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Burning brown fat

By Tim Fulmer, Senior Writer

A team of German researchers has identified a cyclooxygenase-2–mediated pathway in mice that increases levels of lipid-burning brown fat and could thus trigger weight loss to treat obesity.[1] The next challenge is developing compounds that boost the pathway in adipose tissue without increasing cyclooxygenase-2–related inflammation.

Mammals have two types of adipose tissue—white and brown. White adipose tissue (WAT) is specialized for lipid storage and can give rise to obesity when energy intake exceeds energy expenditure. In contrast, brown adipose tissue (BAT) is specialized for thermogenesis, the burning of lipids to generate heat during exposure to cold. In humans, newborns have substantial amounts of BAT, whereas adults have much lower but still measurable quantities.[2–4]

The presence of BAT in adults has caused speculation that boosting its activity or increasing overall BAT levels could be strategies for enhancing energy expenditure and promoting weight loss. The difficulty has been identifying druggable pathways associated with BAT homeostasis.

In the new work, researchers led by Stephan Herzig, head of molecular metabolic control at the **German Cancer Research Center**, built on previous work by others that had shown that inhibiting cyclooxygenase-2 (COX-2), a key enzyme in prostaglandin synthesis, could lead to decreased energy expenditure and increased fat accumulation in mice.[5,6] More generally, COX-2 has been shown to be one of several factors that contribute to inflammation associated with adiposity.[7]

The researchers thus hypothesized that COX-2 activity might be important for the development of thermogenic BAT and that increasing levels of the enzyme in adipose tissue could generate more BAT and trigger weight loss.

To confirm the importance of COX-2 in adipose tissue, the researchers first measured *Cox-2* expression in adipose tissue from a variety of mouse models of impaired energy homeostasis.

In mice with genetic or diet-induced obesity and in wasting tumor-bearing mice, *Cox-2* mRNA levels in adipose tissue were unchanged compared with those in tissue from wild-type controls. However, a significant increase in *Cox-2* expression occurred in mice exposed to four weeks of cold ($p<0.05$). Moreover, uncoupling protein 1 mitochondrial proton carrier (UCP1), a key mediator of BAT thermogenesis, was also upregulated following exposure to cold.

Those findings strongly suggested that Cox-2 was indeed important for the development and/or recruitment of BAT. The next question was whether increasing Cox-2 levels in adipose tissue would lead to weight loss.

To help answer that question, the researchers looked at mice that were engineered to overexpress *Cox-2* in adipose tissue. On a normal diet, those animals developed clusters of BAT-like cells within WAT and had a 20% reduction in body weight without loss of muscle mass or a reduction in bone length compared with wild-type controls.

Finally, following 16 weeks on a high-fat diet, the *Cox-2*-overexpressing mice showed no significant weight gain, whereas wild-type mice gained weight throughout the feeding period.

The *Cox-2*-overexpressing mice were also better protected against hyperglycemia, hyperinsulinemia and glucose intolerance.

The findings, published in *Science*, suggest a mechanism whereby WAT increases expression of *COX-2* in response to cold, leading to increased levels of prostaglandin, which then acts locally on cells in WAT to trigger development of fat-burning BAT (*see* **Figure 1, "Getting slimmer with brown fat"**).

Corresponding author Herzig told *SciBX* that his group now wants to better understand the mechanistic details of how COX-2 and prostaglandin trigger cells in WAT to develop into BAT.

That work will be important to help "identify the most selective agonists for this pathway," said Patrick Seale, assistant professor of cell and developmental biology in the Institute for Diabetes, Obesity and Metabolism at the **University of Pennsylvania School of Medicine**.

Simply increasing COX-2 activity in adipose tissue may not be the ideal approach, because that could lead to side effects, especially increased inflammation, Seale told *SciBX*.

COX-2 is the target of a class of NSAIDs that includes Celebrex celecoxib from **Pfizer Inc.** Another COX-2 inhibitor, Vioxx rofecoxib from **Merck & Co. Inc.**, was withdrawn from the market in 2004 because of concerns over increased risk of cardiovascular events associated with long-term use.

As possible alternatives to directly boosting COX-2 levels, Seale sug-

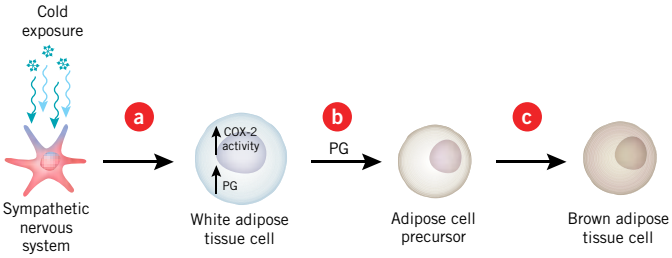

Figure 1. Getting slimmer with brown fat. Research published in *Science* by a German team suggests that activating a cyclooxygenase-2 (COX-2)-mediated pathway in adipose tissue could trigger formation of lipid-burning brown adipose tissue (BAT) and induce weight loss to treat obesity.

Unlike white adipose tissue (WAT), which stores lipids and thus can give rise to obesity, BAT is specialized for burning lipids to generate heat during cold exposure.

In response to a stress condition such as cold [**a**], the sympathetic nervous system releases hormones that act on WAT to upregulate the activity of COX-2, which in turn triggers an increase in prostaglandin (PG) levels within WAT [**b**]. Prostaglandins then induce surrounding adipose precursor cells to develop into BAT [**c**]. The resulting increase in lipid-burning BAT could lead to weight loss.

gested "systemic delivery of a highly specific prostaglandin or a synthetic analog" that would induce less of an inflammatory response.

Once the mechanism is better worked out, Herzig said, he would like to generate BAT *ex vivo* and use the tissue for transplantation studies, first in obese mice and eventually perhaps in obese patients.

The animal models used in the *Science* paper are patented, according to Herzig. He did not disclose the licensing status of the patents.

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COMPANIES AND INSTIUTIONS MENTIONED

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Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
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