Digestive and Liver Disease 51 (2019) 1164–1165

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Editorial

Sphingosine lipid signaling in alcoholic liver injury☆,☆☆

Alcoholic liver disease (ALD) is one of the most common liver diseases worldwide yet there are currently no effective pharmacologic treatment options available [1]. More importantly, liver transplantation remains the only definitive treatment for end-stage liver failure [2]. The clinical manifestations of ALD exist as a spectrum of mild to severe disease ranging from simple steatosis to alcoholic hepatitis and cirrhosis [3]. The pathophysiology of ALD remains poorly understood, but is believed to be a combination of various stressors such as oxidative and ER stress, inflammation and a disruption of the gut-liver barrier [4,5]. The difficulty in developing viable treatment options for ALD lies in part in its pathologic complexity and a lack of an effective mouse model that can recapitulate the full spectrum of human disease. This is especially true for advanced stages of ALD where there are currently no reliable mouse models that can consistently reproduce alcohol-induced liver fibrosis.

Alcohol injures hepatocytes, which sensitizes resident liver macrophages (Kupffer cells) to mount a pro-inflammatory response and is aided by the recruitment of circulating monocytes to release inflammatory mediators such as IL-1β, IL-6, MCP and TNFα [6]. Moreover, alcohol has been shown to cause gut dysbiosis and leaky gut syndrome. Alcohol promotes the overgrowth of bacterial genera that favor an inflammatory environment [7]. The injured gut epithelium causes the leakage of bacterial products and pro-inflammatory antigens to reach the liver via the hepatic portal circulation. This further contributes to alcohol-induced liver injury in a synergistic manner.

In the current issue of DLD, Kwong et al. [8] examined the role of sphingosine kinase 2 (SphK2) in ALD. Whole body genetic knockout of SphK2 demonstrated a striking observation that a deficiency in SphK2 potentiated alcohol-induced liver injury. The data show that SphK2 deficient mice fed a 60-day alcohol diet produced severe hepatic steatosis and increased liver injury compared to wild type mice. In addition, SphK2 deficient mice had dysregulated hepatic lipid metabolism genes and elevated levels of pro-inflammatory mediators suggesting a causal role for SphK2 in the pathogenesis of ALD. The data presented also underscored the functional protective role of SphK2 in ALD and extends beyond the liver. SphK2 deficiency also proved to be pathologic in the small intestines and could be contributing to alcohol-induced liver injury. Kwong, et al. demonstrated that intestinal stem cell growth was attenuated in SphK2 deficient intestinal crypts and that histologic analysis revealed a consistent pattern of small intestine epithelial disruption that is potentiated with an alcohol diet. These results seem to support the notion that a leaky gut promotes liver injury and ALD.

Kwong et al. were able to specifically link the clinical relevance of SphK2 to the development of ALD. Specifically, the investigators were able to demonstrate a significant down-regulation of SphK2 protein expression in the human livers of alcoholic cirrhosis patients. Typical liver pro-inflammatory cytokines such as IL-1β, IL-6, MCP, and TNFα were also up-regulated in these human samples. Interestingly, bile acid transporter genes were increased, which implicates bile acids as playing a potential role in the pathogenesis of ALD. These data suggest that SphK2 is protective and that SphK2 down-regulation could contribute to the progression of ALD. Though this work by Kwong, et al. identified a novel role of SphK2-deficiency in alcohol-induced liver injury, there are some limitations to their study. The mouse model used in this study is a global knock out of SphK2. In order to determine the exact role of SphK2 in regulating hepatic lipid metabolism and alcohol-induced liver injury, tissue and cell-specific knockouts of SphK2 would be needed to address this. In addition, the role of SphK2 in regulating immune cells, such as Kupffer cells and neutrophils, remains unclear. Overall, this study is novel in that it is the first to determine the role of sphingosine 1-phosphate (S1P) and bile acid-mediated signaling in ALD.

The human data presented by Kwong et al. also raises translational questions that could serve as important therapeutic targets in the treatment of ALD. The down-regulation of SphK2 expression seen in alcoholic cirrhosis and hepatocellular carcinoma is certainly interesting. In addition, Iracheta-Vellve et al. have demonstrated that modulating bile acids could ameliorate alcohol-induced liver injury [9]. Previous studies from Nagahashi, et al. have shown that conjugated bile acids can activate SphK2 via sphingosine 1-phosphate receptor 2 (S1PR2) to regulate hepatic lipid metabolism [10]. It would be worthwhile to determine whether modulating the S1PR2 and SphK2 mediated S1P could attenuate the progression from mild to severe ALD.

Conflict of interest

None declared.

DOI of original article: https://doi.org/10.1016/j.dld.2019.03.020.

☆ Portions of these discussed studies were supported by Baylor Scott & White Institute, the Hickam Endowed Chair, Gastroenterology, Medicine, Indiana University, a VA Research Senior Career Scientist Award.

☆☆ The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

https://doi.org/10.1016/j.dld.2019.04.002
1590-8658/Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

References

[1] Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2018;16:1356–8.
[2] Frazier TH, Stocker AM, Kershner NA, et al. Treatment of alcoholic liver disease. Therap Adv Gastroenterol 2011;4:63–81.
[3] Chacko KR, Reinus J. Spectrum of alcoholic liver disease. Clin Liver Dis 2016;20:419–27.
[4] Ambade A, Mandrekar P. Oxidative stress and inflammation: essential partners in alcoholic liver disease. Int J Hepatol 2012;2012:853175.
[5] Purohit V, Bode JC, Bode C, et al. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol 2008;42:349–61.
[6] Kawaratani H, Tsujimoto T, Douhara A, et al. The effect of inflammatory cytokines in alcoholic liver disease. Mediators Inflamm 2013;2013:495156.
[7] Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019.
[8] Kwong EK, Liu R, Zhao D, Zhu W, Li X, Wang X, et al. The role of sphingosine kinase 2 in alcoholic liver disease. Dig Liver Dis 2019, in press.
[9] Iracheta-Vellve A, Calenda CD, Petrasek J, et al. FXR and TGR5 agonists ameliorate liver injury, steatosis, and inflammation after binge or prolonged alcohol feeding in mice. Hepatol Commun 2018;2:1379–91.
[10] Studer E, Zhou X, Zhao R, et al. Conjugated bile acids activate the sphingosine-1-phosphate receptor 2 in primary rodent hepatocytes. Hepatology 2012;55:267–76.

Gianfranco Alpini*
Indiana Center for Liver Research, Richard L. Roudebush VA Medical Center, Division of Gastroenterology & Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

*Correspondence to: Indiana Center for Liver Research, Richard L. Roudebush VA Medical Center and Indiana University, Gastroenterology, Medicine, 1481 W 10th street, Dedication Wing – Room D-7151, Indianapolis, IN 46202, United States
E-mail address: galpini@iu.edu

27 March 2019