Lipid species offer insights into metabolic health

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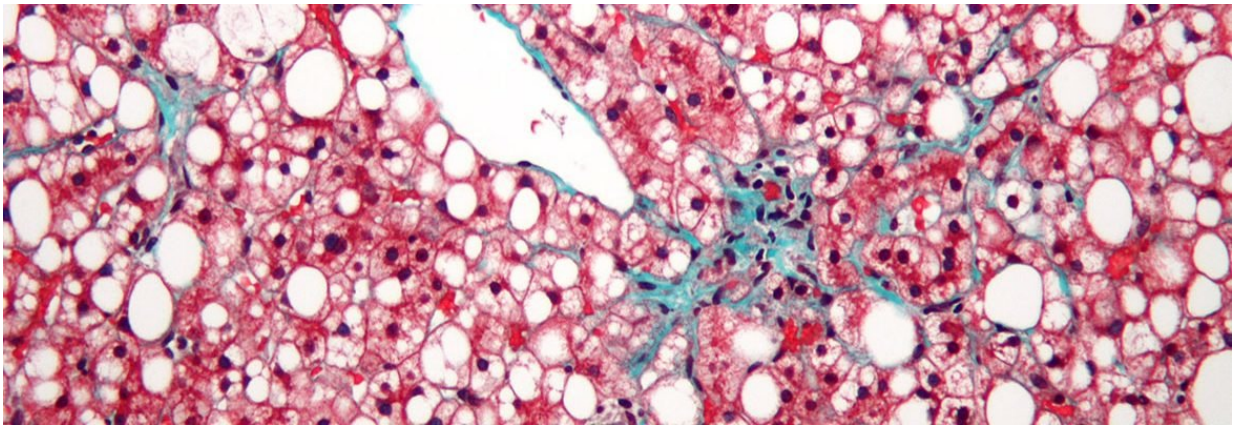

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Heart disease is the number one killer in the United States, and high triglyceride levels in the blood are cited as just one of several risk factors. Millions of lipid panels, blood tests that look at cholesterol levels as well as triglycerides, are performed in clinics each year.

Two new Morgridge Institute for Research studies suggest the current tests, which measure the abundance of lipid classes, are insufficient. Rather, lipids identified and studied at the individual species level—instead of grouped in classes—may be better signatures of metabolic health.

The results were published online June 13, 2018, in *Cell Systems* as open access papers, one focusing on plasma lipid species and the second on liver lipid species.

Lipids, or fats, are incredibly important to human health, yet one of the hardest biomolecules to study. Harnessing advances in mass spectrometry technology, Morgridge scientists measured almost 150 lipid species in the blood and liver of mice and identified some that can act as signatures of healthy or unhealthy metabolic states.

For patients getting a lipid panel—something the American Heart Association suggests for everyone over the age of 20—results will include a reference to triglyceride levels. These tests look at triglycerides in bulk, as a group, and measure how much is in the blood.

But Molly McDevitt, a graduate student in Dave Pagliarini's Lab at Morgridge and co-first author on the papers, says looking at individual species of triglycerides provides a much more accurate picture.

"We don't even know how many different triglycerides there are—hundreds, thousands," says McDevitt. "We found that some triglycerides correlate positively with a fatty liver, while others correlate negatively with a fatty liver. Lumping all triglycerides into one class masks these subtler associations."

In this study, the scientists identified seven triglyceride species in the blood that associated with either healthy or fatty liver.

Non-alcoholic fatty liver disease (NAFLD)—a disease in which the liver gets fat and cells start dying, eventually leading to organ failure—was a focus in this work, though the results also impact other diseases related to lipid metabolism like diabetes, obesity and metabolic syndrome.

The work was co-led by Johan Auwerx's team from EPFL in Switzerland, and Morgridge affiliate and University of Wisconsin-Madison professor Josh Coon contributed expertise in mass spectrometry to the studies.

Identifying biomarkers for disease

One of the questions posed across the two papers: does measuring the lipids in plasma (a simple blood test) tell you something about what's happening in an organ? Often, in order to identify a fatty liver, an invasive liver biopsy is required. Taking a blood sample would be a much simpler way to diagnose it.

The studies are still in the early stages, but the results look promising.

"As we move from measuring a bulk lipid class in serum to specific lipids, we're finding that some do indeed predict what's happening in the liver," says Dave Pagliarini, director of the Morgridge Metabolism Theme. "That gives us confidence that we might be able to discover biomarkers in plasma that report on what's happening in organ metabolism."

Using multi-omics approaches to further discovery

By combining lipids data with other biomedical datasets, an approach known as multi-omics, the scientists were able to identify and prioritize sets of genes they know are causing the changes in lipid levels.

"We might find a location on the DNA that contains 400 genes, and it would be really hard to follow up on all of those," McDevitt says. "By using the different layers of the multi-omic approach, like the phenotypes and the gene expression levels, it helps us narrow down that

list to something much easier to handle."

Future work will investigate regions of the genome the team found linked to the various lipids. The goal is to identify the genes responsible for lipid changes and uncover the mechanisms of how they do what they do.

"This is really a jumping-off point," Pagliarini says. "These large-scale studies now provide us and others in the community the opportunity to prioritize these genes for new mechanistic insights."

More information: Pooja Jha et al, Genetic Regulation of Plasma Lipid Species and Their Association with Metabolic Phenotypes, *Cell Systems* (2018). DOI: 10.1016/j.cels.2018.05.009

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