBP-1 and increase its nuclear translocation. *Nature Medicine* advance online publication, March 28, 2010. DOI:10.1038/nm.2099

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