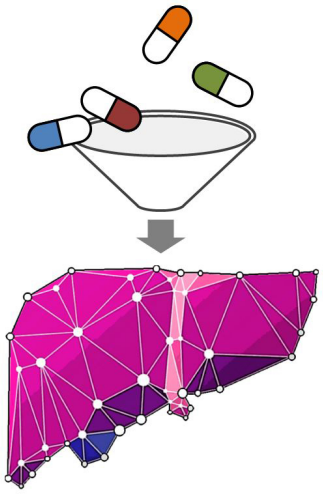
New treatment for fatty liver disease and type 2 diabetes burns up fat in liver

2 March 2017



Researchers found that the liver has the ability to burn up accumulated fats. They are now planning clinical tests of a mixture of substances that will set this process in motion. Credit: KTH Royal Institute of Technology

Researchers in Sweden are planning the clinical trial of a new treatment for nonalcoholic fatty liver disease and type 2 diabetes which harnesses liver cells' own ability to burn accumulated fats.

In a study involving 86 people with varying degrees of fatty liver disease, researchers from KTH Royal Institute of Technology's Science for Life Laboratory (SciLifeLab) research center and Gothenburg University found that the liver has the ability to burn up accumulated fats. The researchers propose a mixture of substances that will set this process in motion.

One of the most common chronic liver problems in the world, the accumulation of fat in the liver – or hepatic steatosis – is the key characteristic of non-alcoholic fatty liver disease (NAFLD). It is linked to obesity, insulin resistance, type 2 diabetes and cardiovascular diseases. Up to 30 percent of subjects with NAFLD develop non-alcoholic steatohepatitis (NASH) in which hepatic inflammation and scarring can lead to cirrhosis and liver cancer.

The researchers mapped the metabolic changes caused by accumulated fat in 86 patients' liver cells, and combined this data with an analysis of a genome-scale model of liver tissue. Doing so enabled them to identify the precise metabolic changes individual patients' liver cells undergo due to fat.

The results were published in *Molecular Systems Biology*.

Lead author Adil Mardinoglu, a systems biologist at KTH and SciLifeLab fellow, is one of the researchers who had earlier established a connection between NAFLD and low levels of the antioxidant, glutathione (GSH). A proof of concept test showed that accumulated liver was burned off by treating human subjects with a "cocktail" that increases oxidation of fat and synthesis of the antioxidants.

Mardinoglu says the team's metabolic modeling approach, which relied on data from Swedish-based Human Protein Atlas effort, can be used for a number of chronic liver diseases.

Based on the results from the study, an improved intervention using a portfolio of substances has been designed. "This mixture can potentially decrease the amount of the fat accumulated in the liver," Mardinoglu says. "There is no such drug available at present and we are planning for further clinical trials later this year."

The approach combines systems biology and clinical medicine in a manner not previously done. "The results are exciting, and we have now designed a mixture of substances that will boost the oxidation of fat and generate antioxidants in the

liver tissue," says senior co-author Jan Borén from University of Gothenburg.

The researchers believe that the mixture of substances could also be used to treat accumulated liver fat due to alcoholic fatty liver disease and type 2 diabetes. "Considering NAFLD and diabetes are common conditions that regularly co-exist and can act synergistically to drive adverse outcomes, such a mixture of substances might also be used in the treatment of subjects with diabetes," says co-author, Ulf Smith of University of Gothenburg.

Mathias Uhlén, director of the Human Protein Atlas project and co-author of the paper, says: "I am extremely pleased that the resource created through the Human Protein Atlas effort has been used in the analysis of clinical data obtained from NAFLD patients and that this analysis has led to the design of a mixture of substances that can be used for treatment of this clinically important patient group.

More information: Personal model-assisted identification of NAD+ and glutathione metabolism as intervention target in NAFLD, *Molecular Systems Biology*, DOI: 10.15252/msb.20167422

Provided by KTH Royal Institute of Technology