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REGULATION OF PERIPHERAL GLUCOSE UPTAKE BY REGULATING GLUT4 ENDOCYTOSIS

Statement of the Problem: In diabetes, the body's response to insulin is impaired, resulting in elevated levels of blood glucose. Peripheral-tissue glucose uptake is an important regulatory point in controlling blood glucose. After a meal, insulin causes most glucose to be quickly taken up by muscle and adipose tissue. This process is carried out by the fusion of storage vesicles containing GLUT4, a glucose transporter, with the cell surface membrane. Failure of this process results in insulin resistance and elevated blood glucose. To prevent hypoglycemia under fasting conditions, GLUT4 on the cell surface is normally kept low by continuous endocytosis. Because AP2- and clathrin-binding sites have been mapped in GLUT4, this basal endocytosis has been thought to be a signaling-independent, passive process. Yet this concept creates a dilemma: how is this process inhibited during insulin stimulation to avoid a futile cycle of endocytosis and cell surface fusion?

Methodology & Findings: We recently identified TXNIP (thioredoxin-interacting protein) as a negative regulator of the class I members of the SLC2 family of glucose transporters, which includes GLUT4. We discovered that TXNIP associates with GLUTs and mediates GLUT endocytosis via the clathrin-dependent pathway, effectively reducing glucose influx. Using TXNIP WT and KO mice, we found that the absence of TXNIP results in higher fasting glucose uptake into muscle and adipose tissue. Using tissue cultures, we found that insulin-induced AKT activation leads to TXNIP phosphorylation that disrupts the TXNIP/GLUT4 interaction, acutely inhibiting GLUT4 endocytosis.

Conclusion & Significance: Our results indicate that GLUT4 endocytosis is actually a regulatable process, both in fasting and insulin-stimulated states. Together with our previous finding that cellular energy stress stimulates glucose uptake via AMPK phosphorylation of TXNIP, it points to TXNIP as a key node of regulation of blood glucose by both exercise and insulin.

Biography

Ning Wu received her Ph.D. in the Department of Biochemistry from the University of Toronto in 2002. She then served as a research associate at The Scripps Research Institute in the Department of Chemistry. In 2004, She joined the Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School, as a research fellow where the primary lab focus was to understand the signaling pathways that regulate normal mammalian cell growth and the defects that cause cell transformation. She joined Van Andel Research Institute in 2013 as an assistant professor in the Center for Cancer and Cell Biology.

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