Getting to the root of fatty liver disease

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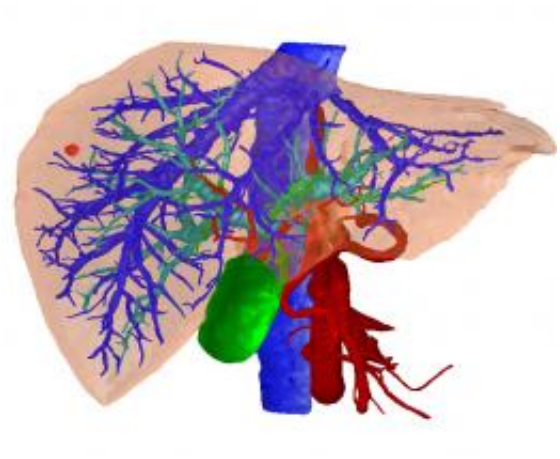

3D-illustration of a human liver with blood vessels (red and blue) and bile duct (green) Source: Prof. Dr. Hans-Peter Meinzer, Deutsches Krebsforschungszentrum

Researchers have identified a molecular switch that appears to be a common feature in the development of fatty liver disease. The discovery made in mice is consistent with data from human patients, suggesting that it may provide an underlying explanation for the development of fatty liver in people with obesity and metabolic syndrome.

The culprit is the reduced concentration of a little-known transcriptional co-factor known as transducin beta-like (TBL) 1, according to the report in the April issue of Cell Metabolism.

"We haven't entirely solved it yet, but we've seen that a lower abundance

of TBL1 is common to multiple mouse models," said Stephan Herzig of DKFZ-ZMBH Alliance in Germany. "Most importantly, in human livers, the more fat there is the lower this transcriptional co-factor."

The new finding is part of a larger effort by the research team to uncover a series of molecular switches with important functions in metabolism. "These molecular switches turn other genes or genetic programs on or off," he explained.

In the new study, Herzig's team went in search of components of that regulatory machinery that might be important in the case of fatty liver disease, a condition that is tightly associated with several components of metabolic syndrome, including diabetes and heart disease.

"Fatty liver may be one reason for the further development of insulin resistance," Herzig said. "It appears to contribute to some of the long-term complications and is an independent risk factor for cardiovascular complications."

The researchers looked to mice with fatty liver disease of various genetic or dietary causes. In every case, those mice also showed impaired activity of TBL1 in the liver. When the researchers disabled TBL1 in the livers of healthy mice, they too went on to show high triglycerides and the buildup of fat in the liver.

In human patients, TBL1 levels were also inversely related to the amount of fat in an individual's liver. In other words, as TBL1 levels go down, it appears that liver fat levels go up.

The new findings are the first to connect TBL1 to a biological function in any tissue, Herzig said. He doesn't yet know what causes TBL1 levels to decline. It may be that the transcriptional co-factor responds directly to signals delivered via fatty acids.

Their studies in mice did uncover something intriguing. The development of fatty liver following deactivation of TBL1 actually led to apparent improvements in blood sugar levels and insulin sensitivity in the mice. That's despite the fact that fatty liver in animals and humans usually is found along with insulin resistance.

In fact, Herzig says, there have been other recent studies suggesting that the storage of fat in the liver might help to protect other tissues. "If you store fat in the liver, it might prevent fat overload in other places," he said.

That may not be good in the long run, he says, but fat buildup in the liver can, to some degree, be reversed without long-term damage to that organ. Perhaps the ill consequences often associated with fatty liver disease depend on a "second hit," such as inflammation.

The changes observed in other parts of the body following the researchers' manipulations of the liver also highlight the fascinating complexity of our metabolisms.

"A change in one organ can influence other organs," Herzig said. "It's not good enough to focus on organs one at a time. To understand the entire system, we will have to understand how organs communicate with one another."

More information: Hepatic deficiency in transcriptional co-factor TBL1 promotes liver steatosis and hypertriglyceridemia. Cell Metabolism, 2011, DOI: 10.1016/j.cmet.2011.02.011

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