Researchers discover new glucose-regulating protein linked with diabetes

May 28 2009

Researchers at the University of California, San Francisco, and collaborators at Harvard Medical School have linked a specialized protein in human muscles to the process that clears glucose out of the bloodstream, shedding light on what goes wrong in type 2 diabetes on a cellular level.

Establishing the function of this protein, which significantly is not present in mice, has broad implications for both the future study and possible therapies for diabetes, according to an article published in the May 29, 2009 issue of the journal "*Science*."

While a significant amount of research into diabetes and many other diseases is conducted in mice, the often-unknown differences between mice and men can create obstacles to direct translation of such research and need to be taken into account in understanding the progression of human disease, according to the researchers.

"Much has been learned from mouse models about glucose metabolism that is relevant to human diabetes, but what happens on a cellular level is now found to be different between the two species," said Frances Brodsky, DPhil, senior author on the paper and a UCSF professor in the Departments of Bioengineering and Therapeutic Sciences, Pharmaceutical Chemistry, and Microbiology and Immunology. "This research shows one significant species-specific difference that will influence our understanding of mechanisms of type 2 diabetes."

In humans, muscles play a key role in clearing glucose from the bloodstream, Brodsky explained. In normal function, this is controlled by insulin, which stimulates the muscle cells to import glucose by means of a system known as the GLUT4 glucose transporter.

Normally, she said, GLUT4 is stored inside both human and mouse muscles in a special compartment that releases it upon insulin stimulation. Fat cells also form a GLUT4 compartment and take up glucose in response to insulin. In type 2 diabetes, however, the muscle and fat cells fail to respond appropriately to the insulin and the GLUT4 compartment is abnormal. This process was thought to be identical across mammal species.

The current research identified a protein in both human muscle and fat cells, called CHC22, which appears to control the formation of the GLUT4 storage compartments.

The team determined that this protein is a specialized form of a ubiquitous housekeeping protein called clathrin, which Brodsky has studied since the 1980s and is known to be instrumental in moving proteins between cellular compartments. CHC22 was observed to be associated with the abnormal GLUT4 compartments in muscles from diabetic patients which, for some reason, do not mobilize to the muscle cell surface when stimulated by insulin.

Notably, she said, while mice also have an insulin-responsive GLUT4 compartment, they lack the CHC22 protein. As a result, this work has implications for developing better models for the study of type 2 diabetes.

The paper highlights the differences between humans and mice and offers insights into aspects of the GLUT4 transport mechanism within cells that are specialized in humans, according to a commentary on the

paper that appears in the same journal.

Brodsky said the Harvard team on this research produced the mouse capable of expressing CHC22 in its muscles and fat, which was analyzed in the study. These mice have features of diabetes, because the protein disrupts their GLUT4 transport pathway, which normally operates without CHC22. Also instrumental to the study was a human muscle cell line produced by the collaborator at University of Texas Southwestern.

Source: University of California - San Francisco