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Gut microbiota alteration and modulation in hepatitis B virus-related fibrosis and complications: Molecular mechanisms and therapeutic inventions

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Abstract

Hepatitis B virus (HBV) has posed a threat to public health, mainly resulting in liver damage. With long-term accumulation of extracellular matrix, patients with chronic hepatitis B are at high risk of developing into liver fibrosis and cirrhosis and even life-threatening hepatic carcinoma. The occurrence of complications such as spontaneous bacterial peritonitis and hepatic encephalopathy greatly increases disability and mortality. With deeper understanding of the bidirectional interaction between the liver and the gut (gut-liver axis), there is a growing consensus that the human health closely relates to the gut microbiota. Supported by animal and human studies, the gut microbiota alters as the HBV-related liver fibrosis initials and progresses, characterized as the decrease of the ratio between "good" and "potentially pathogenic" microbes. When the primary disease is controlled *via* antiviral treatment, the gut microbiota dysfunction tends to be improved. Conversely, the recovery of gut microbiota can promote the regression of liver fibrosis. Therapeutic strategies targeted on gut microbiota (rifaximin, probiotics, engineered probiotics and fecal microbiota transplantation) have been applied to animal models and patients, obtaining satisfactory results.

Key Words: Hepatitis B virus; Gut microbiota; Liver fibrosis; Liver cirrhosis; Hepatic encephalopathy; Fecal microbiota transplantation

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Core Tip: Intimate connection between the gut microbiota alteration and hepatitis B virus (HBV)-related fibrosis and complications has been supported by animal and human studies. Researchers and clinicians are making effort to control and reverse fibrosis by rebuilding a healthy gut microbiota. We herein discuss the gut microbiota alteration in HBV-related fibrosis and therapies targeted on reconstruction of gut microbiota homeostasis.

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INTRODUCTION

Hepatitis B virus (HBV) has brought about substantial global health problems, giving rise to approximately 1.5 million new infections in 2019[1]. Balancing the pathogenic ability and immunity defense, some patients may experience chronic HBV infection, and even chronic hepatitis B (CHB). The different phrases are designed by the presence of hepatitis B e antigen (HBeAg), HBV DNA levels, alanine aminotransferase (ALT) values and liver inflammation, and CHB is mainly characterized by elevated ALT levels and moderate/severe liver diseases[2]. Chronic HBV infection tends to be asymptomatic initially, however, tissue repair against chronic inflammation may result in an immoderate accumulation of extracellular matrix (ECM), so CHB patients are at high risk of developing progressive fibrosis and life-threatening cirrhosis. Complications, such as portal hypertension, spontaneous bacterial peritonitis (SBP)[3] and hepatic encephalopathy (HE)[4], are difficult to prevent and address. With hepatocellular carcinoma (HCC) coming along stealthily[5], approximately 820000 deaths were caused by HBV infection-related causes in 2019[1].

The human intestine, as an organ directly connected with the outside world, is colonized by microbes progressively after birth[6]. The human gut microbiota is now considered to be composed of approximately 10^{14} bacteria[7], 200-300 fungal species[8] and abundant bacteriophages[9], and is increasingly seen as a significant superorganism[10]. Predominant strains in the adult intestine belong to *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria*: *Bacteroidetes* and *Firmicutes* are the most dominant phyla and are mainly composed of gram-negative bacteria and gram-positive clostridia respectively[11]. The composition of the gut microbiota is influenced by age, race, nutrition, diet, immunity, disease and medication use, and has a strong interaction with the host[12-14]. The intimate association between gut microbiota homeostasis and multiple organ disease progression has been confirmed in the past decade, especially in some metabolic disorders[15], and intestinal and liver diseases[16].

The liver is closely connected with the gut *via* the gut-liver axis, defined as the bidirectional interaction between the liver and the gut *via* transport of bile acids, immunoreactive substances, nutrients, *etc.*[17]. When impairment of intestinal barriers and disturbances of the gut microbiota occur, gut-derived microbe/antigen translocation may lead to invasion of the liver. The association between gut microbiota alterations and chronic liver diseases (CLDs) has received great attention.

