Knowing how brown fat cells develop may help fight obesity

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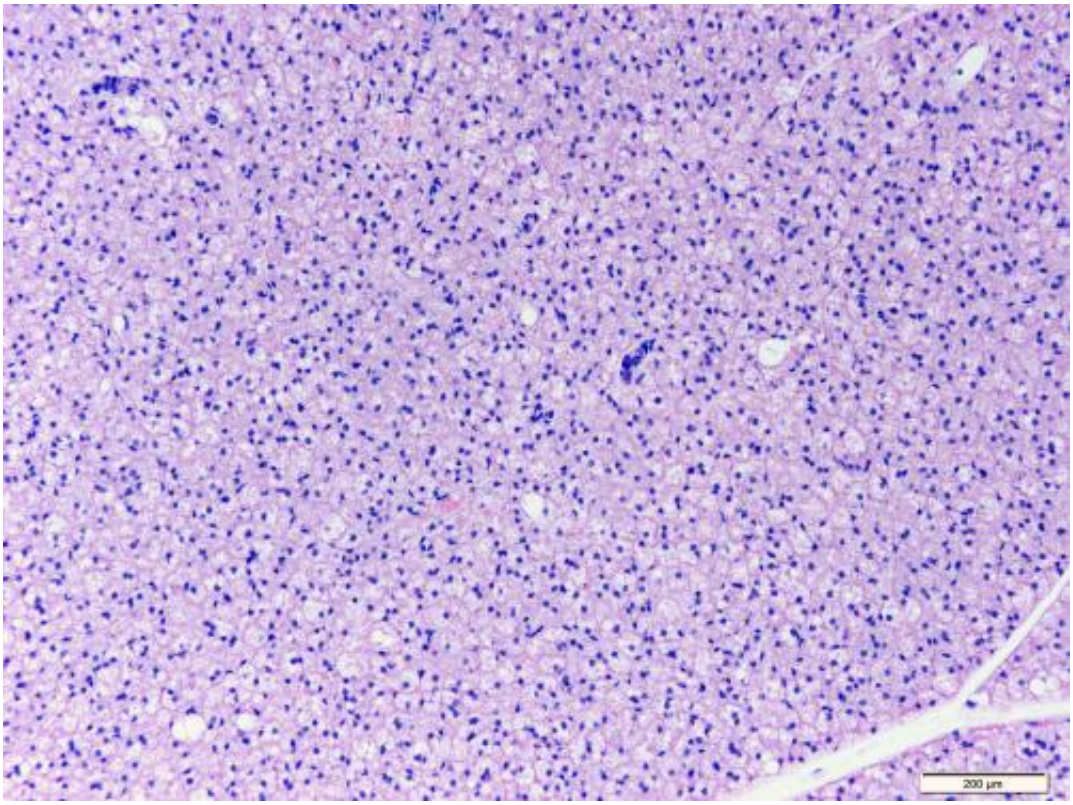

This shows isolated interscapular brown fat tissue fixed and stained by hematoxylin and eosin. Hematoxylin stains DNA in the nucleus purple. The pinkish eosin stain is mitochondria (along with other cytoplasmic proteins), stained stronger in brown fat Credit: Sona Rajakumari and Jeff Ishibashi, Perelman School of Medicine, University of Pennsylvania

Brown fat is a hot topic, pardon the pun. Brown fats cells, as opposed to

white fat cells, make heat for the body, and are thought to have evolved to help mammals cope with the cold. But, their role in generating warmth might also be applied to coping with obesity and diabetes.

The lab of Patrick Seale, PhD, at the Perelman School of Medicine, University of Pennsylvania, studies what proteins guide the development, differentiation, and function of fat cells. Seale and postdoctoral fellow Sona Rajakumari, PhD, along with Jun Wu from the Dana-Farber Cancer Institute, found that a protein switch called early B cell factor-2 (Ebf2) determines which developmental path fat precursor cells take – the brown vs. white cell trajectory.

"Brown fat cells are the professional heat-producing cells of the body," says Seale. Because of this they are protective against obesity as well as diabetes. Seale is an assistant professor of Cell and Developmental Biology and a member of the Institute for Diabetes, Obesity and Metabolism. The investigators published their findings this week in *Cell Metabolism*.

The team showed that Ebf2 regulates the binding activity of PPAR-gamma, a protein that regulates differentiation of developing cell types and is the target of anti-diabetic drugs. Ebf2 affects PPAR-gamma's ability to determine if precursor cells go down the white or brown fat cell path. The team surmises that Ebf2 may alter epigenetic proteins at brown fat genes to expose PPAR-gamma binding sites.

Brown fat cells are thought to counteract obesity by burning off excess energy stored in lipid, but white fat cells store energy. Indeed, brown fat cells contain many smaller droplets of lipids and the most mitochondria (containing pigmented cytochromes that bind iron)of any cell type, which make them brown. Rajakumari conducted a genome-wide study of PPAR-gamma binding regions in white versus brown fat cells. She found that brown cell-specific binding sites also contained a DNA-

recognition site for Ebf2 transcription factors and that Ebf2 was strongly expressed in brown fat cells only. When she overexpressed Ebf2 in precursor white fat cells they matured into brown fat cells. The brown fat cell status of the reprogrammed white fat cells was confirmed in that they consumed greater amounts of oxygen (a surrogate measure of heat production), had a greater number of mitochondria, and had an increased expression of genes involved in heat production, all characteristics of normal brown fat cells.

Rajakumari also looked at whether Ebf2 was required for brown fat cell development in animals by studying mice in which Ebf2 had been knocked out. Brown fat cells are typically located on the back, along the upper half of the spine and toward the shoulders. In contrast, excess abdominal concentrations of white fat cells are associated with metabolic dysfunction, insulin resistance, and heart disease.

She found that in late-stage embryos of these knockouts, white fat cells took the place of where brown fat cell reserves were in normal mice, indicating that stem cells differentiate into white fat in the absence of Ebf2.

Over the past few years, PET scan studies on glucose uptake by different tissues suggested that the amount of brown fat cells in people is inversely correlated with body mass index and age. This suggested that brown fat cells might play an unappreciated role in human metabolism. What's more, researchers started to suggest that "turning on" brown fat could be a new way to fight obesity and burn the extra stored lipids in white fat cells.

Ebf2 is the earliest known protein in the timeline of the development and differentiation of brown fat cells. "Many times the earlier in the developmental stage that a guiding protein is active, the more powerful it is in driving a certain process of differentiation," notes Seale. "Ebf2 is

not really a readily druggable target, but perhaps a protein related to it is." Because Ebf2 is a transcription factor, it doesn't have a clear binding pocket, but the researchers propose that it might be possible to pharmacologically block or stimulate the interaction of Ebf2 with a partner protein.

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