Findings in mice have potential to curb obesity, Type 2 diabetes

July 5 2011

Scientists at the National Institutes of Health have uncovered a pathway in mice that allows white fat – a contributor to obesity and type 2 diabetes – to burn calories in a way that's normally found in brown fat and muscle. The findings are in the July 6 edition of *Cell Metabolism*.

White fat is used to store calories. However, too much white fat (obesity) increases the risk of type 2 diabetes and other diseases. Brown fat generates heat to maintain body temperature and, like muscle, has lots of iron-containing, calorie-burning mitochondria in its cells. Changing white fat into brown fat or muscle is a potential new approach to treating obesity and type 2 diabetes, although the research is a long way from being applicable to people.

The findings were exciting and unexpected, said Sushil Rane, Ph.D., a researcher at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases and the paper's senior author. "We weren't looking to have white fat acquire the properties of brown fat, but that's what we found, with the fat getting browner from increased mitochondria and displaying genes typically expressed in muscle. It was a striking difference.

"Efforts to reduce obesity by dieting are mostly unsuccessful in the long term, so finding ways to prevent excess fat storage is an urgent medical need," Rane said. "Our discovery that white fat can be reduced by partially transforming it to brown fat and muscle opens up new avenues to combat the obesity epidemic."

Researchers made their discovery in mice by reducing the actions of a protein called TGF-beta in two ways: through genetic engineering and using an antibody — a different protein that finds and blocks the TGF-beta protein. The TGF-beta proteins determine the capacity of cells to grow and function normally. Without the TGF-beta actions, the researchers saw that the mice's white fat was getting browner with more mitochondria. The increased metabolic activity due to the mitochondria led to burning calories, thus lessening obesity.

"The default function of white fat is to store energy. This discovery identifies a potential way for it to burn energy instead," said Marc Reitman, M.D., Ph.D., chief of the NIDDK Diabetes, Endocrinology, and Obesity Branch.

The TGF-beta blocking antibody is also being tested as a cancer treatment in people through a trial at the National Cancer Institute. Due to the potential side effects of the antibody, including compromising the immune system, it has not been tested or proven for treatment of human obesity or type 2 diabetes. The researchers next plan to design a more targeted approach to partially transform white fat of mice into the brown fat or muscle-like state without compromising the immune system.

"So many great discoveries are the result of hard work and an openness to being surprised by findings, and to follow where those surprises lead," said NIDDK Director Griffin P. Rodgers, M.D. "If continuing research supports current findings, this discovery has the potential to improve the treatment of obesity and the prevention of type 2 diabetes."

More information: "Protection from obesity and diabetes by blockade of TGF-beta/Smad3 signaling" was published in *Cell Metabolism* online on July 5, 2011.