This review will concentrate on gut microbiota alterations in HBV-related liver fibrosis and summarize the cutting edge of new therapeutic strategies. We will summarize and discuss: (1) Gut microbiota alteration in HBV-related liver fibrosis; (2) Gut microbiota-related mechanisms of liver fibrosis; (3) Gut microbiota dysfunction in liver fibrosis complications; and (4) Gut microbiota-related treatment toward HBV-related fibrosis and complications.

GUT MICROBIOTA ALTERATION IN HBV-RELATED LIVER FIBROSIS

HBV-infected populations tend to obtain a gut microbiota that differs from that of healthy people (Table 1). Depending on host and viral factors, patients with HBV infection may experience different phrases[2]. In this part, gut microbiota alteration in the HBV persistence and different stages of HBV infection will be discussed.

HBV persistence

After the infection, HBV may be spontaneously cleared or cause chronic infection in different individuals: 95% of adult-acquired infections result in spontaneous clearance, while over 90% of newborn infections lead to chronic infections[18]. The same phenomenon has been observed in animal

Table 1 Gut microbiota alteration and additional findings in hepatitis B virus-related fibrosis

Ref.	Population (n)	Detection method	Gut microbiota alteration	Additional findings
Lu <i>et al</i> [30]	Healthy volunteers (n = 32); HBV carriers (n = 30); CHB (n = 31); Decompensated HBV-LC (n = 31)	qPCR	Phylum <i>Bacteroidetes</i> ↓ <i>Firmicutes</i> ↓ Family <i>Bifidobacteria/Enterobacteriaceae</i> ↓	Copies of operons that code for virulence factors markedly increased. Fecal sIgA and TNF-α in decompensated HBV-LC patients were higher than other groups
Xu <i>et al</i> [142]	Healthy volunteers (n = 15); CHB (n = 16); HBV-LC (n = 16)	qPCR	Species (<i>Bifidobacterium</i> specific) <i>B. catenulatum</i> ↓ <i>B. longum</i> ↓ <i>B. dentium</i> ↑	<i>B. dentium</i> , which was considered to be an opportunistic pathogen, increased in HBV-LC patients. Species composition of <i>Bifidobacterium</i> shifted from beneficial to pathogenic
Wu <i>et al</i> [143]	Healthy volunteers (n = 38); Decompensated HBV-LC (n = 61); HBV-LT (after LC) (n = 74)	qPCR	Species (<i>Lactobacilli</i> specific) <i>L. rhamnosus</i> ↓ <i>L. fermentus</i> ↓	Less complex fecal <i>lactobacilli</i> composition was found especially in decompensated HBV-LC patients
Wei <i>et al</i> [38]	Healthy volunteers (n = 120); HBV-LC (n = 120); CTP-A (n = 40); CTP-B (n = 40); CTP-C (n = 40)	Solexa sequencing	Phylum <i>Bacteroidetes</i> ↓ <i>Proteobacteria</i> ↑ Family <i>Enterobacteriaceae</i> ↑ Genera <i>Veillonella</i> ↑	A negative correlation was observed between the Child-Turcotte-Pugh scores and <i>Bacteroidetes</i> ($P < 0.01$)
Wang <i>et al</i> [23]	Healthy volunteers (n = 22); CHB (n = 85); CP-A (n = 76); CP-B (n = 9)	16S rRNA sequencing	Family <i>Lachnospiraceae</i> ↓ <i>Rikenellaceae</i> , ↓ <i>Porphyromonadaceae</i> ↓ <i>Ruminococcaceae</i> ↓ <i>Veillonellaceae</i> ↑	<i>Streptococcus</i> , <i>Veillonella</i> , <i>Streptococcus</i> and <i>Haemophilus</i> had strong correlations with liver function indices and serum metabolites. They were significantly higher in patients with higher Child-Pugh scores. The gut microbiota may be partially involved in the abnormal accumulation of serum metabolites
Deng <i>et al</i> [29]	Healthy volunteers (n = 20); HBV-LC (n = 80); CP-A (n = 30); CP-B (n = 31); CP-C (n = 19)	16S rRNA sequencing	Phylum <i>Firmicutes/Bacteroidetes</i> ↑ Genera <i>Megamonas</i> ↓ <i>Veillonella</i> ↓	Gut microbiota alteration mentioned on the left were all independent risk or protective factors for HBV-LC. Serum endotoxin increased in patients with higher CP classes ($P = 0.000$)
Zeng <i>et al</i> [140]	Healthy volunteers (n = 15); CHB (n = 21); HBV-LC (n = 25); HBV-HCC (n = 21)	16S rRNA sequencing	Phylum <i>Proteobacteria</i> ↑ <i>Bacteroidetes</i> ↑ <i>Firmicutes</i> ↓ Family <i>Bifidobacteria/Enterobacteriaceae</i> ↓	Higher <i>Bacteroidetes/firmicutes</i> ratio represented for higher LPS exposure
Wang <i>et al</i>	Healthy volunteers (n = 21); CHB (n = 69); F0-1 (n = 25)	16S rRNA sequencing	Genera <i>Prevotella</i> ↑	Genera responsible for bile acid metabolism decreased in CHB fibrosis patients

