Reducing liver protein SIRT1 levels

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A new study led by Boston University School of Medicine (BUSM) demonstrates that the abnormal metabolism linked to obesity could be regulated in part by the interaction of two metabolic regulators, called the NAD-dependent deacetylase SIRT1 and fibroblast growth factor 21 (FGF21). Using experimental models, the researchers found that a lack of SIRT1 protein in the liver led to lower levels of a liver secreted protein FGF21, which resulted in an increased likelihood of developing fatty liver disease and obesity.

When levels of FGF21 in the liver of experimental models were elevated, some of the white fat cells became some of brown fat cells, producing more heat and burned calories. White fat stores energy as large fat droplets, while brown fat has much smaller fat droplets and is specialized to burn them, yielding heat. In humans, there is evidence that more brown fat is associated with a lower body weight. Finding a way to turn white fat into brown fat could potentially lead to a decrease in obesity and other metabolic diseases.

This study, which is published in *Gastroenterology*, was led by Mengwei Zang, MD, PhD, and her team in the department of medicine at BUSM.

In previous experiments, Zang's laboratory showed that elevated liver SIRT1 protein limited the development of fatty liver in experimental models when the diet was high in fat. However, the mechanism was not known. To determine how this happens, Zang laboratory used a unique mouse model that did not have liver SIRT1 protein, which resulted in an elevation in hepatic fat levels, an increase in body weight, and a decrease in nighttime oxygen consumption. It also led to decreased levels of liver FGF21, which were associated with abnormal fat metabolic changes in liver and adipose tissues.

However, when levels of liver and serum FGF21 were elevated, some white fat cells changed and became brown fat cells, which could increase whole-body oxygen consumption and produce more heat. These changes in the fat cells caused by elevated FGF21 protein could help explain how the experimental mice experienced more weight loss, had less fat mass and slowed the progression of fatty liver.

"Excess abdominal white fat in humans promotes heart disease, diabetes and other metabolic diseases, and it would be potentially therapeutic if we could transform white fat into brown fat by elevating FGF21 levels," said Zang, the study's corresponding author.

Provided by Boston University Medical Center