

Release

Wayne State scientists make key discovery in fatty liver disease

Research may impact prevention and treatment of metabolic disease

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DETROIT -- A research team at the Wayne State University School of Medicine has found an underlying link to non-alcoholic fatty liver disease (NAFLD), obesity and diabetes that nearly one-third of Americans carry in their systems.



About 100 million people – 30 percent to 40 percent of the population -- in the United States are estimated to have NAFLD, per the National Institute of Diabetes and Digestive and Kidney Diseases. Globally, NAFLD affects 15 percent to 40 percent of the general population, and is intrinsically linked to metabolic disorders such as obesity, type 2 diabetes, atherosclerosis, and liver cancer.

“However, currently no effective medicine to treat patients with NAFLD is available. There are knowledge gaps in understanding the molecular basis by which chronic stress causes lipid buildup in the liver. There is a critical need to identify molecular mechanisms driving NAFLD under chronic stress conditions,” said principal investigator and Professor Kezhong Zhang, Ph.D., of WSU’s Center for Molecular Medicine and Genetics and the Department of Biochemistry, Microbiology and Immunology.

Zhang and team made a key discovery in a stress-induced small RNA decay pathway in non-alcoholic fatty liver disease that could significantly impact the understanding, prevention, and treatment of cardiovascular and metabolic diseases.

NAFLD – closely associated with human obesity, type-2 diabetes, and atherosclerosis – is the buildup of extra fat in liver cells, not caused by alcohol. Chronic stress conditions, such as high-fat diets, air pollution and irregular circadian rhythm related to shift workers or abnormal life style, are major causes of NAFLD, he said.

The group discovered a novel stress-triggered small RNA (or microRNA) degradation pathway in the liver, and revealed how this stress signal pathway is critically involved in the progression of NAFLD under the high-fat diet. The related discoveries were published in the top-tier journal *Science Signaling*: <http://stke.sciencemag.org/content/11/530/eaao4617> (<http://stke.sciencemag.org/content/11/530/eaao4617>).

“Our findings have direct impact on understanding the fundamental process by which cell stress modulates microRNA profile and subsequent gene expression landscape associated with metabolic disease,” Zhang said. “The newly-identified stress-triggered microRNA decay pathway in metabolism will have profound impact on many areas of biomedical research.”

Zhang, the senior author of the research article, has long studied mechanisms and impact of stress responses in health and disease. His team also revealed that high-fat diets can repress the cell stress sensor protein IRE1 α , which functions as an enzyme called RNase to cut stress-inducible microRNAs. The select microRNAs, once cleaved by IRE1 α , will be degraded before going through the regular biosynthesis and maturation process. The new pathway, named "IRE1 α -dependent microRNA decay," decreased the abundance of lipid metabolism enzymes, leading to lipid buildup in the liver.

The scientists showed that IRE1 α -dependent microRNA decay pathway was impaired in the livers of both mice fed a high-fat diet and human NAFLD patients. The cell stress sensor IRE1 α regulates a subset of microRNA families that are functionally involved in lipid metabolism and inflammation in the liver. The regulatory signals originated from IRE1 α are further amplified with a spectrum of the microRNA targets. These findings reveal a novel target -- IRE1 α -- to explore for treating nonalcoholic steatohepatitis, the advanced stage of NAFLD, and associated metabolic disorders.

"One stress sensor protein (IRE1 α) dictates a network of lipid metabolism enzymes through modulating microRNAs in the liver. Therefore, IRE1 α represents an ideal target for controlling lipid metabolism associated with the development of metabolic disease, such as obesity, type-2 diabetes and fatty liver disease." Zhang said. "Indeed, we have been working on several non-toxic small molecules that can either suppress or activate IRE1 α in the liver. Our work provides an effective avenue to modulating lipid metabolism for potential therapeutic benefit for NAFLD."

Wayne State University researchers Jiemei Wang, Yining Qiu, Zhao Yang, Hyunbae Kim and Chunbin Zhang contributed to the work. Other collaborators included scientists from University of Iowa, Sanford Burnham Prebys Discovery Institute of San Diego, University of Ulsan of Korea, Northwestern University, University of Michigan and The Ohio State University.

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About Wayne State University School of Medicine

Founded 150 years ago (<https://www.youtube.com/watch?v=ylozvQQRJcA>), the Wayne State University School of Medicine educates more than 1,000 medical students annually in Midtown Detroit. In addition to undergraduate medical education, the school offers master's degree, Ph.D. and M.D./Ph.D. programs in 14 areas of basic science to about 400 students annually.

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