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EDITORIAL

Gut microbiota alteration in hepatobiliary diseases: cause-and-effect relationship

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The human gut microbiota is a complex microbial community that regulates host immune responses as well as contributes to the maintenance of overall human health. Gut microbiota dysregulation increases the susceptibility of the host to many diseases and disorders, including tumors and infectious, cardiovascular, and digestive diseases [1–4]. Particularly, the association of hepatobiliary diseases with the microbial communities and their metabolites has become a research hotspot owing to the anatomic intestinal-hepatic axis that exists among the liver, portal vein, biliary tract, and intestinal tract.

In this issue, Hao et al. [5] provide important new insights into the understanding of dysbiosis and metabolic dysregulation in patients with choledocholithiasis concurrent with cholangitis (CC). Metagenomic sequencing and liquid chromatography/mass spectrometry (LC/MS) analyses were performed to define the gut microbiota and metabolome, respectively. The authors discovered that microbial dysbiosis in CCs is manifested by a lower microbial α-diversity and a significant difference in microbiota β-diversity, compared to microbial diversity in healthy controls. Simultaneously, the abundance of 12 bacterial species was altered, and their combination might have diagnostic value for CC. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed that pathways related to *Escherichia coli* biofilm formation, lipopolysaccharide (LPS) biosynthesis, and propionic acid and glutathione metabolism were significantly altered in CCs. Metabolome analysis identified 47 markedly changed metabolites and implicated the dysregulated metabolism of tryptophan and ceramides in CCs. Additionally, several metabolic modules involved in bile inflammation in CCs have been identified (Fig. 1). These findings support the notion that the alteration of both the composition and function of gut microbiota and their metabolites are closely involved in the pathogenesis of CCs and provide more insight into the understanding of the related disease mechanisms.

Gut microbiota disorders are related to the occurrence and development of numerous liver and biliary tract diseases. Choledocholithiasis and gallstones are metabolism-related diseases. The relationship between the gut microbiota and bile acid (BA) is closely related to gallstone formation. Anatomically, the bile duct, which serves as a part of the digestive tract, connects the liver and intestines. BA, which affects the distribution and structure of the microflora, is synthesized from the liver and discharged into the intestine through the biliary tract, where it is metabolized by the gut microbiota. BA synthesis and excretion are major cholesterol and lipid catabolism pathways, and thus, BA metabolism disorder is an important factor in stone formation [6]. In a physiological setting, bile is rich in Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The microbes in the gut and bile of patients with gallbladder stone are significantly different from those in healthy individuals and are manifested by a significant increase in the families *Bacteroidaceae, Prevotellaceae, Porphyromonadaceae,* and *Veillonellaceae*, and a decrease in the family *Propionibacteriaceae* [7]. Moreover, cholecystectomy can have a significant impact on the gut microbiota, such as an increase in the phylum Bacteroides. This disorder may pose new challenges to existing gallstone treatments [8]. Previous studies demonstrated that gut microbiota disorder may lead to retrograde colonization or infection, which may damage biliary epithelial cells and affect the synthesis, metabolism, and reabsorption of cholesterol and bile acids, and regulation of liver and biliary immunity; however, the related mechanisms of

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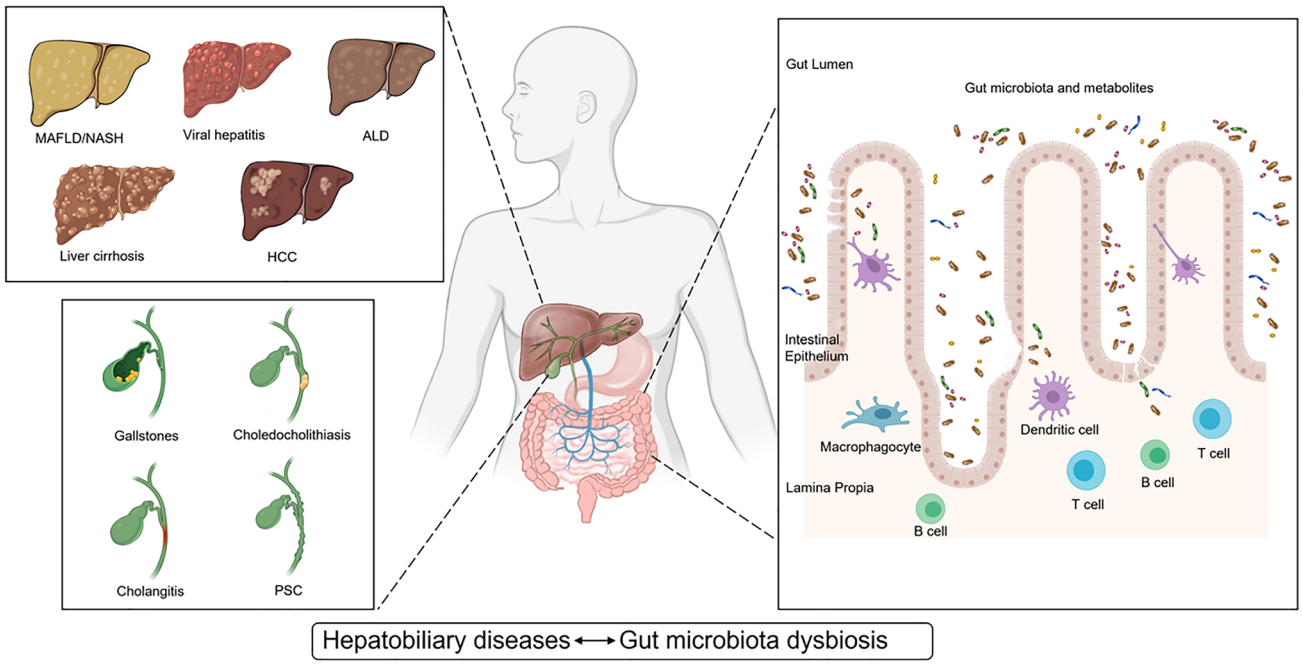

Fig. 1 The relationship of gut microbiota with hepatobiliary diseases

gut microbiota with certain biliary tract diseases, including gallstone disease, remain unclear.

