A new candidate pathway for treating visceral obesity

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Brown seems to be the color of choice when it comes to the types of fat cells in our bodies. Brown fat expends energy, while its counterpart, white fat stores it. The danger in white fat cells, along with the increased risk for diabetes and heart disease it poses, seems especially linked to visceral fat. Visceral fat is the build-up of fat around the organs in the belly.

So in the battle against obesity, brown fat appears to be our friend and white fat our foe.

Now a team of researchers led by Jorge Plutzky, MD, director of The Vascular Disease Prevention Program at Brigham and Women's Hospital (BWH) and Harvard Medical School has discovered a way to turn foe to friend.

By manipulating the metabolic pathways in the body responsible for converting vitamin A—or retinol—into retinoic acid, Plutzky and his colleagues have essentially made white fat take on characteristics of brown fat. Their findings put medical science a step closer in the race to develop novel anti-obesity therapies.

The study is published online on May 6, 2012 in *Nature Medicine*.

Retinoids, which are molecules derived from vitamin A metabolism, are responsible for many biological functions. One such function is the control of fat cell development and actions. A key step in retinoid

metabolism occurs with help from an enzyme called retinaldehyde dehydrogenase 1, or Aldh1a1. The researchers saw that in humans and mice, Aldh1a1 is abundant in white fat cells, especially in the more dangerous visceral fat (sometimes referred to as abdominal fat or belly fat).

When Aldh1a1 was inhibited in white fat cells, those cells began acting like brown fat cells. One of the defining characteristics of brown fat is its ability to release energy as heat. Mice with either deficiency or inhibition of Aldh1a1 become protected against exposure to cold. The researchers saw this classic indicator of brown fat and its ability to generate heat by oxidizing fat (a chemical reaction involving oxygen) in their research.

Especially exciting for the prospects of targeting Aldh1a1 for therapeutic benefit, the researchers found that knocking down expression of the Aldh1a1 gene by injecting antisense molecules into mice made fat by diet resulted in less visceral fat, less weight gain, lower glucose levels, and protection against cold exposure as compared to control mice.

"Brown fat, and mechanisms that might allow white fat to take on brown fat characteristics, has been receiving increasing attention as a possible way to treat obesity and its complications," said Plutzky. "Although more work is needed, we can add specific aspects of retinoid metabolism to those factors that appear involved in determining white versus brown fat."

According to the Centers for Disease Control and Prevention, one-third of adults in the United States are obese. Current methods to reduce obesity include exercise, dietary therapy, medications and surgery.

Provided by Brigham and Women's Hospital