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Big data studies scrutinize links between fatty liver disease and how cells make energy

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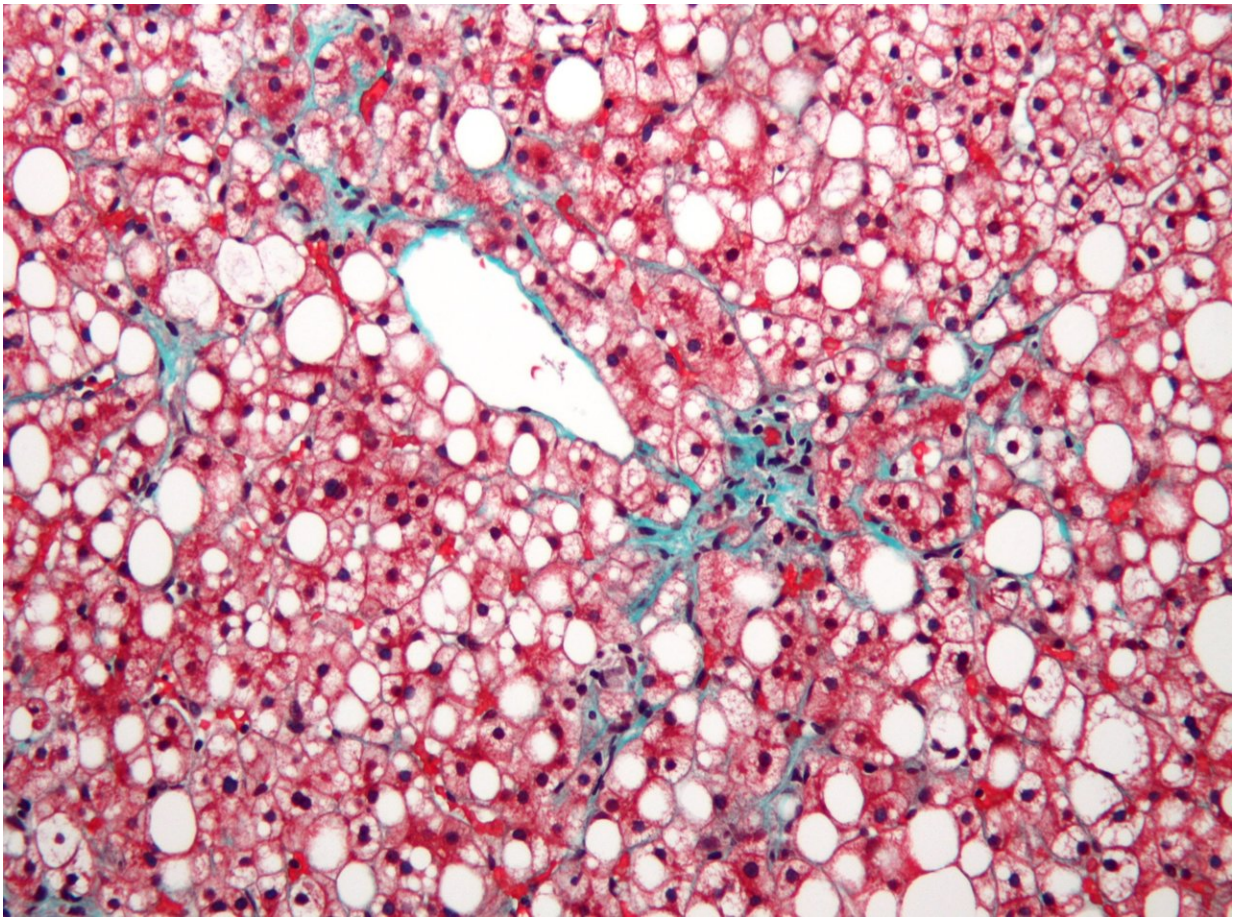

Recent high-throughput studies of lipids and proteins in liver mitochondria from patients and mice with nonalcoholic steatohepatosis (NASH) or its precursor, nonalcoholic fatty liver disease (NAFLD), investigate how mitochondrial energy production stutters and fails in the course of disease. This micrograph shows a liver biopsy with fatty accumulations (white) and the beginnings of scarring (green) that characterize NAFLD. Credit: Wikimedia user Nephron

Nonalcoholic fatty liver disease affects up to 40 percent of American adults. Though the condition produces no noticeable symptoms, one out of every five people with it will go on to develop a more serious condition called NASH (short for nonalcoholic steatohepatosis).

The inflammation caused by NASH can result in scarring, commonly referred to as cirrhosis, and even cancer or organ failure. With those consequences in mind, researchers are trying to learn all they can about nonalcoholic fatty liver and how it progresses to NASH.

