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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Curing Fatty Liver with Oxysterols?

Nonalcoholic fatty liver disease (NAFLD) affects a quarter of the global population and is one of the most common causes of liver transplantation in the United States.[1] NAFLD encompasses a spectrum of liver pathologies, including nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH). In addition to liver failure, alterations in hepatic lipid metabolism in NAFLD drive the development of atherogenesis and increases the risk of cardiovascular disease.[2,3] As such, identifying effective treatment modalities for NAFLD will not only improve liver function but are likely to be beneficial for cardiovascular outcomes as well.

Although the molecular pathogenesis of NAFLD remains incompletely understood, therapeutic targeting of hepatic lipid metabolism has become a popular strategy for its treatment. Bile acid signaling remains a priority given its important role as a nexus for cholesterol and lipid homeostasis. As such, several pharmaceutical companies are targeting bile acid metabolism for the potential treatment of NAFLD. For example, the bile acid activated Farnesoid X receptor (FXR) agonist, obeticholic acid, completed a phase 3 clinical trial, which demonstrated modest improvements in fibrosis in patients with NASH.[4] However, obeticholic acid did not gain Food and Drug Administration approval because of safety concerns and overall modest efficacy.[4] Despite this, there are several active late-stage clinical studies evaluating the effectiveness of either mono or combination therapies of FXR agonists for the treatment of NASH.

Cytochrome P-450 7A1 (CYP7A1) is a liver-specific enzyme that is critical for bile acid synthesis from cholesterol.[5] A homeostatic negative feedback loop exists to control bile acid production, because excess bile acids suppress CYP7A1 expression.[5] Disruption of cholesterol homeostasis is documented in NAFLD, suggesting cholesterol levels and its conversion to bile acids in the liver are key in the progression of NAFLD.[6,7] Cholesterol 25-Hydroxylase (Ch25h) is a key enzyme required in the synthesis of bile acids from cholesterol. Ch25h catalyzes the production of 25-hydroxycholesterol (25-HC), which acts as an endogenous ligand of the Liver X receptor (LXR). The activated LXR in turn promotes bile acid synthesis from cholesterol, in part, via CYP7A1. Thus, 25-HC and Ch25h may serve as therapeutic opportunity to promote cholesterol conversion to bile acids in the liver.[7]

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Dong et al[8] test the hypothesis that Ch25h and its product, 25-HC, are protective against fat accumulation in the murine liver. The authors show Ch25h expression is decreased under obesogenic conditions and whole-body *Ch25h* deficiency exacerbates hepatic steatosis in high-fat diet fed mice. Using RNA sequencing, expression of genes involved in bile acid synthesis, including CYP7A1, was reduced in Ch25h-deficient mice, correlating with elevated liver fat. Moreover, Dong et al[8] performed gain-of-function experiments to determine if Ch25h overexpression or daily administration of 25-HC is sufficient to prevent steatosis and inflammatory gene expression under high-fat diet fed conditions in mice. Strikingly, both Ch25h overexpression or administration of 25-HC led to improvements in fatty liver that correlated with upregulation of bile acid production.

Mechanistically, 25-HC is known to activate LXR, which in turn induces the expression of CYP7A1 to promote cholesterol conversion to bile acids.[9] Consistently, Dong et al[8] showed that treatment with 25-HC or overexpression of Ch25h increased the expression of CYP7A1. These findings are congruent with results from transgenic overexpression CYP7A1, which protected mice from diet-induced obesity.[10] Therefore, the efficacy of Ch25h and 25-HC in mice may be dependent on the LXR-CYP7A1 axis leading to the activation bile acid synthesis from cholesterol. Collectively, the present report supports a protective role of cholesterol conversion to 25-HC in NAFLD.

In addition to bile acid metabolism, the present study also revealed that very-low-density lipoprotein (VLDL) secretion was enhanced following Ch25h overexpression or administration of 25-HC.[8] Here, the authors documented an increase in the expression of ApoB100 in the VLDL serum fraction of 25-HC-treated mice, suggesting increased hepatic VLDL-triglyceride section. These beneficial effects of increased cholesterol conversion to bile acids and increased VLDL secretion are consistent with the higher free cholesterol/phosphatidylcholine ratio previously detected by a lipidomic analysis in NASH livers by Puri et al.[11] Collectively, these data indicate an involvement of an elevated free cholesterol/phosphatidylcholine ratio in the pathogenesis of NASH. Further experimentation is needed to elucidate the precise mechanisms underlying the beneficial effects of 25-HC administration on neutral lipid deposition, increased VLDL-triglyceride secretion, and bile acid production. As a result, future studies that evaluate the efficacy of Ch25h overexpression and 25-HC administration in fibrotic and inflammatory associated mouse models of NASH are warranted.

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