Researchers investigate the multi-omic landscape of steatosis-to-NASH progression in mice

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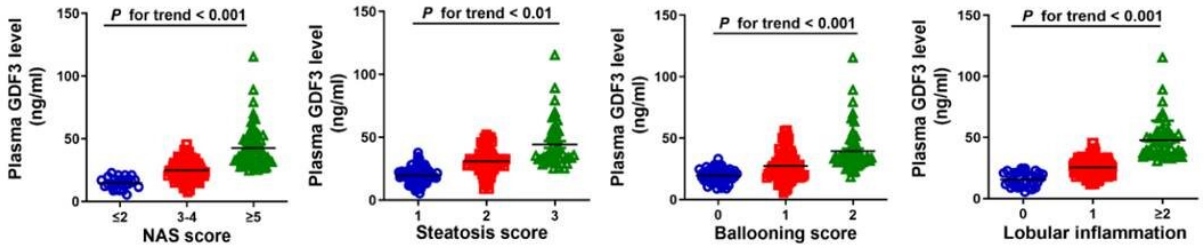

Plasma GDF3 levels are significantly associated with histologic features in patients with NASH. Credit: *Life Metabolism* (2022). DOI: 10.1093/lifemeta/loac034

The global prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated to be > 25% and will continue to rise. NAFLD comprises a spectrum of liver disorders ranging from simple steatosis (NAFL) to nonalcoholic steatohepatitis (NASH). While NAFL is generally considered to be a benign condition, NASH is prone to develop into severe end-stage liver diseases. However, the molecular mechanisms of steatosis-to-NASH progression remain poorly understood.

Using two models of diet-induced NAFL and NASH mice, researchers from Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong

University School of Medicine and the First Affiliated Hospital of Anhui Medical University and other collaborators have worked together to present comprehensive multi-omic profiles to identify genes, non-coding RNAs, proteins, and plasma metabolites involved in steatosis-to-NASH progression. This study entitled "A multi-omic landscape of steatosis-to-NASH progression" is published in *Life Metabolism*.

In this study, using two periods of HFHC diet-feeding, the authors performed a large-scale integrative analysis of liver tissues from NAFL and NASH mice with their age-matched normal controls. Overall, the multi-omics study captured 176 mRNAs, 1131 lncRNAs, 48 miRNAs, 295 proteins, and 53 plasma metabolites that are altered in NAFL mice compared to the age-matched normal mice.

Meanwhile, 1745 mRNAs, 5161 lncRNAs, 146 miRNAs, 674 proteins, and 82 plasma metabolites were altered in NASH mice compared to the age-matched normal mice. Through comparisons of these alterations in two mouse models, a total of 1630 mRNAs, 4547 lncRNAs, 110 miRNAs, 500 proteins, and 46 plasma metabolites were specifically altered in NASH mice compared to NAFL mice. Thus, this study provides a valuable resource to explore the molecular mechanisms of steatosis-to-NASH progression.

In addition, through transcriptomic analysis, the authors found that growth differentiation factor (GDF3) was specifically up-regulated in the livers and plasma of NASH mice. In agreement, plasma GDF3 concentrations were markedly increased in patients with NASH compared to patients with NAFL or healthy individuals. Plasma GDF3 levels were strongly associated with the NAFLD activity score (NAS) and individual histologic features, including steatosis, ballooning, and lobular inflammation.

The authors further evaluated the diagnostic potential of circulating

GDF3, which demonstrated that it could be a non-invasive diagnostic biomarker for NASH patients with high accuracy (AUROC = 0.90).

Collectively, this study explored the molecular characterization of steatosis-to-NASH progression in mice through a large-scale system biology approach, which may provide a valuable resource for exploring the molecular mechanisms of NASH progression. Moreover, GDF3 might be considered as a potential non-invasive diagnostic for NASH patients, although further studies are required for explore its role in NASH progression.

More information: Liping Xiang et al, A multi-omic landscape of steatosis-to-NASH progression, *Life Metabolism* (2022). DOI: 10.1093/lifemeta/loac034

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