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Editorial on gut-liver axis

The role of the gut microbiome in chronic liver diseases: Present insights and future outlook

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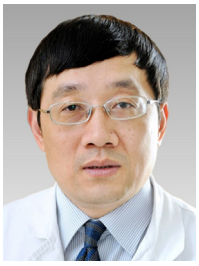

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The human gastrointestinal tract harbors trillions of microbes including bacteria, viruses, and fungi that facilitate digestion and nutrient absorption, thereby affecting host metabolism and immunity. The liver communicates with the gut through portal vein, systemic circulation, and biliary tract to form the gut-liver axis [1]. The liver receives 70%–75% of its blood supply from the portal vein, positioning it as the first organ to encounter gut-derived microbes, microbial products, and toxins when microflora balance and gut barrier function are disrupted, which could contribute to the development of chronic liver diseases [2]. While alterations in gut microbial composition have been noted across various diseases, the causal connections remain elusive, and there are situations where the absence of microbiota does not impact the disease progression [3]. Therefore, it is imperative to review the role of gut microbiota and its products in pathogenesis of liver diseases such as nonalcoholic fatty liver disease (NAFLD), drug-induced liver injury (DILI), and cholestatic liver disease, etc.

NAFLD along with its more progressed form, nonalcoholic steatohepatitis (NASH), are common comorbidities of obesity and type 2 diabetes mellitus (T2DM). As the main reason for referrals to secondary care services, NAFLD has become the leading cause of chronic hepatitis and asymptomatic elevated serum transaminase, and also the important cause of liver cirrhosis and hepatocellular carcinoma (HCC) [4]. To accurately reflect the pathogenesis and stratify patients for management, metabolic dysfunction-associated fatty liver disease (MAFLD) [5] and metabolic dysfunction-associated steatotic liver disease (MASLD) [6] were proposed as replacement of NAFLD in 2020 and 2023, respectively. Despite the nomenclatures, recent studies in animals and humans demonstrated a causal role of gut microbiota in NAFLD [7]. For example, Xin et al. [8] reported that *Escherichia fergusonii* promotes the pathogenesis of steatohepatitis and fibrosis in nonobese rats by secreting msRNA 23487, providing a potential biomarker for predicting steatohepatitis in nonobese patients with NAFLD. In this special issue of *Hepatobiliary & Pancreatic Diseases International*, Wu and Fan [9] summarized current studies and highlighted the potential role of the gut microbiome in serving as a non-invasive diagnostic tool and a target for therapeutic interventions in clinical settings. This review is anticipated to enhance researchers' comprehension of how gut microbiota impacts the advancement of NAFLD, shedding light on underlying mechanisms and potential management.

Extensive evidence shows that the majority of drugs undergo hepatic metabolism, and some of them have been associated with hepatotoxicity, leading to instances of DILI. With an incidence of 14–19 cases in 100 000 people, DILI is one of the most common causes of acute liver failure and acute-on-chronic liver failure [10]. It is well known that gut microbiota exhibits a broad spectrum of

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enzymatic activities that have profound effects on drug metabolism in the liver, thereby contributing to the individual variability in the drug-induced hepatotoxicity. Considering that alterations of gut microbiota are associated with differences in individuals, region, medicine, and diet, even the same bacterial strain can exhibit some difference. Among the three groups of DILI (direct, idiosyncratic, and indirect), Chu et al. [11] reviewed the role of gut microbiota in direct DILI by mainly focusing on the changes in the gut microbial composition, abundance, distribution, and associated metabolites. Moreover, they summarized the role of immune response associated with gut dysbiosis in DILI.

The gut microbiota can produce bioactive compounds that may act as signal molecules to the host. Bile acids are endogenous molecules synthesized from cholesterol in the liver and subsequently transformed into secondary bile acids by the gut microbiota [12]. The functions of bile acids include absorption of lipids and fat-soluble vitamins, regulation of cholesterol catabolism and biliary secretion, modulation of gut microbiota, and acting as endogenous ligands of farnesoid X receptor (FXR)/G protein-coupled bile acid receptor 1 (GPBAR1) [13]. In order to clarify the role of bile acids and their associated signaling in maintaining metabolic homeostasis, Bhattacharya et al. [14] presented a comprehensive view of diverse knockout (KO) models utilized to explore bile acid synthesis and its implications in human diseases, offering valuable insights into the potential of bile acids as therapeutic targets. Cholesterol 7a-hydroxylase (Cyp7a1) is a rate-limiting enzyme for bile acid synthesis in classical pathway, accounting for more than 75% of total bile acid production [15]. Therefore, a genetic ablation of *Cyp7a1* in mice has been predominantly used to study bile acid synthesis and cholesterol metabolism. They also addressed the differences between humans and mice when caused by the same bile acid synthesis gene deficiencies. By generating various *in vivo* mouse models, this review offers a thorough examination of the manipulation of specific bile acids and their significance in enterohepatic signaling.

Hepatobiliary complications (steatosis, cholestasis, and gallbladder stones) commonly arise in patients with chronic intestinal failure (IF) who receive prolonged parenteral nutrition (PN), which is known as intestinal failure-associated liver disease (IFALD). The prevalence of IFALD in children and infants is estimated to be over 20%, with the incidence higher in preterm infants and children with IF [16]. Previous studies suggest that the development of IFALD is a multifactorial process, in which gut dysbiosis plays a critical role in conjunction with other factors, such as PN duration, increased intestinal permeability, and compromised immune response [17–19]. Overall, PN is associated with a reduced microbial diversity and a general shift from Firmicutes to lipopolysaccharide-producing Bacteroidetes and Proteobacteria [20]. Given our own long-standing interest in understanding the pathogenesis of IFALD, we are intrigued by the potential role of gut microbiota and their products in driving disease progression. Our review in this special issue provided a timely update in the field of gut microbiota and IFALD by summarizing recent studies related to alterations of gut microbial composition and how specific expansion of pathogens promotes the progression of IFALD. We also discussed microbiota-targeted interventions, including pre/probiotics, fecal microbiota transplantation, and antibiotics to mitigate IFALD [21].

In summary, clinical studies have revealed alterations of gut microbiome in patients with various liver diseases, which could serve as future non-invasive biomarkers for diagnosis or prognosis of liver disease. Although early studies in the microbiome research field published descriptive work, advances have been made to shift to mechanistic studies that highlight fundamental principles of disease. To correct gut dysbiosis, the fastest way is through fecal microbiota transplantation. In a recent editorial from Dr. El-Omar, he proposed a personalized fecal microbiota transplantation based on multiomic profile, which combines taxonomy with transcriptomics, metabolomics and host genetics for better therapeutic effects [22]. With the rapid advancement of microbiological technologies in the field of microbiology, more patients with liver diseases will benefit from this revolution.

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Competing interest

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