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Glucose uptake relies on newly identified protein

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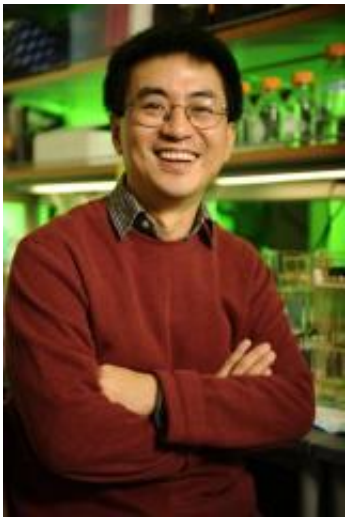

Zhen Y. Jiang, Ph.D. is an assistant professor in Sanford-Burnham's Diabetes and Obesity Research Center. Credit: Sanford-Burnham Medical Research Institute

All cells need glucose (sugar) to produce the energy they need to survive. High glucose levels in the bloodstream (such as occur after a meal), trigger the pancreas to produce insulin. In turn, muscle and fat cells respond to insulin by moving GLUT4, a glucose transporter, from intracellular storage out to the cell surface. There, GLUT4 can take up the glucose the cell needs from the bloodstream.

Now, a new study led by Zhen Y. Jiang, Ph.D. at Sanford-Burnham

Medical Research Institute (Sanford-Burnham) identifies the protein -- called CDP138 -- responsible for ensuring that GLUT4 is properly inserted in the cellular membrane. These results, appearing September 7 in Cell Metabolism, provide a new understanding of glucose metabolism -- an important finding considering that impaired insulin action and glucose metabolism contribute to the development of type 2 diabetes.

"This is a newly identified protein that's involved in an important step in glucose uptake," said Dr. Jiang, assistant professor in Sanford-Burnham's Diabetes and Obesity Research Center, located in Orlando's Medical City at Lake Nona.

There are two main steps that get GLUT4 from intracellular storage to the cell surface in fat and muscle tissue. First, a vesicle containing the stored transporter moves to (and docks at) the outer membrane. Second, GLUT4 from the docked vesicle inserts into the membrane. Insulin triggers this process and a protein pathway spearheaded by a protein called Akt2 is known to initiate both steps.

In this study, the research team set out to determine how the cell specifically controls that final step—fusion of the glucose storage vesicles and the cell's outer membrane. To do this, they went looking for Akt2 substrates—other proteins that Akt2 acts upon. Through phosphoproteomics and RNA interference (RNAi)-based functional analyses, they came upon a protein they called CDP138. Then, to pinpoint its exact function, they genetically dampened CDP138 in live fat cells. As a result, the researchers found that this previously unknown protein is required for optimal insulin-stimulated GLUT4 transport to the cell surface and fusion of GLUT4-containing vesicles with the membrane. Through these functions, CDP138 was also required for glucose transport in live fat cells. Drilling deeper, the team also identified the exact part of the CDP138 protein that is chemically modified by Akt2 and showed that, without that region, CDP138 was

unable to carry out its function.

It's possible that CD138 contributes to diabetes in humans. Preliminary experiments suggest that mice engineered to be obese have lower CD138 levels than normal mice. It remains to be seen whether this is the case in humans and whether CD138's correlation with obesity is a cause of obesity or an effect—or simply a correlation.

"We are now generating a mouse model that lacks CD138," Dr. Jiang said. "Over the next year, we'll be looking to see if these mice experience changes in their glucose metabolism in response to insulin and exercise."

Provided by Sanford-Burnham Medical Research Institute