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Commentary

Implications of BMP9/10 for patients with liver cirrhosis

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Liver cirrhosis consists of an asymptomatic compensated phase and a decompensated phase, which can cause two pulmonary vascular complications: hepatopulmonary syndrome (HPS) characterized by hypoxia, intrapulmonary microvasculature dilatation, angiogenesis and arterio-venous malformations (AVMs) [1]; and portopulmonary hypertension (PoPH) characterized by increased pulmonary vascular resistance and pulmonary arterial hypertension (PAH) in the absence of other etiologies of PAH [2]. Previous studies have shown that PoPH and HPS are associated with markedly reduced bone morphogenetic protein (BMP) 9/10 [3, 4] and increased soluble endoglin (sEng) levels [5]. Approximately 4–40% of cirrhotic patients could develop into HPS [6] and PoPH can develop in 1–6% of patients with portal vein hypertension [7]. Both of these complications can increase the mortality rate in liver cirrhotic patients and there are few effective precautionary or therapeutic measurements except liver transplantation [8, 9]. The study recently published in *EBioMedicine* by Owen and co-workers contribute to the literature from three aspects.

First is a better understanding of the molecular mechanisms of HPS and PoPH. Vascular syndromes seldom arise as primary diseases, they often present secondary to liver cirrhosis. It is known that impaired liver anabolic and catabolic functions together with portal hypertension trigger various vascular dysfunction cascades, which affect pulmonary vasculature [10]. Portosystemic shunts caused by portal vein hypertension allows locally generated or accumulated vasoactive compounds to get access between different vascular compartments bypassing the liver. On the other hand, the change of intestinal microbiome and their related bi-products carrying strong vasoactive, endothelial-targeting and cytotoxic properties can further complicate and disseminate vascular dysfunction, which result in imbalance of vasoactive compounds and angiogenesis via disruption of transforming growth factor-β (TGF-β), prostaglandins, endothelin (ET), nitric oxide or vascular endothelial growth factor signalling pathways, as well as the development of hypoxia injury, oxidative stress, HPS or PoPH eventually. The results showed by Owen et al. that reduced BMP9/10 production leading to reduced endothelial function, when combined with the additional impact of sEng on other factors, such as TGF-β, at the hepatic or pulmonary level, may promote HPS or PoPH, indicate that the interaction of BMP and these signalling pathways might be the next pathophysiological exploratory direction of HPS and PoPH.

Second is clinical prediction of HPS or PoPH. So far, the diagnostic criteria of HPS or PoPH is based on observable clinical manifestations. Once diagnosed, the treatment options are limited. So, establishing a risk prediction model of HPS or PoPH becomes vital for patients with liver cirrhosis. Based on the results of Owen et al., which is the identification of circulating biomarkers that are indicative of the switch from a state associated with low mortality to one associated with high mortality, reduced BMP9/10 and elevated sEng might be a manifestation of the onset of the pulmonary complications of patients with liver cirrhosis, so easy-to-detect plasma BMP9/10 and sEng should be candidates for prediction model construction. Whilst the sample size of this study was small due to the low prevalence of HPS and PoPH, even the largest cohort of PoPH patients reported by Savale et al., included only 637 patients (mean age 55±10 years; 58% male). Therefore, multicentre cohort studies are needed, to recruit enough cases to perform multivariate analysis for screening other risk factors, and ROC analysis for model construction and validation.

Third is the potential therapeutic target of HPS and PoPH. As we know, drug treatment of HPS and PoPH, such as the use of angiogenesis inhibitors, probiotics, ET receptor antagonists, caspase inhibitors, endothelin receptor antagonists, or phosphidiesterase-5 inhibtors, is only moderately effective in a best case scenario. The effectiveness of transjugular intrahepatic portosystemic shunt (TIPS) is still unclear. To date, liver transplantation is the only effective option. However, it is hard to perform because of high costs and limited number of donor livers. According to the result of Owen et al., which suggests that loss of pulmonary endothelial homoeostasis might be induced by low circulating levels of BMP9/10, supplementation with exogenous ligands might represent a non-invasive disease-modifying alternative to the only current therapeutic indication, liver transplantation.

In summary, it has been proven that reduction of BMP9/10 is associated with the onset of HPS or PoPH in patients with liver cirrhosis. Further studies with large sample sizes are needed to clarify the exact mechanism of BMP signalling, to pave the way for new strategies in the management of liver cirrhosis.

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Author contributions

DJ and GC wrote the manuscript. YY revised the manuscript, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

All authors declare no competing interests.

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References

[1] Koch DG, Fallon MB. Hepatopulmonary syndrome. Clin Liver Dis 2014;18(2):407–20 http://dx.doi.org/10.1016/j.cld.2014.01.003.

[2] Iqbal S, Smith KA, Khungar V. Hepatopulmonary syndrome and portopulmonary hypertension. Clin Chest Med 2017;38(4):785–95. http://dx.doi.org/10.1016/j.ccm.2017.08.002.

[3] Rochon ER, Krowka MJ, Bartolome S, Heresi GA, Bull T, Roberts K, et al. . BMP 9/10 in pulmonary vascular complications of liver disease. Am J Respir Crit Care Med. 2020. http://dx.doi.org/10.1164/rccm.201912-2514le.

[4] John M, Kim KJ, Bae SDW, Qiao L, George J. Role of BMP-9 in human liver disease. Gut 2019;68(11):2097–100. http://dx.doi.org/10.1136/gutjnl-2018-317543.

[5] Owen NE, Alexander GJ, Sen S, Bunclark K, Polwarth G, Pekpe-zaba J, et al. Reduced circulating BMP10 and BMP9 and elevated endoglin are associated with disease severity, decompensation and pulmonary vascular syndromes in patients with cirrhosis. EBioMedicine 2020;56:102794. http://dx.doi.org/10.1016/j.ebiom.2020.102794.

[6] Soulaidopoulos S, Cholongitas E, Giannakoulas G, Vlachou M, Goulis I. Review article: update on current and emergent data on hepatopulmonary syndrome. World J Gastroenterol 2018;24(12):1285–98. http://dx.doi.org/10.3748/wjg.v24.i12.1285.

[7] Savale L, Guimas M, Ebstein N, Fertin M, Jevnikar M, Renard S, et al. . Portopulmonary hypertension in the current era of pulmonary hypertension management. Journal of Hepatology. 2020. http://dx.doi.org/10.1016/j.jhep.2020.02.021.

[8] Cosarderelioglu C, Cosar AM, Gurakar M, Pustavoitau A, Russell SD, Dagher NN, et al. Portopulmonary hypertension and liver transplant: recent review of the literature. Exp Clin Transplant 2016;14(2):113–20.

[9] Sendra C, Carballo-Rubio V, Sousa JM. Hepatopulmonary syndrome and portopulmonary hypertension: management in liver transplantation in the horizon 2020. Transplant. Proc 2020. http://dx.doi.org/10.1016/j.transproceed.2020.02.057.

[10] Shenoda B, Boselli J. Vascular syndromes in liver cirrhosis. Clin J Gastroenterol 2019;12(5):387–97. http://dx.doi.org/10.1007/s12328-019-00956-0.