Gut microbiota and hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths yearly (1). Due to the asymptomatic nature of early HCC, the majority of HCC patients are usually detected at middle or late stages by biopsy or imaging methods, for which there are no effective treatment options. Accumulating evidence showed that the alpha-fetoprotein (AFP) has limited diagnostic value because of the low sensitivity in HCC, only 10–20% of patients with early-stage HCC have increased serum AFP (2,3).

The gut microbiome has emerged as a central factor affecting human health and disease in recent years. In addition to important contributions of gut microbiota in metabolism and immunity to the host, gut dysbiosis also plays a key role in chronic hepatitis, such as alcoholic liver disease, viral-induced liver disease, nonalcoholic fatty liver disease and even end-stage liver disease (4). About 70% of liver blood supply is from portal vein which contains a large amount of intestinal microbial antigens and metabolites. A previous study indicated that microbiota products drive pro-inflammatory gene expression by activating the innate immune system, thus promoting liver inflammation (5). Interestingly, through epigenetic mechanisms, nutritional imbalance caused by gut dysbiosis is closely associated with the clinical outcome of patients with end-stage liver disease, and the use of probiotics obviously reduced the complications and prolonged the survival of patients with end-stage liver disease (6).

Recently, increasing evidences demonstrated the involvement of the gut microbiota in the pathogenesis of HCC via the gut-liver axis. A recent study showed that hepatic translocation of a Gram-positive gut microbial component promotes HCC development in murine models (7). Another study reported that probiotics modulated gut microbiota and suppressed HCC growth in mice (8). Interestingly, intestinal sterilization with antibiotics reduces occurrence and growth of HCC lesions in animal models (9). These studies highlight the significant roles of homeostasis of gut microbiota both in chronic liver disease and HCC.

The change of gut microbial diversity is a non-invasive diagnostic biomarker on some diseases. A metagenome-wide association study analysis demonstrated the correlation between the imbalances in gut microbiome and atherosclerotic cardiovascular disease, and showed a good diagnostic potential in atherosclerotic cardiovascular disease cohort (10). Another metagenome-wide association study analysis showed a moderate degree of gut microbial dysbiosis in type 2 diabetes patients, and demonstrated useful gut microbial markers for classifying type 2 diabetes (11). Qin *et al.* revealed a major change of the gut microbiota in cirrhotic patients with the quantitative metagenomics approach, and found specific microbial genes that identify patients with liver cirrhosis with a high specificity (12). A fecal metagenomic and metabolomic study on colorectal cancer patients found apparent shifts in microbiome, and identified microbiome markers to discriminate cases of intramucosal carcinoma from the healthy controls (13).

In a recent issue of *Gut*, the fecal microbial characteristics in HCC patients and the diagnostic value of gut microbiome for HCC were clarified by Ren *et al.* via 16S rRNA Miseq sequencing (14). In their study, samples collected from different regions of China were randomly

divided into three stages to construct HCC classifier and validate its diagnosis efficacy. They found that fecal microbial diversity was significantly decreased in cirrhosis versus healthy controls, while it was markedly increased in early HCC versus cirrhosis. Ren *et al.* concluded that the altered microbial community might play an important role in HCC initiation and progression. Moreover, butyrate-producing bacterial genera which help to maintain bacterial energy metabolism and gut health were decreased, and producing lipopolysaccharide genera which lead to liver inflammation and oxidative damage were increased in early HCC, thereby contributing to the development of HCC. Another important finding of Ren *et al.*'s study is the identification of the optimal 30 specific microbial markers for early and advanced HCC. More importantly, diagnostic value of these microbial markers was identified through a cross-region validation with large cohorts from East China, Central China and Northwest China. These results suggested a significant role of gut microbiota in the development of HCC, and implied that fecal microbial markers might be a potential non-invasive tool for early diagnosis and early therapy for HCC.

It is undoubted that gut microbiota plays a critical role in the pathogenesis of HCC. The study by Ren *et al.* is the first to characterize gut microbiome in HCC patients instead of animal models, and provide potential evidences for the diagnostic value of microbial markers for early HCC. Ren *et al.*'s study also provided the potential new therapeutic strategies of inhibiting HCC progression via adjusting gut microbiota.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2019.10.34/coif). The authors have no conflicts of interest to declare.

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References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
2. Biselli M, Conti F, Gramenzi A, et al. A new approach to the use of α-fetoprotein as surveillance test for hepatocellular carcinoma in patients with cirrhosis. Br J Cancer 2015;112:69-76.
3. Xing H, Zheng YJ, Han J, et al. Protein induced by vitamin K absence or antagonist-II versus alpha-fetoprotein in the diagnosis of hepatocellular carcinoma: A systematic review with meta-analysis. Hepatobiliary Pancreat Dis Int 2018;17:487-95.
4. Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol 2017;14:527-39.
5. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology 2014;146:1513-24.
6. Vasco M, Paolillo R, Schiano C, et al. Compromised nutritional status in patients with end-stage liver disease: Role of gut microbiota. Hepatobiliary Pancreat Dis Int 2018;17:290-300.
7. Loo TM, Kamachi F, Watanabe Y, et al. Gut microbiota promotes obesity-associated liver cancer through PGE2-mediated suppression of antitumor immunity. Cancer Discov 2017;7:522-38.
8. Li J, Sung CY, Lee N, et al. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc Natl Acad Sci U S A 2016;113:E1306-15.
9. Zhang HL, Yu LX, Yang W, et al. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. J Hepatol 2012;57:803-12.
10. Jie Z, Xia H, Zhong SL, et al. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun 2017;8:845.

11. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012;490:55-60.

12. Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014;513:59-64.

13. Yachida S, Mizutani S, Shiroma H, et al. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. Nat Med 2019;25:968-76.

14. Ren Z, Li A, Jiang J, et al. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. Gut 2019;68:1014-23.