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Importance of the gut microbiota in the gut-liver axis in normal and liver disease

gut microbiota in the gut-liver axis

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Abstract

The gut microbiota is of growing interest to clinicians and researchers. This is because there is a growing understanding that the gut microbiota performs many different functions, including involvement in metabolic and immune processes that are systemic in nature. The liver, with its important role in detoxifying and metabolizing products from the gut, is at the forefront of interactions with the gut microbiota. Many details of these interactions are not yet known to clinicians and researchers, but there is growing evidence that normal gut microbiota function is important for liver health. At the same time, factors affecting the gut microbiota, including nutrition or medications, may also have an effect through the gut-liver axis.

Key Words: Gut microbiota; Liver; Gut-liver axis; Immunity; Non-alcoholic fatty liver disease

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Core Tip: The gut microbiota plays an important immune and metabolic role in the body both under physiologic conditions and in the development of various liver diseases.

INTRODUCTION

The gut microbiota is a subject of increasing interest to clinicians and researchers due to the growing body of new data on its important metabolic and immune roles in the organism[1–4]. The human gastrointestinal tract is continuously colonized by a vast array of microorganisms, including bacteria, archaea, fungi, and viruses, and the number of these microorganisms is estimated to be comparable to or significantly greater than the number of human cells[5–7]. It is estimated that the microbiota's collective genome may contain 100 times more genes than the human genome[8–10]. Of course, these microorganisms are closely related to the human body. The gut microbiota population is known to be dominated by anaerobic bacteria, with 90% of the gut microbiota consisting of Bacteroidetes (Gram-negative) and Firmicutes (Gram-positive), followed by Actinobacteria (Gram-positive) and Proteobacteria (Gram-negative)[11,12].

The relationship between macroorganisms and microbiota has deep evolutionary roots and is well-known in animals. This symbiotic relationship serves many important physiological purposes, including the participation of bacteria in the digestion of food substances that are inaccessible to macroorganism digestive enzymes, as well as the synthesis of substances required by the macroorganism and participation in immune mechanisms. The gut microbiota produces metabolites such as short-chain fatty acids (SCFAs)[13,14]. The three primary SCFAs are acetate, propionate, and butyrate. These SCFAs are formed from dietary fibers such as resistant starch, cellulose, and pectin. SCFAs serve as an energy source for the intestinal epithelium and also enter the bloodstream through the portal vein, where they participate in various processes, including immune mechanisms. Short-chain fatty acids play a role in regulating immune cell activation in various organs, including the liver[13]. Butyrate, for instance,

promotes the functional maturation of liver-resident natural killer cells (LrNK) in the liver by acting through hepatocytes and Kupffer cells[15]. Furthermore, the gut microbiota has been linked to liver regeneration[16]. During hepatectomy, the gut microbiota is associated with hepatocyte proliferation through the activity of CD1d-dependent natural T-killer (NKT) and Kupffer cells[17,18].

The gut microbiome of mammals and humans is highly diverse, consisting of thousands of known species. Dietary patterns significantly impact this diversity. Studies have demonstrated that alterations in dietary patterns, both in humans and animals, can modify the composition of the gut microbiota. Research has shown that mice fed a Western diet experienced a decrease in Bacteroidetes and an increase in Firmicutes in their gut compared to normal mice[19,20]. Similarly, captive great apes have a different microbiota profile compared to their wild counterparts, which is similar to the microbiome of humans from non-urbanized societies. Furthermore, obesity has been linked to changes in the composition of the gut microbiota. The proportion of Bacteroidetes has been found to decrease in obese individuals compared to those who are lean. However, this proportion has been shown to increase with weight loss on two types of low-calorie diets[21]. It is worth noting that bariatric surgery also impacts the composition of the gut microbiota, which is an area of increasing interest[22].

The human body has mechanisms that promote microbial colonization of the gut and mechanisms to control this microbial population. The intestinal microbiome is a complex regulated system that is closely related to the human body. For example, goblet cells produce mucus that contains mucins and has two layers that separate bacteria from underlying intestinal epithelial cells (IECs)[11]. The layers have a comparable protein composition, which includes the gel-forming mucin Muc2 as a significant structural component[23]. Additionally, the inner mucus layer is tightly packed, immobile relative to the epithelium, and free of bacteria, while the outer mucus layer is mobile, colonized by bacteria, and has a larger volume due to proteolytic cleavage of Muc2 mucin. The spatial separation of bacteria and the intestinal epithelium is maintained by antibacterial substances secreted by the epithelium and

secretory immunoglobulin A[24,25]. The composition of the colonic mucosal barrier is determined by the microbiota[26]. Symbiotic bacteria use various strategies to circumvent the intestinal immune system, including actively suppressing epithelial proinflammatory signaling pathways[25].

