Gene mutation is linked to accumulation of fat, other lipids in liver

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A team of scientists from the University of Utah and the University of California at San Francisco has discovered that the mutation of a gene encoding a ketone body transporter triggers accumulation of fat and other lipids in the livers of zebrafish. This discovery, published in the Feb. 1, 2012, issue of *Genes & Development*, reveals that transport of ketone bodies out of the liver is a critical step in energy metabolism during fasting. It also provides a new approach for studying the development of fatty liver disease in humans.

Nonalcoholic fatty liver disease (NAFLD), or abnormally high accumulation of lipids in the liver, is the most common cause of chronic liver disease worldwide. Lipids are a broad group of molecules that include fats, triglycerides, and cholesterol. In some people, NAFLD causes no complications, but in others, excess fat in the liver can lead to inflammation or development of scar tissue, resulting in permanent liver damage or even liver failure. NAFLD may also increase the risk of heart disease in people who are overweight or obese. The increasing prevalence of NAFLD in the United States is due, in large part, to the obesity epidemic and it is estimated that more than 6 million U.S. children already have fatty liver disease.

"Currently, there are a limited number of treatment options for decreasing excess fat in the liver and there are no methods for reversing damage to liver tissue due to NAFLD," says Amnon Schlegel, M.D., Ph.D., investigator in the University of Utah Molecular Medicine program, assistant professor of internal medicine at the University of

Utah School of Medicine, and senior author on the study. "By identifying and characterizing novel genes that regulate accumulation of lipids in the liver, we may be able to gain new insight into the physiological processes that lead to NAFLD."

Previous research has shown that many of the proteins known to control lipid metabolism in humans are also present in zebrafish. Schlegel and his colleagues began by identifying a zebrafish mutant known as red moon (rmn), which developed abnormal lipid accumulation in liver cells, without evidence of associated liver inflammation or liver damage, when exposed to fasting conditions. Schlegel and his colleagues then used a molecular genetic technique called positional cloning to isolate the gene disrupted by the rmn mutation. They found that the rmn mutation inactivated slc16a6a, a gene thought to encode a protein required in the transport of nutrients during fasting.

"Until now, the activity of the Slc16a6a protein has not been functionally characterized in any organism," says Schlegel, who's also an adjunct assistant professor of biochemistry at the U medical school. "Our studies indicate that Slc16a6a is a protein involved in the transport of β-hydroxybutyrate."

β-hydroxybutyrate is a ketone body, a compound that is produced in the liver when blood glucose is low and fatty acids are broken down for energy. During periods of fasting, most body tissues can use fatty acids as an energy source, but the brain relies on β-hydroxybutyrate and other ketone bodies for fuel. Schlegel and his colleagues discovered that, in rmn mutants deprived of nutrition, loss of Slc16a6a function disabled secretion of ketone bodies from liver cells and increased lipid accumulation in the liver. They also found that introducing the human form of the SLC16A6 protein into rmn mutant livers restored ketone body secretion.

"Our research has uncovered a previously unrecognized, but critical step, in the complicated physiology of fasting," says Schlegel. "We still don't know whether altered fasting liver metabolism influences the development of NAFLD, but knowing that Slc16a6a is required for secretion of ketone bodies from liver cells during fasting may have implications for our understanding and treatment of other medical conditions where ketone bodies play a role. These include uncontrolled type 1 diabetes, obesity, and childhood metabolic disorders caused by defects in fatty acid metabolism."

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