# 'Fatostatin' is a turnoff for fat genes

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A small molecule earlier found to have both anti-fat and anti-cancer abilities works as a literal turnoff for fat-making genes, according to a new report in the August 28th issue of the journal *Chemistry and Biology,* a Cell Press journal.

The chemical blocks a well known master controller of fat synthesis, a transcription factor known as SREBP. That action in mice that are genetically prone to obesity causes the animals to become leaner. It also lowers the amount of fat in their livers, along with their blood sugar and cholesterol levels.

"We are frankly very excited about it," said Salih Wakil of Baylor College of Medicine. "It goes to the origin of [fat synthesis] - all the way back to gene expression."

Unlike cholesterol-lowering statins in use today, which block a single enzyme in the pathway, the chemical, which the researchers call fatostatin, "hits fat from the very beginning," added Motonari Uesugi, who is now at Kyoto University.

In doing so, fatostatin influences many of the genes involved in fat production and in various aspects of metabolic syndrome - a collection of risk factors including obesity, high cholesterol and insulin resistance - in one go.

Studies in cell culture showed that fatostatin, previously known only as 125B11, significantly lowers the activity of 63 genes, including 34

directly associated with fatty acid or cholesterol synthesis. Many of those were known to be under the control of SREBP.

More detailed analysis reveals that the drug candidate blocks SREBP by preventing it from becoming active and entering the nucleus, where it would otherwise switch on the fat-making program. It operates by binding another protein (called SCAP), which serves as SREBP's escort into the nucleus.

Obese mice injected with fatostatin show noticeable reductions in their weight despite little difference in their eating habits, the researchers report. After four weeks of treatment, the animals weighed 12 percent less and had 70 percent lower blood sugar levels. Their cholesterol levels (both LDL and HDL) were down too. The concentration of fatty acids in their blood was actually higher, a sign of their greater demand for fat to burn.

While the livers of the obese mice were heavy and pale with fat, treated animals' livers were more than 30 percent lighter and were a healthy-looking red.

Although less obvious, the SREBP-blocking ability might also explain the molecule's earlier reported effects against prostate cancer cells in culture as well. Cells need fatty acids and cholesterol to build their cell membranes and continue growing, they explain.

Fatostatin is not the first molecule to act on SREBP, according to the researchers, but it appears to do so in a somewhat different way than those described previously. Many steps remain, but they are optimistic that fatostatin could prove to be clinically useful in the context of obesity, and perhaps cardiovascular disease and diabetes as well.

"Hopefully down the road, fatostatin or a derivative of fatostatin may be

helpful," said Wakil, who has been studying the enzymes involved in fat synthesis ever since he discovered them in the late 1950s. "It could have a broad impact on the key diseases we all suffer from."

Fatostatin or its analogs may also serve a tool for gaining further insights into the regulation of SREBP and fat metabolism, Uesugi said.

Source: Cell Press (news : web)