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Editorial

FXR deficiency and alcoholic liver disease: Tissue is the issue

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Alcoholic liver disease (ALD), one of major causes of liver disease with significant morbidity and mortality, represents a broad spectrum including steatosis, alcoholic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma [1]. In spite of the healthcare burden of ALD, the field remains under researched and there are no approved safe and effective therapies for this disease [2,3].

Identifying pathological mechanisms and therapeutic targets in animal models is crucial to develop new therapies and conduct clinical trials in humans. The current understanding in the

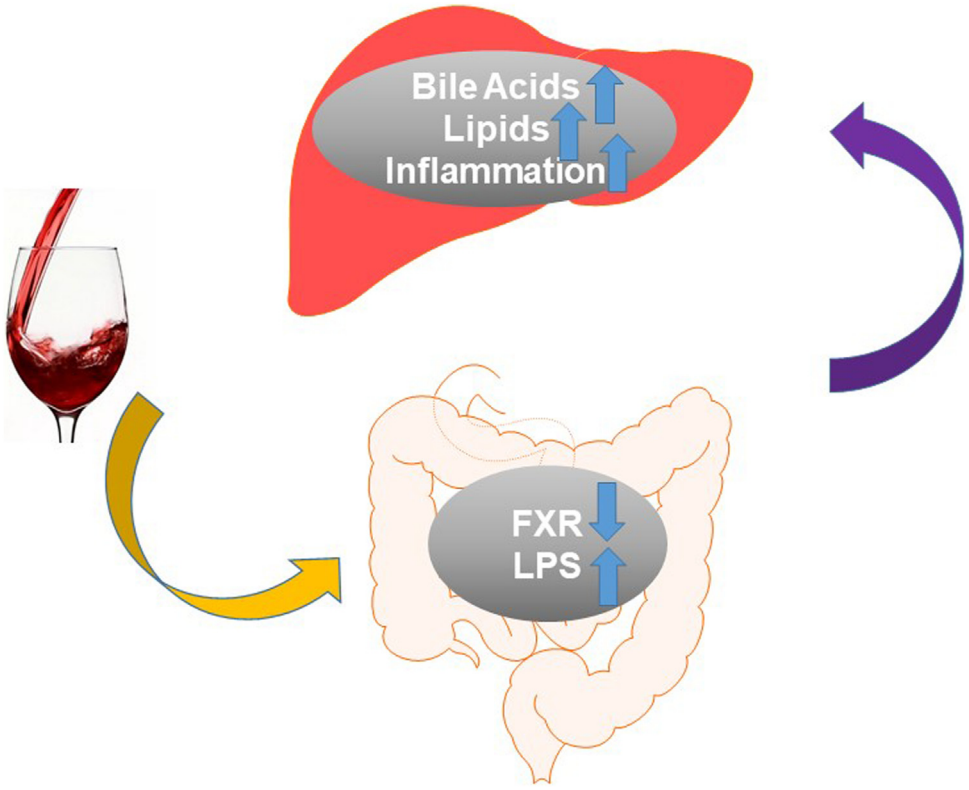

Fig. 1. Alcohol and farnesoid X receptor (FXR) signaling: alcohol consumption suppresses FXR activity and liver injury mediated by (a) increased bile acid and lipid pool and (b) lipopolysaccharide (LPS) translocation from the gut resulting in inflammatory signaling.

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pathogenesis of ALD incorporates changes in the gut microbiome with increased intestinal permeability leading to translocation of the bacterial lipopolysaccharide, inflammatory signaling with activation of the toll-like receptor-4 on the hepatic macrophages, oxidative stress which is multifactorial, hepatic stellate cell activation resulting in laying down of collagen and sinusoidal endothelial hemodynamic changes, and activation of hepatic regenerative pathways [1,3,4]. Recently, the role of bile acids (BAs) has been recognized in the pathogenesis of many liver diseases including ALD, as cell signaling molecules to activate farnesoid X receptor (FXR), one of the nuclear receptor superfamily of transcription factors [5,6]. FXR expressed widely in various tissues including liver, intestines, kidneys, and adrenals regulate BA synthesis, metabolism of lipids and glucose, inflammation, and fibrosis [5] (Fig. 1). It is known that alcohol consumption suppresses intestinal FXR (Fig. 1) and mediates ALD [7], however, the data are scanty on the tissue specific effects of the FXR and its role in the pathogenesis of ALD.