[59]	F2-4 (n = 44)		<i>Bacteroides</i> ↓ <i>Ruminococcus</i> ↓	
Chen <i>et al</i> [28]	Healthy volunteers (n = 21); HBV carriers (n = 23); CHB (n = 28); HBV-LC (n = 25)	16S rRNA sequencing	Phylum <i>Actinobacteria</i> ↑ <i>Bacteroidetes</i> ↓ <i>Firmicutes</i> ↓ <i>Proteobacteria</i> ↑	HBV-LC patients had higher bacterial network complexity with lower abundance of potential beneficial bacterial taxa
Yang <i>et al</i> [27]	Healthy volunteers (n = 31); HBV carriers (n = 24); CHB (n = 56); HBV-LC (n = 54); HBV-ACLF (n = 52)	16S rRNA sequencing	There are fluctuations in the changes	HBV carriers might be the most suitable donors for FMT for higher α diversity and abundance of potential beneficial bacteria
Wang <i>et al</i> [37]	Healthy volunteers (n = 877); CHB (n = 252); HBV-LC (n = 162); HBV-ACLF (n = 212)	16S rRNA sequencing; metagenomic sequencing	Species <i>Enterococcus faecium</i> ↑	High abundance of <i>Enterococcus</i> is associated with progression while that of <i>Faecalibacterium</i> is associated with regression of HBV-ACLF

HBV: Hepatitis B virus; CHB: Chronic hepatitis B; ACLF: Acute-on-chronic liver failure; CP: Child-Pugh scores; CTP, Child-Turcotte-Pugh scores; FMT: Faecal microbiota transplantation; LC: Liver cirrhosis; LT: Liver transplant; qPCR: Quantitative polymerase chain reaction.

experiments, in which hepatitis B surface antigen (HBsAg) of immature mice remained positive[19]. The age-related difference in immune clearance of HBV is consistent with the stabilization time of the gut microbiota, and maturation appears to facilitate HBV clearance by diminishing the tolerance phenotype and stimulating the immunoreactive pathway[19,20]. Similarly, if the gut microbiota was greatly imbalanced by antibiotics, the depletion can impair intestinal barrier function and weaken the ability of humoral and cellular immunity to clear HBV: adult mice with a mature gut microbiota managed to clear HBV after 6 wk of infection, while they failed to do so after antibiotic use[19,21].

Acute HBV infection

Due to the difficulty of studying acute HBV infection in humans, animal studies have been used: the ratio of *Firmicutes*/*Bacteroides* increased in the early stages of infection (Day 14) and decreased significantly over time (Day 49) in two mouse groups that were constructed with different plasmids[22].

Chronic HBV infection and non-end-stage CHB

Compositional changes have already occurred in the gut microbiota in early-stage CHB patients: in the Child-Pugh A and B groups, the abundance of 5 operational taxonomic units (OTUs) belonging to *Actinomyces*, *Clostridium sensu stricto*, unclassified *Lachnospiraceae* and *Megamonas* increased, while 27 OTUs decreased, which belong to *Alistipes*, *Asaccharobacter*, *Bacteroides*, *Butyricimonas*, *Clostridium IV*, etc. [23].

