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Study identifies liver gene that regulates cholesterol and fat blood levels

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Researchers have identified a microRNA liver gene, miR-27b, which regulates lipid (cholesterol or fat) levels in the blood. This regulator gene controls multiple genes involved in dyslipidemia—abnormal blood cholesterol levels that can contribute to heart disease. Study details published in the February issue of *Hepatology*, a journal of the American Association for the Study of Liver Diseases (AASLD), describe a new in silico approach to identify the significance of microRNAs in regulating disease-related gene pathways.

The Human Genome Project (HGP) was completed in April, 2003 and the world had a map of the 3 billion DNA letters making up the human genome. One of the HGP leaders was Dr. Francis Collins, currently NIH Director and contributor to the present study. "The HGP provided the basic instruction book for human biology," explains Dr. Collins. "Further genomic studies, such as the investigation of microRNAs, have built upon the efforts of the HGP to explain how the genome carries out its functions, and helps identify genes involved in the development of disease."

For the present study, lead author Dr. Kasey Vickers from the NIH/NHLBI Lipoprotein Metabolism Section (presently at Vanderbilt University School of Medicine) and colleagues performed high-throughput small RNA sequencing of mouse liver and detected roughly 150 microRNAs. The team used a novel in silico approach to identify microRNA regulatory hub genes involved in lipid metabolism. In human and mouse livers miR-27b was determined to be the strongest hub with

27 predicted targets.

"We found liver miR-27b levels to be sensitive to high triglycerides (hyperlipidemia) in the blood and liver," said Dr. Vickers. The team reported a nearly 3-fold increase in miR-27b levels in the liver of mice on a high-fat diet, with 42% of calories from fat. In human liver tissue cells, researchers determined that miR-27b regulates mRNA and protein expression of key lipid-metabolism genes (Angptl3 and Gpam). Vickers added, "Using a mouse model of dyslipidemia and atherosclerosis, we found hepatic miR-27b and its target genes to be inversely altered, and thus contributing to risk for cardiovascular disease."

The senior author of the study, Dr. Praveen Sethupathy from the University of North Carolina at Chapel Hill School of Medicine, leads an interdisciplinary laboratory that weaves together computational and experimental approaches to understand the role of microRNAs in complex metabolic diseases. "MicroRNAs are thought to impart stability to gene networks, particularly in the face of changes to the environment, such as diet," he says. "MicroRNAs represent promising therapeutic targets for a variety of metabolic diseases, but a lot more work remains to be done in order to fully appreciate how and when they function."

In a related editorial published in this month's issue of Hepatology, Dr. Carlos Fernández-Hernando from the New York University School of Medicine confirms the emergence of microRNAs in regulating cholesterol and fatty acid metabolism. He writes, "Altogether these data (by Vickers et al.) strongly suggest that miR-27b regulates lipid metabolism, but its role in regulating lipid levels in other cells, such as macrophages and neurons, remains unclear." Dr. Fernández-Hernando highlights the importance of the new in silico approach used by the researchers to identify microRNAs in regulating genes involved in the same bodily process, suggesting this method could be used to identify microRNAs in controlling genetic networks.

More information: "MicroRNA-27b is a Regulatory Hub in Lipid Metabolism and is Altered in Dyslipidemia." Kasey C. Vickers, Bassem M. Shoucri, Michael G. Levin, Han Wu, Daniel S. Pearson, David Osei-Hwedieh, Francis S. Collins, Alan T. Remaley and Praveen Sethupathy. *Hepatology*; (DOI: 10.1002/hep.25846); Print Issue Date: February, 2013.
URL: doi.wiley.com/10.1002/hep.25846

Editorial: "The Emerging Role of miRNAs in the Regulation of Lipid Metabolism." Carlos Fernández-Hernando. *Hepatology*; (DOI: 10.1002/hep.25960); Print Issue Date: February, 2013.
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