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When food intake stops, enzyme turns off production of fats, cholesterol

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Massachusetts General Hospital (MGH) investigators have found that an enzyme with several important roles in energy metabolism also helps to turn off the body's generation of fats and cholesterol under conditions of fasting. The report in *Genes & Development* describes how SIRT1, one of a group of enzymes called sirtuins, suppresses the activity of a family of proteins called SREBPs, which control the body's synthesis and handling of fats and cholesterol. The findings could lead to new approaches to treating conditions involving elevated cholesterol and lipid levels.

"SIRT1 had previously been shown to act as an energy sensor, promoting the use of stored fat in response to food deprivation; however, its function in shutting down fat and cholesterol synthesis was unknown," says Amy Walker, PhD, of the MGH Cancer Center, the study's lead author. "These findings point to SIRT1 as a master regulator of physiologic energy stability that controls the synthesis and storage of fat, as well as its usage as fuel."

Under normal conditions, the body produces appropriate levels of fats and cholesterol, both of which are essential to life. A high-fat diet can cause abnormal elevations in fat and cholesterol levels in the blood, which may lead to cardiovascular disease, type 2 diabetes, hypertension and other serious disorders. If the body is deprived of food for a short time, it shuts down the production and storage of fat and cholesterol and shifts to using stored fats as the primary source of energy. Fasting also is known to turn off the activity of SREBP proteins, and the research team

investigated whether direct suppression of SREBPs by SIRT1 was responsible for the metabolic shift.

A series of experiments in worms, fruitflies and mice showed that the versions of SIRT1 present in those animals suppressed SREBP activity and the associated synthesis and storage of fats. They also showed in mouse and human cells that SIRT1 acts on SREBP by removing a protective molecule, marking the protein for degradation, and that inhibiting SIRT1 activity caused levels of SREBP to rise. Treating genetically obese mice fed a high-fat diet with an agent that increases sirtuin activity suppressed the expression of SREBP-regulated fat synthesis genes and also reduced the amount of fat stored in the animals livers.

"This study is significant because it explains the signals that tell the body to burn fat in response to fasting or dieting," says David Sinclair, PhD, a professor of Pathology at Harvard Medical School (HMS) who helped discover the genes that code for sirtuins but was not involved with this MGH-led study. "This improved understanding could help treat and prevent metabolic diseases such as atherosclerosis and type 2 diabetes."

Sirtuins have also been associated with the increased longevity in response to reduced calorie intake observed in several species of animals. Drugs that stimulate sirtuin activity are currently being investigated for treatment of diabetes and related conditions.

"Sirtuin activators could strengthen SIRT1 functions that may be suppressed in individuals with cardiometabolic disorders," explains Anders Näär, PhD, of the MGH Center for Cancer Research, senior author of the current study. "Our results suggest these agents may be able to 'trick' the body into responding as though it was experiencing fasting, with beneficial metabolic consequences, but that hypothesis needs to be tested in future studies." Näär is an associate professor of Cell Biology

and Walker is an instructor in Medicine at HMS.

Provided by Massachusetts General Hospital