The gut microbiota has a close bidirectional relationship with the liver[27]. The liver is connected to the gut through the portal vein system, which carries blood from the gastrointestinal tract. This blood contains various substances, including bacterial lipopolysaccharide (LPS), that can significantly impact the liver's structure and function. The liver can also affect the gut microbiota through the enterohepatic circulation of bile acids[28]. Therefore, the gut-liver axis is a bidirectional communication and its disruption has important clinical implications. Alcoholic liver disease, non-alcoholic liver disease, and biliary tract diseases have been linked to changes in the gut microbiome. Alterations in the gut microbiome can affect the development and severity of liver steatosis, inflammation, and fibrosis through multiple interactions with immune and other cells[29].

In recent years, there has been an increased interest in the role of gut microbiota as a key factor in the development of liver steatosis. Metabolic-associated fat liver disease (MAFLD) or non-alcoholic fatty liver disease (NAFLD) is an important medical problem and is of growing interest to clinicians and researchers[30,31]. NAFLD is characterized by the accumulation of excessive fat in the liver (steatosis) in patients who do not consume significant amounts of alcohol. The disease is thought to be caused by a complex interplay of internal and external factors, including nutritional disorders and disturbances in the gut microbiota structure. Changes in the gut microbiota have been associated with NAFLD and are dependent on the clinical stages of the disease[32,33]. The study found that disease progression corresponded with a decrease in microbiota diversity and an increase in Gram-negative bacteria, as well as a decrease in Gram-positive bacteria[33–35]. The development of a pro-inflammatory and metabolically toxic gut microbiota environment leads to disruption of the intestinal barr

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Patients with alcoholic liver disease (ALD) have increased intestinal permeability and elevated systemic levels of gut-derived microbial products [40]. Bacterial lipopolysaccharide contributes to inflammation in ALD through activation of Toll-like receptor 4 (TLR4)[41,42].

The gut microbiota plays an important role in the progression of liver cirrhosis and the development of disease decompensation, including through bacterial translocation and inflammation[20,43]. The use of antibiotics is considered a treatment for complications of liver cirrhosis[20,44].

Dysbiosis of gut microbiota is also known to be associated with cholelithiasis[45]. Progression of cholelithiasis is characterized by changes in the bacterial community of bile, including a decrease in the number of Proteobacteria and an increase in the number of Firmicutes and Bacteroidota in groups of patients compared to healthy controls[46]. Bile acids may promote the growth of some bacteria that metabolize bile acids and at the same time inhibit the growth of other bacteria sensitive to bile[47]. In turn, the gut microbiota regulates the expression of several of the enzymes involved in bile acid formation, including CYP7A1, CYP7B1, and CYP27A1[47,48].

Thus, a growing body of evidence demonstrates the important role of the gut microbiota, making it a therapeutic target[49]. As diet is one of the key factors influencing changes in gut microbiota composition, dietary modification is an important component of the treatment of many diseases. In addition, exercise has a favorable effect on the gut microbiota profile[50–52]. There is a growing number of studies on fecal transplants, but their therapeutic potential is still unclear[53]. Studies on the potential use of probiotics for the prevention and treatment of liver disease are also of interest[54–56]. In general, despite a fairly large body of accumulated knowledge, there is currently no sufficiently convincing data on effective effects on the gut microbiota to achieve the goals of treatment and prevention of liver disease.

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CONCLUSION

Thus, the gut microbiota is an important metabolic and immune "organ" that has close bidirectional links to liver function. The gut microbiota has extensive biological functions, many details of which are only beginning to be understood. Active study of

the function of the gut microbiota in recent years has led to a better understanding of its role in the development and progression of various liver and biliary diseases. Obviously, studying only changes in the structure of the microbiota in various diseases and conditions is not able to answer all questions, since data on the ratio of bacteria do not provide an understanding of their functional activity. In addition, it may also be relevant that bacteria may change their activity in response to patients taking different medications. In this regard, pharmacomicrobiomics represents a promising new area of research[57,58]. It should also be noted that the therapeutic potential of the gut microbiota has limited application to date and is mainly related to dietary modification. In this regard, new studies of the gut microbiota-liver axis may be useful to improve approaches to the treatment of liver diseases.

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