Maintaining a healthy intestinal environment is vital to liver health. There is a bidirectional communication among the liver, gut, and gut microbiota, known as the microbiota–gut–liver axis. The liver connects to the intestines through the biliary system and portal vein, and when intestinal integrity is impaired, the gut microbes and their products enter the portal venous system in large quantities. Furthermore, the Kuffer cells and other liver cells are activated by these metabolites and release a variety of inflammatory factors that may cause further damage to the intestinal mucosa and distant organs. Numerous liver disease types, such as alcohol-related liver disease, metabolic-associated fatty liver disease, non-alcoholic steatohepatitis, hepatocellular carcinoma, primary cholangitis, primary sclerosing cholangitis, and liver cirrhosis, have been reported to be associated with gut microbiota-associated changes [9].

Accumulating evidence indicates that the microbiota may affect the metabolic phenotype of the host through metabolite production [10]. These biologically active microbial metabolites are sensitive fingerprints of microbial functions and can penetrate the blood circulation and tissues of the host as messengers of inter-world signals. These fingerprints can be used for diagnostic purposes, and further understanding of the specificity of microbial metabolite-producing strains can identify strains or specific metabolites for therapeutic purposes. Additionally, functional feature analyses of the microbiota indicated that alterations in the gut microbiota might contribute to disease development through metabolic pathways.

The current study by Hao et al. provides intriguing data suggesting that gut dysbiosis and metabolic dysregulation are involved in the pathogenesis of CCs. Notably, there are certain limitations and several critical concerns that require attention. First, as the author stated, a larger multicenter trial is required to fully determine the profile of the gut microbiome and metabolome in CCs, and the cause-and-effect relationship has not been confirmed. Second, the study lacked pathological changes in the liver of CC patients. Moreover, the majority of significantly altered metabolites were clustered into lipids; the in-depth lipidome analysis by LC/MS–MS could potentially provide further insight into the pathogenesis of CC. Considering the close relationship between liver–bile–gut anatomy and physiology, in the setting of biliary diseases, whether the changes in gut microbiota would cause inflammation and pathophysiological changes, and subsequently cirrhosis, still requires classification. In addition, the role of metabolites derived from gut microbes in the pathogenesis of CC remains elusive. Therefore, future research will be aimed at determining whether alterations in gut microbiota and metabolite profiles are the cause or consequence of liver diseases and intestinal permeability alterations, particularly in the setting of human cholangiopathies.

To address the above-mentioned issues, the interaction between gut microbiota and hepatobiliary diseases has been increasingly recognized in the past decade. Dysbiosis and

changes in microbiota classification have been observed in patients with a variety of liver and gallbladder diseases. Since most human studies are inadequate to provide mechanistic insights, certain preclinical efforts have been made to identify the potential causal components of gut microbiota changes. Several in vivo studies in animal models support the close relationship between the hepatobiliary system and the gut in disease development and progression. However, whether animal studies can be translated directly to humans is unclear. As humans are different from animal species, conclusions from animal experiments are insufficient for human application. Therefore, we should focus on clinically relevant samples (for example, human fecal samples and human bacterial strains) based on the molecular basis of host–microbiota interactions to improve translation of microbiome study results from animals to humans [11].

To improve the translation of gut microbiota studies to a clinical setting, increased efforts should be made in the future. First, countries and regions should increase investment in microbial research and promote the industrialization and commercialization of gut microbiome-related applications. Financial investment is the basis for the rapid development of gut microbiota research. Second, in-depth research and sustainable development of gut microbiota studies require the integration and participation of microbiologists, immunologists, bioinformatic specialists, epidemiologists, and clinical expertise. Moreover, technical methods and research platforms should be improved to study the functions and potential roles of a large number of unknown and/or uncultured microorganisms. Metagenomics and cultural genomics are improving to facilitate such analyses, however, extensive attention is required. Furthermore, when we describe the microbiome, technical platforms should be standardized, so that the results can be replicated and compared in various laboratories. How can standardization and repeatability issues be resolved in microbiome research? This fundamental question requires scientists to work on a global scale, standardize methodologies, and share additional open databases among researchers [12].

Studying the gut microbiome is still in its infancy, and further investigation in the field will comprehensively explain the scenario of the gut microbiome in hepatobiliary diseases, which will aid in the development of novel therapeutic strategies. With the development of multi-omics methods, the focus has shifted from analyzing changes in the number and abundance of microbes to the structure and function of the microflora, specific strains, and even strain levels. Therefore, we are closer to more accurate diagnostic tools and effective treatments to improve health of patients with hepatobiliary disease.

Hepatobiliary diseases consist of major liver diseases including metabolic-associated fatty liver disease (MAFLD), non-alcoholic steatohepatitis (NASH), chronic viral hepatitis, alcohol-related liver disease (ALD), alcohol liver cirrhosis, primary hepatocellular carcinoma (HCC), and biliary tract diseases [gallstones, choledocholithiasis, cholangitis, primary sclerosing cholangitis (PSC) and so on]. During the disease progression of the above-mentioned diseases, there are usually simultaneous alterations of both gut microbiota and corresponding metabolites such as increase of harmful bacteria together with decrease of beneficial bacteria. Meanwhile, the intestinal epithelium is damaged and the microbiota are translocated into portal vein, which further activates the host immune system. Accordingly, the alterations of gut microbiota and metabolite profiles will further exacerbate the status of the diseases.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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