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Breakthrough research of essential molecule reveals important targets in diabetes and obesity

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Insulin is the most potent physiological anabolic agent for tissue-building and energy storage, promoting the storage and synthesis of lipids, protein and carbohydrates, and inhibiting their breakdown and release into the circulatory system. It also plays a major role in stimulating glucose entry into muscle tissue, where the glucose is metabolized and removed from the blood following meals. But gaps exist in understanding the precise molecular mechanisms by which insulin regulates glucose uptake in fat and muscle cells.

A research team led by Assia Shisheva, Ph.D., professor of physiology in Wayne State University's School of Medicine, has made breakthrough advancements on a molecule that may provide more answers to this mystery.

The conserved phospholipid enzyme, PIKfyve, was discovered in Shisheva's lab in 1999. Based on studies in cultured cells, the lab has implicated PIKfyve in the insulin-regulated glucose transport activation, which led to the development of a unique mouse model with PIKfyve ablation, or removal, in muscle (MPlfKO), the tissue responsible for the majority of postprandial glucose disposal.

In Shisheva's recent paper, "Muscle-specific PIKfyve gene distribution causes glucose intolerance, insulin resistance, adiposity and hyperinsulinemia but not muscle fiber-type switching," published online

in the *American Journal of Physiology - Endocrinology and Metabolism*, Shisheva and her research team characterize whether this new model exhibits metabolic defects.

"Our team found a striking metabolic phenotype in the MPIfKO mice consisting of glucose intolerance and insulin resistance at an early age and on a normal diet," said Shisheva, a resident of Royal Oak. "We also revealed that PIKfyve is essential for normal insulin signaling to GLUT4/glucose transport in muscle and provided the first in vivo evidence for the central role of PIKfyve in the mechanisms regulating healthy blood glucose levels, or glucose homeostasis."

In addition, the research team found that these metabolic disturbances were followed by increased animal fat (adiposity) and elevated levels of insulin (hyperinsulinemia), but not abnormal amounts of lipids or cholesterol in the blood (dyslipidemia).

"The combined phenotype manifested by the MPlfKO mouse closely recapitulates the cluster of typical features in human prediabetes including systemic glucose intolerance and insulin resistance, hyperinsulinemia and increased visceral obesity without dyslipidemia," said Shisheva.

"Therefore, our mouse model, in addition to providing novel mechanisms of insulin resistance, represents a valuable tool for exploring new preclinical strategies to improve treatments in individuals with prediabetes."

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