Deficiency of chromatin regulator DPF2 disrupts hepatic bile acid homeostasis and exacerbates liver injury and fibrosis in MASH

Yumei Zhou[1], Yubo Wang[1], Junxiao Ren[1], Miguel A. Gutierrez-Monreal[2], Annie Cheng[1], Jessica E Meerson[1], Mostafa F Abdelhai[1], Zhiyong Cheng[3,4,5], Karyn A. Esser[2], Bishuang Cai[6], Peng Zhao[7], Feng Yue[1,2,4,5*]

[1]Department of Animal Sciences, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, FL 32611, USA
[2]Department of Physiology and Aging, College of Medicine, University of Florida, Gainesville, FL 32610, USA
[3]Department of Food Science and Human Nutrition, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, FL 32611, USA
[4]Nutritional Science Doctoral Program, Center for Nutritional Science, University of Florida, Gainesville, FL 32611, USA.
[5]Center for Integrative Cardiovascular and Metabolic Diseases, University of Florida, Gainesville, FL 32610, USA
[6]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA
[7]Department of Biochemistry & Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease characterized by hepatocellular injury, chronic inflammation, and fibrosis, with increased risks of cirrhosis, hepatocellular carcinoma, and cardiovascular disease. Metabolic dysfunction and transcriptional reprogramming in hepatocytes are key drivers of MASH progression, yet the chromatin regulators that maintain hepatocyte metabolic homeostasis remain poorly defined. Here, we identify Double PHD Fingers 2 (DPF2), a histone reader within the canonical BRG1/BRM-associated factor (cBAF) chromatin remodeling complex, as a previously unrecognized epigenetic regulator of hepatic metabolism and MASH progression. Analysis of human liver single-nucleus RNA-seq data reveal reduced hepatocyte DPF2 expression in fibrotic liver, while hepatic expression of long isoform DPF2 (DPF2-L) is decreased during diet-induced MASH in mice. Using Albumin-Cre-mediated *Dpf2* knockout ($Dpf2^{HKO}$) mice, we found that DPF2 deficiency induces spontaneous hepatic steatosis and liver injury under chow-fed conditions. Following 20 weeks of Gubra-Amylin NASH (GAN) diet feeding, $Dpf2^{HKO}$ mice exhibit markedly exacerbated liver injury, fibrosis. Transcriptomic analyses reveal broad suppression of pathways governing bile acid synthesis, transport, detoxification, and signaling in $Dpf2^{HKO}$ liver, including reduced expression of *Nr1h4* (FXR). Consistent with these transcriptional changes, hepatic and circulating bile acid levels are elevated in $Dpf2^{HKO}$ mice after both 4 and 20 weeks of GAN diet feeding. These findings identify DPF2 as an important epigenetic regulator of hepatic bile acid homeostasis and suggest that disruption of the FXR-centered bile acid regulatory network contributes to liver injury and fibrosis following DPF2 loss. Our study establishes a framework for defining how chromatin-dependent control of hepatocyte metabolism influences MASH progression and identifies DPF2-associated chromatin regulation as a potential mechanistic link between bile acid dysregulation and progressive liver disease.