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Turning the white fat brown

a new approach to obesity?

Laura Dean, MD[1]

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When temperatures fall, adults can shiver to keep warm. Babies, however, are born without the ability to shiver, and with their larger head-to-body ratio, they lose heat faster than adults do. But they have protection from the cold in the form of brown adipose tissue (BAT), otherwise known as brown fat. Unlike white fat, brown fat generates heat, and it covers the backs of infants, creating a warm shawl.

Whereas white fat cells store extra calories in the form of large fat droplets that in excess make us obese, brown fat cells contain smaller fat droplets that metabolize glucose and fat instead of storing it. Their cells have a high density of mitochondria, which contain iron that give the tissue a reddish brown color, and unique to mitochondria in BAT, they also contain an uncoupling protein 1 (UCP1, also known as thermogenin).

The oxidative phosphorylation that takes place in all mitochondria generates a proton gradient across the mitochondrial membrane that results in the production of energy in the form of ATP. But in the presence of UCP1, the proton gradient is reduced—protons that were pumped out into the intermembrane space are able to return to the mitochondrial matrix, resulting in less ATP production, and the energy from substrate oxidation is converted to heat, accounting for the thermogenic properties of BAT (1).

About 5% of the total mass of an infant is made up of brown fat, and until recently it was thought that stores of brown fat disappeared by adulthood. However, in 2009, it was found that adults still have small, but physiologically significant, reserves of brown fat in their shoulders and neck (2-4). The amount of brown fat varies—older people have less brown fat than younger people, and often no brown fat is detectable in obese people—the amount of BAT inversely correlates with body mass index.

In mice, two types of brown fat have been identified—constitutive (present from birth) and recruitable ("browning" of white fat can occur when levels of brown fat are insufficient to maintain body temperature) (5). Brown fat has been found to protect mice against obesity when they are overfed, and mice with more brown fat are leaner and healthier (5).

Several key genes have been identified as driving the production of brown fat in humans. Brown fat cells are thought to arise from myoblast precursor cells through the action of two proteins, PRDM16 and C/EBP-beta (6). Together, these proteins form a transcriptional complex, and through inducing peroxisome proliferator-activated receptor (PPAR)-gamma expression, this complex has the power to switch the lineage of specific precursor cells to brown fat cells. However, in order to do so, PRDM16 has to interact with the enzyme euchromatic histone-lysine N-methyltransferase 1 (EHMT1) (7).

EHMT1 is essential in determining the fate of brown fat cells. While EHTM1 was originally identified as a histone methyltransferase, it also has non-histone targets. It appears that EHMT1 functions as the "engine" of the

Author Affiliation: 1 NCBI; Email: dean@ncbi.nlm.nih.gov.

PRDM16-C/EBP-b transcriptional complex, and without this engine, the PRDM16 complex can not drive precursor cells to brown adipocytes. The characteristics of brown fat cells are lost and cells are induced to differentiate in to muscle cells (7).

Looking at the loss of the "brown fat switching gene", *EHMT1*, in humans

Studies of *Ehmt1*^{adipo} knockout mice, in which the mouse *EHMT1* gene has been specifically deleted from brown adipocyte precursor cells only (a whole body knock out of *Ehmt1* is lethal), found the knockout mice gained more weight than normal mice, even though they ate identical diets. The knockout mice also showed higher blood glucose levels, greater insulin resistance, and increased amounts of fat in their liver—all characteristic traits of diabetes and other metabolic diseases (7).

And in patients with Kleefstra syndrome, in which a microdeletion at 9q34.3 results in the deletion of the *EHMT1* gene along with approximately 20 other genes, about 40-50% of the patients are obese. This is likely to be the first example in which the loss or alteration of a human gene has effected the development of brown fat and resulted in obesity (8, 9).

Future studies of *EHMT1* will investigate whether this gene could be a drug target—activation of *EHTM1* and increasing brown fat production could potentially be a new type of treatment for obesity. Current medicines for obesity are limited to either suppressing appetite or inhibiting intestinal fat absorption, but the treatment results and side effects mean for many, a new approach to obesity treatment cannot come quickly enough.

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