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Researchers identify liver pathway linked to negative impacts of high-fat, high-cholesterol diet

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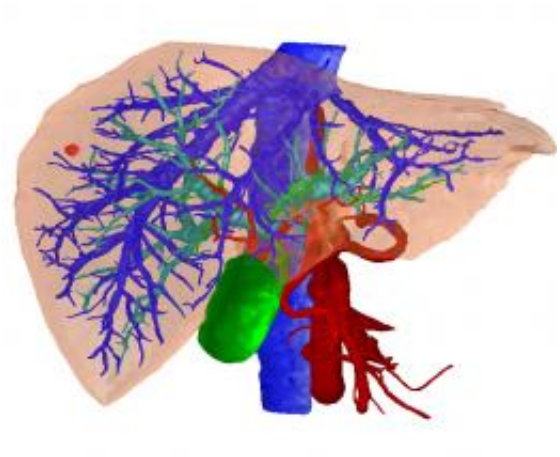

3D-illustration of a human liver with blood vessels (red and blue) and bile duct (green) Source: Prof. Dr. Hans-Peter Meinzer, Deutsches Krebsforschungszentrum

It's no secret that a high-fat, high-cholesterol "junk food" diet has been linked to major health problems, including high blood cholesterol and the buildup of plaques in the arteries, known as atherosclerosis.

Research led by the University of Michigan Life Sciences Institute has identified a pathway in the liver, controlled by a protein known as BAF60a, that contributes to these negative effects by stimulating the production of bile—which helps the body to absorb more cholesterol and

other fats from the foods we eat.

Mice genetically engineered to have livers lacking BAF60a had cholesterol levels about 40 percent lower than normal mice when both were fed a junk food diet, according to findings scheduled for online publication Nov.12 in *Cell Reports*.

"From a basic science perspective, we are continuing to learn about how several variants of BAF60 play different important roles in metabolic regulation in diverse cell types—fat, muscle, liver," said study senior author Jiandie Lin, a faculty member at the LSI, where his lab is located. "And this latest research uncovers a new pathway in the liver that may point the way toward new therapeutic approaches to lowering cholesterol and reducing the risk of atherosclerosis."

The mice were fed a specially formulated diet high in fat and sugar to simulate a bad "Western diet." About 40 percent of calories came from fat and another 40 percent from sugar.

From an evolutionary perspective, it makes sense that our ancestors' bodies would want to kick into high gear to take full advantage of a rare source of fat, said Zhuo-Xian Meng, the study's lead author and a research investigator in Lin's lab.

"But now the environment has changed, fatty foods are everywhere and this adaptive response becomes maladaptive," Meng said.

It's long been known that eating high-cholesterol foods stimulates the production of bile, but the specifics of how the body regulates liver bile production and the absorption of fats in the intestines are not fully understood.

BAF60a is one cog in complex biological machinery linking signals

resulting from the intake of food and nutrients to genetic programs directing the regulation of the body's metabolism.

In a series of experiments, the researchers worked to understand why removing BAF60a from the liver—though not from other tissues—led to the lower cholesterol levels in the mice on the Super Size Me-style diet.

"We needed to figure out why this was happening," said Lin, who is also an associate professor of cell and developmental biology at the U-M Medical School.

Did BAF60a affect liver's ability to make its own cholesterol? Did it affect the uptake of cholesterol by the liver? No, both of these factors were very similar in both the normal mice and the genetically altered mice, the researchers found.

"When we did microarray studies and examined thousands of genes in these two different sets of mice, one of the most striking set of genes that were affected in the knockout mouse liver were the genes related to bile acid synthesis," Lin said.

Bile is made in the liver and eventually released into the intestines, where it helps the body absorb fats. The researchers tested their hypothesis using cholesterol tagged with a radioactive marker, finding that the genetically altered mice absorbed dietary cholesterol at a much slower rate than their counterparts; they also excreted more cholesterol in their feces.

Another experiment showed that deactivating BAF60a in the livers of mice used to model atherosclerosis was able to partially protect them from the disease, lowering cholesterol levels by 30 percent and significantly reducing the formation of lesions.

As part of a research program investigating the underpinnings of obesity and metabolic disorders, the Lin lab has also been examining how the family of BAF60 proteins operates in muscle and fat cells.

"The activity and the level of these factors are fine-tuned in response to different metabolic cues," Lin said. "So we feel that this is part of a broader sensing mechanism—cells sense the environment, cells sense the metabolic state. Then, by either increasing or dialing down the amount of these proteins available in the cells, the body is able to adjust the metabolic activity and function of a particular tissue or organ."

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