Milestone 10

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GLUT4 traffic control

Insulin is essential for glucose homeostasis and one of its key functions is to drive glucose uptake into adipocytes and myocytes. Insulin's role in this process became apparent in 1921 and the concept was refined well into the 1950s, with several studies demonstrating accelerated transport of glucose into these tissues in response to insulin. Yet, the underlying mechanisms remained elusive for nearly three decades.

The way towards understanding insulin-stimulated glucose uptake has been paved by studies between the late 1970s and 1980. These studies demonstrated that in adipocytes, insulin increases the number of functional glucose transporters in the plasma membrane. Furthermore, this activity was shown to be mediated by the translocation of the yet unknown 'transport system' from the intracellular stores associated with the membrane fraction, known as low-density microsomes.

By the end of the 1980s, several glucose transporters had been identified in different tissues and cell types, including erythrocytes, liver, kidney, intestine and brain. However, it was unclear whether insulin-stimulated glucose transport specific for adipocytes and myocytes was mediated by one of these known systems that is differently regulated, or whether it relied on a unique type of transporter that was selectively expressed in these tissues. The key answer to this question was published in *Nature* in 1988 by James and colleagues. In this work, the authors isolated the microsomal membrane fraction from rat adipocytes and raised a monoclonal antibody that would specifically recognize the putative insulin-stimulated glucose transporter. This antibody selectively labelled muscle and adipose tissues and did not react with cells that did not show insulin-stimulated glucose transport. This study provided clear evidence that the insulin-stimulated glucose transporter in muscle and adipose tissue is molecularly distinct from the previously reported glucose transport systems. The following year, the gene encoding this unique transporter was cloned and its chromosomal location mapped by several different laboratories. In reflection of its similarity to GLUT1–3 glucose transporters, which had already been cloned, the protein was termed GLUT4.

"the insulin-stimulated glucose transporter in muscle and adipose tissue is molecularly distinct"

Identification of GLUT4 as a unique glucose transporter whose subcellular localization is regulated by insulin raised questions about the physiological implications of these trafficking events. Decreased responsiveness of cells to insulin will inevitably lead to diminished glucose uptake from the bloodstream and hyperglycaemia, which are hallmarks of type 2 diabetes. Various mechanisms contribute to this glucose uptake defect, and aberrant trafficking of GLUT4 in skeletal muscle is one of them. Hence, modulation of GLUT4 subcellular localization has emerged as a potential therapeutic strategy against insulin resistance in type 2 diabetes.

Exploring the therapeutic potential of modulating GLUT4 trafficking requires a thorough understanding of the molecular machineries and signalling networks implicated in translocating GLUT4 from the intracellular pool to the plasma membrane upon cell stimulation with insulin. Work across the years from multiple groups has revealed that GLUT4 undergoes endosomal recycling, with fast endocytic rates that favour the retention of the majority of GLUT4 molecules in intracellular membranous compartments. When insulin is present, it binds to its receptor on the surface, inducing PI3K–AKT signalling. One of the substrates of AKT in adipocytes and myocytes is a GTPase-activating protein termed TBC1D4 (also known as AS160), which regulates the activity of RAB GTPases — key mediators of membrane dynamics — thereby linking insulin signal reception to GLUT4 trafficking.

Despite this progress, many gaps still remain in our understanding of the molecular underpinnings of insulin-stimulated glucose uptake. Further dissection of the molecular machineries governing GLUT4 intracellular trafficking, their regulation and their links to insulin signalling will be required to translate these findings into practical interventions.

Paulina Strzyz Senior Editor,
Nature Reviews Molecular Cell Biology

Milestone study

James, D. E. et al. Insulin-regulatable tissues express a unique insulin-sensitive glucose transport protein. *Nature* **333**, 183–185 (1988)

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