In the current issue, Kong et al. investigated the role of FXR in the extra hepatic tissues [8], as their previous study showed that hepatic FXR does not play a major role in mediating ALD [9]. Using the whole body FXR knock out mice (*FXR* $^{-/-}$), this elegant study confirmed the role of whole body FXR deficiency in causing ALD. Specifically, the study findings showed that *FXR* $^{-/-}$ mice developed liver injury compared to wild type mice after alcohol feeding, with hepatic steatosis and increased aminotransferases activities and BA levels. Imbalance between hepatic import and export of lipids in the *FXR* $^{-/-}$ mice led to steatosis and cell ballooning. Further, other markers for liver injury were elevated including Cd14 and Lcn2. Specifically, elevated Cd14, a lipopolysaccharide receptor regulating intracellular endocytosis of LPS [10], suggests gut inflammation and lipopolysaccharide translocation, and a potential role of intestinal FXR in causing the ALD. One important finding is elevated BA levels in FXR$^{-/-}$ except ursodeoxycholic acid, suggesting protective effect of ursodeoxycholic acid.

Overall, comprehensively designed experiments with novel and significant data are encouraging to the clinical translational researchers to continue exploring benefits of FXR agonist obeticholic acid in patients with ALD. In this regard, the results are eagerly awaited of a recently completed phase-2 clinical trial within the National Institute of Alcoholism and Alcohol Abuse consortium, which assessed the role of obeticholic acid in alcoholic hepatitis patients (*NCT02039219*). Another randomized clinical translational trial is in progress to examine the effect of obeticholic acid on the FXR signaling (*NCT02654236*). This study lays framework for studies using intestine FXR$^{-/-}$ mice to confirm tissue specific role of intestinal FXR in the pathogenesis of ALD, as basis for strengthening the gut-liver axis link and conduct clinical trials using the intestinal specific FXR agonists or FXR induced FGF-19 in the treatment of ALD.

Conflict of interest

None of the authors report any financial or any other type of conflicts of interest to disclose.

References

[1] Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011;141:1572–85.
[2] Shah VH. Alcoholic liver disease: the buzz may be gone, but the hangover remains. Hepatology 2010;51:1483–4.
[3] Singal AK, Kodali S, Vucovich LA, Darley-Usmar V, Schiano TD. Diagnosis and treatment of alcoholic hepatitis: a systematic review. Alcohol Clin Exp Res 2016;40:1390–402.
[4] Keshavarzian A, Holmes EW, Patel M, et al. Leaky gut in alcoholic cirrhosis: a possible mechanism for alcohol-induced liver damage. Am J Gastroenterol 1999;94:200–7.
[5] Malhi H, Camilleri M. Modulating bile acid pathways and TGR5 receptors for treating liver and GI diseases. Curr Opin Pharmacol 2017;37:80–6.
[6] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956–65.
[7] Hartmann S, Nusbaum DJ, Kim K, Alameh S, Ho CC, Cruz RL, et al. Role of a small molecule in the modulation of cell death signal transduction pathways. ACS Infect Dis 2018. Epub ahead of print.
[8] Kong B, Zhang M, Huang M, et al. FXR deficiency alters bile acid pool composition and exacerbates chronic alcohol induced liver injury. 2019 [in press].
[9] Zhang M, Kong B, Huang M, Wan R, Armstrong LE, Schumacher JD, et al. FXR deletion in hepatocytes does not affect the severity of alcoholic liver disease in mice. Dig Liver Dis 2018;50:1068–75.
[10] Zanoni I, Ostuni R, Marek LR, Barresi S, Barbalat R, Barton GM, et al. CD14 controls the LPS-induced endocytosis of Toll-like receptor 4. Cell 2011;147:868–80.

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