One avenue of investigation involves mitochondria—the organelles in the cell that produce energy in the form of ATP. Researchers have known for some time that mitochondrial dysfunction has something to do with the onset and progression of nonalcoholic fatty liver. Three recent studies, described below, offer additional information on this front.

The first two studies illuminate how mitochondrial energy production stutters and fails as fatty liver disease progresses. The third describes how changes to the liver during disease progression affect the organ's use of nutrients to produce energy.

Mitochondrial proteins take a hit in a mouse model of fatty liver

Researchers at Northeast Ohio Medical University studied the lifespan of mitochondrial proteins in a mouse model of fatty liver disease. Comparing the amount of protein between healthy mice and a mouse model of nonalcoholic fatty liver disease gave them an estimate of each protein's half-life.

Their findings, published in the journal *Molecular & Cellular Proteomics*, show that many proteins involved in mitochondrial function, especially those directly involved in making ATP, are broken down more quickly than usual in a fatty liver. Not only does this reduce the number of proteins, but the remaining proteins are also less active.

The insult to ATP producing proteins damaged the mitochondria. In an apparent effort to get rid of dysfunctional mitochondria, cells from fatty livers showed more evidence of digesting their mitochondria, but did not increase production of new ones. As a result, the authors observed mitochondrial and ATP shortages in the cells of mice with fatty liver.

The authors proposed that because the overloaded liver cells used fatty acids instead of glucose to make energy, they may have created more reactive oxygen byproducts, which damaged proteins.

Lipid changes in diseased liver may indicate overworked cells

Scientists know that nonalcoholic fatty livers are abnormally full of triglycerides. They need to find out more, though, about changes in other lipids.

In a study in the *Journal of Lipid Research*, researchers from Australia and the Netherlands report what they learned about such changes by using lipidomics to analyze liver biopsies from obese patients with normal livers, fatty ones, and full-blown NASH.

Some of the changes were predictable. For example, the researchers saw an increase in triglycerides and an increase in acylcarnitine, a molecule that shuttles fatty acids to liver mitochondria so that the organelles can make energy. This ties in to the switch to fatty acid metabolism that

other teams have also observed.

The team also found significant changes over the course of disease in several lipid types without obvious connections to fatty liver. Two of those lipids have been linked to mitochondrial energy production. The researchers found that both lipids are elevated in the early stages of fatty liver and stay high as the disease progresses. The researchers think the level of both lipids may increase because mitochondria are working harder to deal with the excess energy from having lots of triglycerides around.

However, mitochondrial overwork can be risky. For example, one of the two lipids, cardiolipin, is vulnerable to a chemical reaction called peroxidation with reactive oxygen byproducts of energy production. Cardiolipin peroxidation can lead to mitochondrial dysfunction.

More detailed study will be needed to determine whether, as the authors hypothesize, mitochondrial overwork contributes to mitochondrial failure and liver disease progression.

Liver cells opt to build lipids, not glucose, in patients with fatty liver

One of the liver's most important roles is to regulate the level of glucose in the blood, supplying energy to other tissues. When the blood supply of glucose is low, liver cells make more available by converting other molecules to glucose. When glucose is plentiful, cells in the liver convert the sugar to other types of molecules or break it down and store the energy as ATP.

In an open-access paper in the September issue of the *Journal of Lipid Research*, scientists at the University of Texas Southwestern Medical

Center studied liver cell metabolism in obese individuals with either normal or fatty livers.

When a person who has been fasting drinks a dose of glycerol in water, their liver cells have a choice to make about the resource. Do they convert the molecule into a quick hit of glucose for energy; use it for longer-term energy storage as a fat molecule; or build nucleotides and amino acids? By analyzing patients' plasma over time after they drank labeled glycerol, the researchers could track how cells used the labeled molecules.

Patients with fatty liver tended to use the glycerol to generate fat molecules more quickly than patients with normal livers and were slower to use it for making new glucose. There was no difference between the groups in a metabolic pathway that contributes to building other types of molecules. Whether these changes in using an incoming energy source affect the progression of fatty liver disease remains to be seen.

More information: Kwangwon Lee et al. Hepatic mitochondrial defects in a mouse model of NAFLD are associated with increased degradation of oxidative phosphorylation subunits., *Molecular & Cellular Proteomics* (2018). DOI: 10.1074/mcp.RA118.000961

Kang-Yu Peng et al. Mitochondrial dysfunction-related lipid changes occur in non-alcoholic fatty liver disease progression, *Journal of Lipid Research* (2018). DOI: 10.1194/jlr.M085613

Eunsook S. Jin et al. Fatty liver disrupts glycerol metabolism in gluconeogenic and lipogenic pathways in humans, *Journal of Lipid Research* (2018). DOI: 10.1194/jlr.M086405