# Muscle gene may provide new treatments for obesity and diabetes

July 27 2010

(PhysOrg.com) -- Skeletal muscle enables us to walk, run or play a musical instrument, but it also plays a crucial role in controlling disease. Rockefeller University scientists have now shown how a specific molecule in skeletal muscle regulates energy expenditure, a finding that may lead to new treatments for certain muscle diseases as well as diabetes, obesity and heart disease.

The researchers, led by Wei Chen, a research associate in the Laboratory of Biochemistry and Molecular Biology, focused on a protein called MED1, which makes up part of a gene regulating machine called the Mediator coactivator complex. MED1 anchors the Mediator to an array of receptors in the cell nucleus that activate genes, and it performs crucial functions in a variety of cells and tissue types, including development of the mammary gland and fat tissues and the oxidation of fatty acids in the liver.

In the new study, Chen and her colleagues focused on MED1's role in skeletal muscle. The researchers created a line of mice genetically modified to lack MED1 only in muscle cells. They found that the *Med1* knockout mice had enhanced sensitivity to insulin and improved glucose tolerance and also resisted becoming obese even when fed a high-fat diet. Gene microarray analysis showed that when *Med1* was deleted, a number of genes that are usually suppressed were activated, says Chen.

"In muscle, MED1 normally suppresses a genetic program that holds in check certain energy expenditure pathways," says Robert G. Roeder,

Arnold and Mabel Beckman Professor and head of the Laboratory of Biochemistry and Molecular Biology. “We found that these genes are unleashed when MED1 function is abrogated.”

One of these genes is *UCP-1*, which produces a key protein that works in certain fat cells to generate heat when animals are exposed to cold. The researchers also found that MED1 plays a role in development of muscle fibers. Muscle is composed of two kinds of fiber, called slow and fast twitch. Slow twitch fibers contract slowly and can keep going for a long time, while fast twitch muscle fibers contract quickly, but get tired sooner. Removing *Med1* caused the muscles to switch from fast to slow twitch fibers, which the researchers think may contribute to the animals’ enhanced tolerance to glucose and sensitivity to insulin.

Chen and her colleagues also observed that some muscle in the *Med1* knockout mice had an increase in the density of mitochondria, which provide energy to cells, a finding which suggests that targeting *Med1* could provide new treatments for muscle diseases caused by malfunctioning mitochondria, including some types of epilepsy.

“Taken together, these dramatic results raise the significant possibility of therapeutical approaches for metabolic syndromes and muscle diseases through modulation of MED1-nuclear receptor interactions,” says Chen.

**More information:** *Proceedings of the National Academy of Sciences* 107: 10196-10201 (June 1, 2010). A muscle-specific knockout implicates nuclear receptor coactivator MED1 in the regulation of glucose and energy metabolism, Wei Chen, Xiaoting Zhang, Kivanc Birsoy and Robert G. Roeder

Provided by Rockefeller University