Letter to the Editor

Insight into the gut microbiome dysbiosis in patients with liver failure after extended-hepatectomy

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Liver cancer remains a leading cause of cancer-related death globally, and surgical resection is the first choice for early-stage patients, as well as advanced patients under certain circumstances. Partial hepatectomy is usually safe and considered a curative option. Liver possesses the outstanding capacity to compensate and restore its functionalities after surgical removal of a substantial part of the liver mass. However, post-hepatectomy liver failure (PHLF) occurs in up to 9% of patients and accounts for most cases of postoperative mortality (1).

The gut microbiome is crucial for body metabolism and liver pathogenesis. Gut dysbiosis is referred to altered composition of the gut microbiota with diversity deprivation and an increased number of pathogenic bacteria (2). A growing amount of evidence suggests that dysbiosis of the gut microbiome may induce critical liver damage. In a recent study, researchers investigated the gut microbiome profiles and functions in hepatitis B virus (HBV) associated hepatocellular cancer (B-HCC) patients with PHLF after extended hepatectomy, and they found that the gut microbiota characteristics may serve as reliable biomarkers for diagnosis and management of PHLF (3). Researchers recruited 30 patients with B-HCC and divided them into two groups [(Group A and B (n=15, respectively)] according to the onset of PHLF. Two groups were further divided into pre-operation (Ebo.PHLF and Enbo.PHLF) and post-operation (Eao.PHLF and Enao.PHLF) groups. Researchers conducted 16S ribosomal RNA gene sequencing to distinguish gut microbial abundance and composition with significant differences. The study excluded patients with a history of alcohol addiction, inflammatory bowel diseases, non-alcoholic fatty liver, gastrointestinal disease, diabetes, etc. No participants received drugs within 4 weeks before surgery that may have an impact on gut bacteria, such as antibiotics.

First of all, based on the diversity analysis, researchers found that extended hepatectomy causes dysbiosis of the intestinal microbiome, which is consistent with previous evidence. The abundance and composition at the genus level of gut microflora differed in Enao.PHLF and Eao.PHLF, which indicated the dominant microflora shifted in PHLF patients. The following analyses revealed a group of bacteria that could serve as non-invasive characteristic biomarkers for PHLF, most notably *Faecalibacterium*. Moreover, gut microbiome dysbiosis may lead to liver injury via interference of amino acid metabolism. The study found that the biosynthesis of several essential amino acids, including lysine, arginine, and alanine, decreased significantly in PHLF patients, and all three acids exhibit essential functions in liver metabolisms, such as inhibition of free radical-mediated damage and liver gluconeogenesis. However, the mechanism of the regulation of amino acid metabolism by gut microbiota remains unclear. In addition, the dysbiosis in microbial abundance and mutual relations might have an impact on the progression of PHLF. The study found that the abundance of multiple bacteria was correlated with the development of PHLF. For instance, increased *Bacteroides* were positively correlated with several

critical metabolism pathways, such as pyrimidine and organic acid metabolism, causing liver injuries.

In general, the functions of the gut microbiome in humans are as follows: (I) absorption of nutrient metabolites; (II) maintenance of the integrity of gut barriers; (III) regulating the activity of innate and adaptive immune cells; (IV) suppress pathogenic bacteria colonization via pH modulation and nutrient competition, etc. When dysbiosis occurs, the balance between gut microflora is compromised, and so are those critical functions either (4). Liver would be the first affected organ due to the unique anatomical relationship with the guts, namely the gut-liver axis. Gut barrier dysfunction and bacterial translocation would produce excessive toxins and other metabolites, and facilitate the transfer process to the liver, causing inflammatory reactions and impairing native immune responses (5).

Traditionally, the important parameters used in evaluating the possibility of liver failure after hepatectomy include future liver remnant volume, age, time duration of hepatic inflow occlusion, cirrhosis, viral hepatitis, fatty liver, etc. This article remedies the lack of studies explaining the relationship between PHLF and the gut microbiome and comes out with substantial results and suggestions, yet there are more questions in this area to be answered. For instance, the mechanisms of the gut–liver axis that links the gut and liver are not well understood. Gut and liver are anatomically linked via the portal vein, evidence shows that gut bacterial composition and metabolites can be transferred to the liver and affect liver homeostasis, but current understanding of the underlying interactions remains superficial. Furthermore, gut microbiome dysbiosis is highly correlated with multiple liver diseases, and the causal relationship among them is nevertheless unclear. Studies indicated that dysbiosis causing inflammatory reactions precedes carcinogenesis in an animal model (6), but it remains difficult to know whether the same occurs in humans, or whether inherent inflammation and impaired gut barrier function cause dysbiosis in the first place.

In summary, this article analyzed the changes in the composition and diversity of gut bacteria in B-HCC patients before and after extended hepatectomy and gave us valuable insight into the relationship between PHLF and the gut microbiome. Certain microbiotas were identified to be used as diagnostic biomarkers for PHLF. Thus far, studies have shown that those changes in the composition of the gut microbiota altering gut permeability and resulting in increased translocation of bacteria and bacterial components are accountable for inducing hepatic injuries, and an understanding of the gut–liver axis and the mechanisms by which modulating the gut microbiota impacts hepatic inflammation, liver injury and carcinogenesis will ultimately place manipulation of the gut microbiota as a potential therapeutic strategy in the future.

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Footnote

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