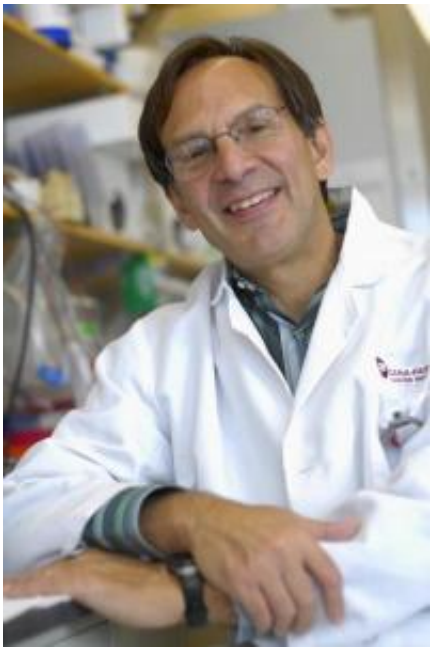
Scientists find molecular link to obesity and insulin resistance in mice

September 27 2012



Bruce Spiegelman, PhD, and his colleagues have identified the first known molecular link between thermogenesis (burning calories to produce heat) and the development of inflammation in fat cells. Flipping the newly discovered molecular switch in white fat cells enabled mice to eat a high-calorie diet without becoming obese or developing the inflammation that causes insulin resistance. Credit: Sam Ogden

Flipping a newly discovered molecular switch in white fat cells enabled mice to eat a high-calorie diet without becoming obese or developing the inflammation that causes insulin resistance, report scientists from Dana-

Farber Cancer Institute.

The researchers say the results, to be published in the Sept. 28 issue of the journal *Cell*, provide the first known molecular link between thermogenesis (burning calories to produce heat) and the development of inflammation in fat cells.

These two processes had been previously thought to be controlled separately. Thermogenesis plays an important role in metabolism and maintaining healthy weight. Inflammation triggers insulin resistance, a precursor of diabetes.

The researchers, led by Bruce Spiegelman, PhD, found that the protein TRPV4, a switch molecule, is highly expressed in white fat cells, which store excess calories and become engorged in obese individuals.

For this study, the investigators bred mice lacking TRPV4 or administered a drug to deactivate it. In the absence of TRPV4, white cells turned on a set of genes that consume energy to produce heat, rather than storing the energy as excess fat. This "thermogenic" process normally occurs in brown or beige fat (commonly called "good fat"), which is found mostly in small animals and human infants to protect against cold.

When the TRPV4-deficient mice were put on a high-calorie diet for several weeks, they did not become obese, and their level of fat cell inflammation and insulin resistance was lowered.

"We have identified a target that, when inhibited, can activate beige adipose tissue and suppress inflammation," said Spiegelman. "This role of TRPV4 as a mediator for both the thermogenic and pro-inflammatory programs in adipocytes, or fat cells, could offer an attractive target for treating obesity and related metabolic diseases."

A co-activator protein, PGC-1 alpha, previously discovered in the Spiegelman laboratory, helps turn on thermogenesis to produce heat. In the new experiments, Spiegelman and his colleagues demonstrated that TRPV4 blocks PGC-1 alpha in white fat cells. Inhibiting TRPV4 in the experimental mice raised the expression of PGC-1 alpha and sparked thermogenesis.

An experimental compound, GSK205, was used to inhibit TRPV4 in the animal studies. Spiegelman said that this technology has been licensed for further development to Ember Therapeutics, a company he co-founded. Spiegelman is an Ember consultant and shareholder.

In terms of potential therapies, Spiegelman said that "any single new approach to something as complicated as metabolic disease is unlikely to work, but our experiments with TRPV4 showed the effectiveness of this strategy and it appears to be quite safe."

Provided by Dana-Farber Cancer Institute