New research establishes how and why diets high in sugar and fat cause liver disease

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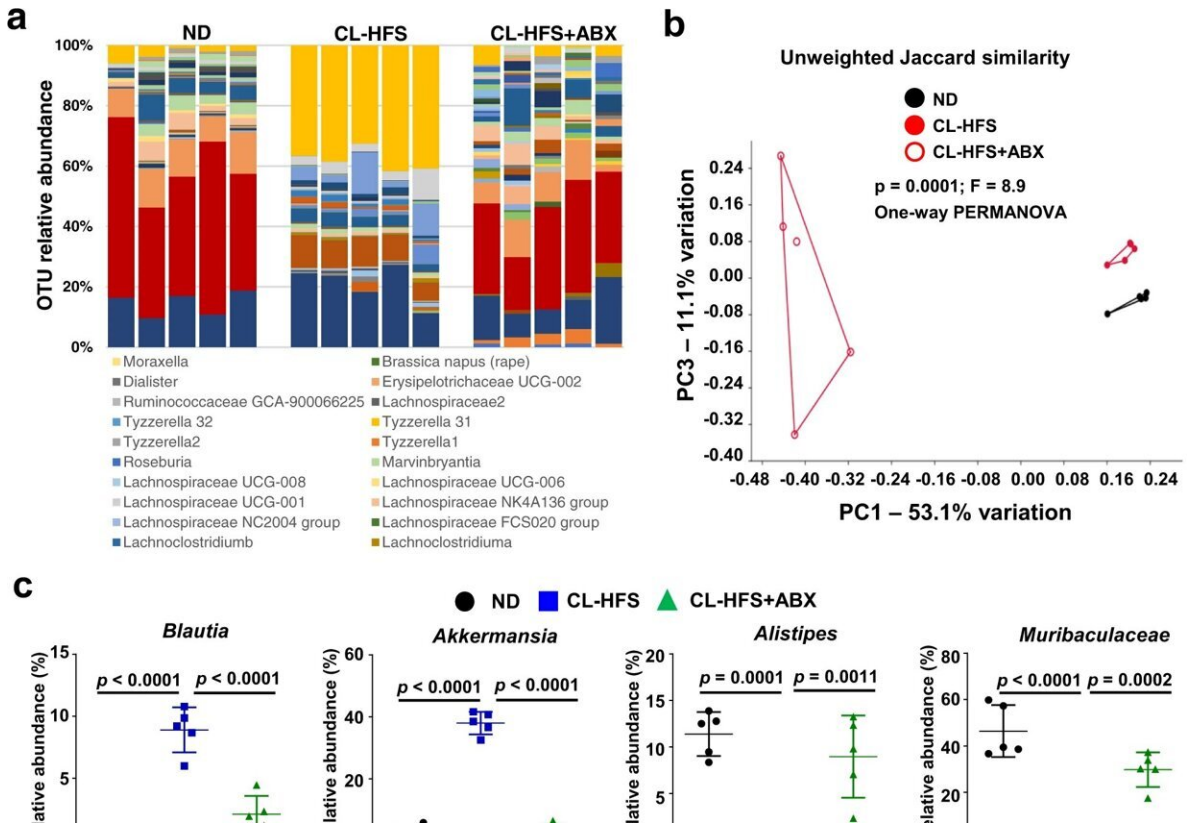

ABX treatment alters the profiles of gut microbiota and hepatic metabolites. Fecal and liver samples were collected from Fig. 2 mice, which were fed with ND or CL-HFS in the absence or presence of ABX for 12 weeks. **a** Effect of ABX on the relative abundance of operational taxonomic unit (OUT) in CL-HFS-fed mice. 16 S rRNA gene sequencing of fecal samples identified the profiles of gut microbiota in three groups of mice. **b** ABX treatment changed gut microbiota similarity. PERMANOVA significance test was performed with Principal-coordinate analysis (PCA) to define the Jaccard similarity index. **c**

