Scientists find new calorie-burning switch in brown fat

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Biologists at The Scripps Research Institute (TSRI) have identified a signaling pathway that switches on a powerful calorie-burning process in brown fat cells.

The study, which is reported in this week's online Early Edition of the *Proceedings of the National Academy of Sciences*, sheds light on a process known as "brown fat thermogenesis," which is of great interest to medical researchers because it naturally stimulates weight loss and may also protect against diabetes.

"This finding offers new possibilities for the therapeutic activation of brown fat thermogenesis," said team leader Anastasia Kralli, associate professor in TSRI's Departments of Chemical Physiology and Cell Biology.

'Revving the Engines'

Most fat cells in our bodies are "white fat" cells that store fat as a reserve energy supply. But we and other mammals also have depots of "brown fat" cells. These apparently evolved not to store but to burn energy—quickly, as a way of generating heat and keeping the body warm in cold conditions, as well as possibly to get rid of excess caloric intake.

Human babies as well as mammals that hibernate have relatively extensive brown fat tissues. Scientists have found in recent years that many adult humans have significant levels of brown fat, which are located mostly in the neck and shoulders, and appear to help regulate body weight and blood sugar.

Low temperatures activate the brown-fat thermogenesis process via the sympathetic nervous system: Nerve ends in brown fat tissue release the neurotransmitter norepinephrine, and that triggers a shift in metabolism within the brown fat cells, which are densely packed with tiny biological energy reactors called mitochondria.

"The mitochondria start generating heat instead of useful chemical energy; it's like revving the engines of a lot of parked cars," said first author Marin Gantner, who was a graduate student in the Kralli laboratory during the study.

Given the potential medical applications—about 100 million people suffer from obesity or diabetes in the US alone—researchers are eager to understand brown fat thermogenesis and how it can be boosted artificially. One clue, reported by other scientists in 1998, is that norepinephrine instructs brown fat cells to express high levels of a protein called PGC-1?, which acts as a general amplifier of energy metabolism and also activates thermogenesis. The Kralli laboratory has shown in past studies that PGC-1? works by activating a molecule called ERR?. But this pathway can't be the only one that triggers thermogenesis, because mice lacking PGC-1? in their fat cells, or ERR?, still show most of the usual thermogenesis response to cold.

A Serendipitous Discovery

In the new study, Gantner, Kralli and their colleagues discovered another thermogenesis activation pathway that works alongside PGC-1? and ERR?.

Originally, however, they were not examining brown fat thermogenesis, but instead were looking for clues to the function of ERR?, a protein about which little was known at the time, except that it was closely related to ERR?, appeared in brown fat cells, and also worked as a so-called nuclear receptor—a molecular switch for gene activation that can be turned on by small lipophilic molecules or a signaling protein partner.

In the hope of finding ERR?'s signaling partner, the team screened about 18,000 different proteins to see which could biochemically activate it. After accumulating a short list of "hits," the scientists

found that one of them, GADD45?, is normally produced in mouse brown fat cells and becomes especially abundant after exposure to cold—hinting that GADD45? and ERR?, much like PGC-1? and ERR?, work together to switch on brown fat thermogenesis.

The team then detailed the signaling in this pathway, from cold-induced norepinephrine release, to upregulation of GADD45? in brown fat cells, to the activation of ERR? and another closely related protein, ERR?, which turned out to be also prevalent in brown fat cells and relevant to thermogenesis. "We focused on ERR? after that," Gantner said.

The team confirmed that the GADD45?-mediated activation of ERR? leads to the metabolic shift in brown fat mitochondria that is characteristic of thermogenesis. The scientists also found that transgenic mice lacking GADD45? can't fully switch on thermogenesis under cold conditions.

In the experiments, GADD45? acted synergistically with PGC-1? to activate brown fat cell activity. "You have to add them together to get the full effect," said Kralli, suggesting that ideally, one would stimulate both pathways to boost brown fat thermogenesis.

More information: "GADD45? regulates the thermogenic capacity of brown adipose tissue" by Marin L. Gantnera, Bethany C. Hazena, Juliana Conkrightb, and Anastasia Krallia. July 31, 2014. *Proceedings of the National Academy of Sciences*. www.pnas.org/content/early/201 … /1406638111.abstract

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