ABX induced a significant alteration in representative bacterial species. ABX treatment significantly reduced the relative abundance of *Blautia* and *Akkermansia* and increased the relative abundance of *Alistipes* and *Muribaculaceae* in the fecal samples of CL-HFS-fed mice. $n = 5$, data are presented as mean ± SD. **d** ABX changed the hepatic metabolite profile. Hepatic metabolites in three groups of mice were analyzed by non-targeted Gas chromatography-mass spectrometry (GC-MS). Heatmap showed Z-scores of 5 metabolites in 30 liver tissues from 10 ND-fed mice, 10 CL-HFS-fed mice, and 10 CL-HFS-fed mice with ABX treatment. ABX treatment markedly reduced the following metabolite production in CL-HFS-fed mice, L-Phenylalanine (Phe), Pyroglutamic acid (PCA), 2-Oleoylglycerol (2-OG), Cysteine (Cys), and L-Valine (Val). $n = 10$, data are presented as mean ± SD. Statistical analysis of data was performed by one-way ANOVA with Tukey's multiple comparison test using GraphPad Prism 8 software. Source data are provided as a Source Data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-35861-1

New research from the University of Missouri School of Medicine has established a link between western diets high in fat and sugar and the development of non-alcoholic fatty liver disease, the leading cause of chronic liver disease.

The research, based in the Roy Blunt NextGen Precision Health Building at MU, has identified the western diet-induced microbial and metabolic contributors to liver disease, advancing our understanding of the gut-liver axis, and in turn the development of dietary and microbial interventions for this global health threat.

"We're just beginning to understand how food and gut microbiota interact to produce metabolites that contribute to the development of liver disease," said co-principal investigator, Guangfu Li, Ph.D., DVM, associate professor in the department of surgery and Department of Molecular Microbiology and Immunology. "However, the specific

bacteria and metabolites, as well as the underlying mechanisms were not well understood until now. This research is unlocking the how and why."

The gut and liver have a close anatomical and functional connection via the portal vein. Unhealthy diets change the gut microbiota, resulting in the production of pathogenic factors that impact the liver. By feeding mice foods high in fat and sugar, the research team discovered that the mice developed a gut bacteria called Blautia producta and a lipid that caused liver inflammation and fibrosis. That, in turn, caused the mice to develop non-alcoholic steatohepatitis or fatty liver disease, with similar features to the human disease.

"Fatty liver disease is a global health epidemic," said Kevin Staveley-O'Carroll, MD, Ph.D., professor in the department of surgery, one of the lead researchers. "Not only is it becoming the leading cause of liver cancer and cirrhosis, but many patients I see with other cancers have fatty liver disease and don't even know it. Often, this makes it impossible for them to undergo potentially curative surgery for their other cancers."

As part of this study, the researchers tested treating the mice with an antibiotic cocktail administered via drinking water. They found that the antibiotic treatment reduced liver inflammation and lipid accumulation, resulting in a reduction in fatty liver disease. These results suggest that antibiotic-induced changes in the gut microbiota can suppress inflammatory responses and liver fibrosis.

Li, Staveley-O'Carroll and fellow co-principal investigator R. Scott Rector, Ph.D., Director of NextGen Precision Health Building and Interim Senior Associate Dean for Research—are part of NextGen Precision Health, an initiative to expand collaboration in personalized health care and the translation of interdisciplinary research for the benefit of society.

The study, "Western diet contributes to the pathogenesis of non-alcoholic steatohepatitis in male mice via remodeling gut microbiota and increasing production of 2-oleoylglycerol" was recently published in *Nature Communications*. The authors declare that they have no conflicts of interest related to the study.

More information: Ming Yang et al, Western diet contributes to the pathogenesis of non-alcoholic steatohepatitis in male mice via remodeling gut microbiota and increasing production of 2-oleoylglycerol, *Nature Communications* (2023). DOI: 10.1038/s41467-023-35861-1

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