To further understand the gut microbiota dynamics in chronic HBV infection and CHB, there are also studies concentrating on the association with clinical indicators reflecting liver function and infection state. The gut microbiota of subjects from the chronic HBV infection group with normal ALT (NALT) levels was rather similar to those from the healthy volunteers, while significantly different from those from the high ALT level group[24]; however, in a recent study, the authors presented a slightly different perspective that the microbial diversity and abundance of *Lactobacillus*, *Clostridium*, and *Bifidobacterium* were lower in CHB-NALT patients than in healthy volunteers[25]. *Streptococcus*, *Veillonella*, *Streptococcus* and *Haemophilus* showed high correlations with some serum metabolites, including aromatic amino acids (phenylalanine and tyrosine), which are assumed to play pathogenic roles the progression of CHB [23]. The gut microbiota also varies according to viral load: HBV-infected individuals with a low viral load showed high diversity and carry a predominance of taxa associated with fatty acid and lipid metabolism[26].

As the disease progresses, the gut microbiota changes dynamically: the α diversity of asymptomatic HBV carriers slightly increased compared with that of healthy donors, while that of patients in the other three groups (CHB, liver cirrhosis, and acute-on-chronic liver failure (ACLF)) decreased with the severity of the disease[27]. The gut microbiota of patients with liver cirrhosis showed lower diversity and higher network complexity[28]. *Veillonellaceae* and *Lachnospiraceae* families were depleted in patients with liver cirrhosis compared with those in healthy volunteers, while *Megamonas* and *Veillonella* genera were depleted and enriched in patients, respectively[29]. Additionally, copy numbers of *Enterobacteriaceae* increased and lactic acid bacteria were depleted, with marked variation in the intestinal community of CHB patients[30]. The *Bifidobacteria*/*Enterobacteriaceae* ratio can be used for tracing the progression of liver disease[30]. With the magnitude of severity of liver disease (estimated as increasing liver Child-Pugh score), partial functional genes were correlated, such as those encoding aspartate-

ammonia ligase, transaldolase, adenylosuccinate synthetase and IMP dehydrogenase[31]. According to the combined results of multiple studies, there is a well-acknowledged decrease in *Firmicutes* abundance and increase in *Proteobacteria* during the progression of HBV-related fibrosis.

HCC and end-stage CHB

Liver cirrhosis is a dangerous premalignant condition with an increasing incidence of genetic aberrations and an elevated risk of HCC[32,33]. HCC patients tend to present a distempered gut microbiota and abnormal metabolites[34]. The butyrate-producing genera were depleted, while lipopolysaccharide (LPS)-producing genera were enriched in liver cirrhosis and HCC patients, and *Clostridioides* abundance was generally observed to be positively related to the tumor size of HCC[35]. In another study, *Bacteroides*, *Lachnospiraceae incertae sedis*, and *Clostridium XIVa* were enriched in HCC patients, and there was a consistency of positive correlation with the tumor burden[36]. By integrating the clinical characteristics and database analysis, serum bile acids may be the communication mediators between these three genera and the host transcriptome[36]. HCC can be secondary to a number of causes, including HBV, *Hepatitis C virus* (HCV) and so on. Compared with non-HBV non-HCV HCC, the abundance of *Prevotella* was much greater in HBV-related HCC group[34]. HBV-related HCC group had higher abundance of pathways related to DNA formation and function (including chaperones and folding catalysts, DNA replication proteins and chromosome), which supported that HBV can impair the normal function of DNA[34].

Additionally, dynamic alteration of gut microbiota is a valuable indicator to predict the prognosis of end-stage liver disease. The richness of *Enterococcus* was significantly higher in the HBV-related ACLF progression group, while a high abundance of *Faecalibacterium* was associated with regression (groups were divided according to the model for end-stage liver disease at discharge)[37]; a higher abundance of *E. coli* is consistent with an increasing level of LPS ligand in the circulation of patients with end-stage liver disease[38-40].

GUT MICROBIOTA-RELATED MECHANISMS OF LIVER FIBROSIS

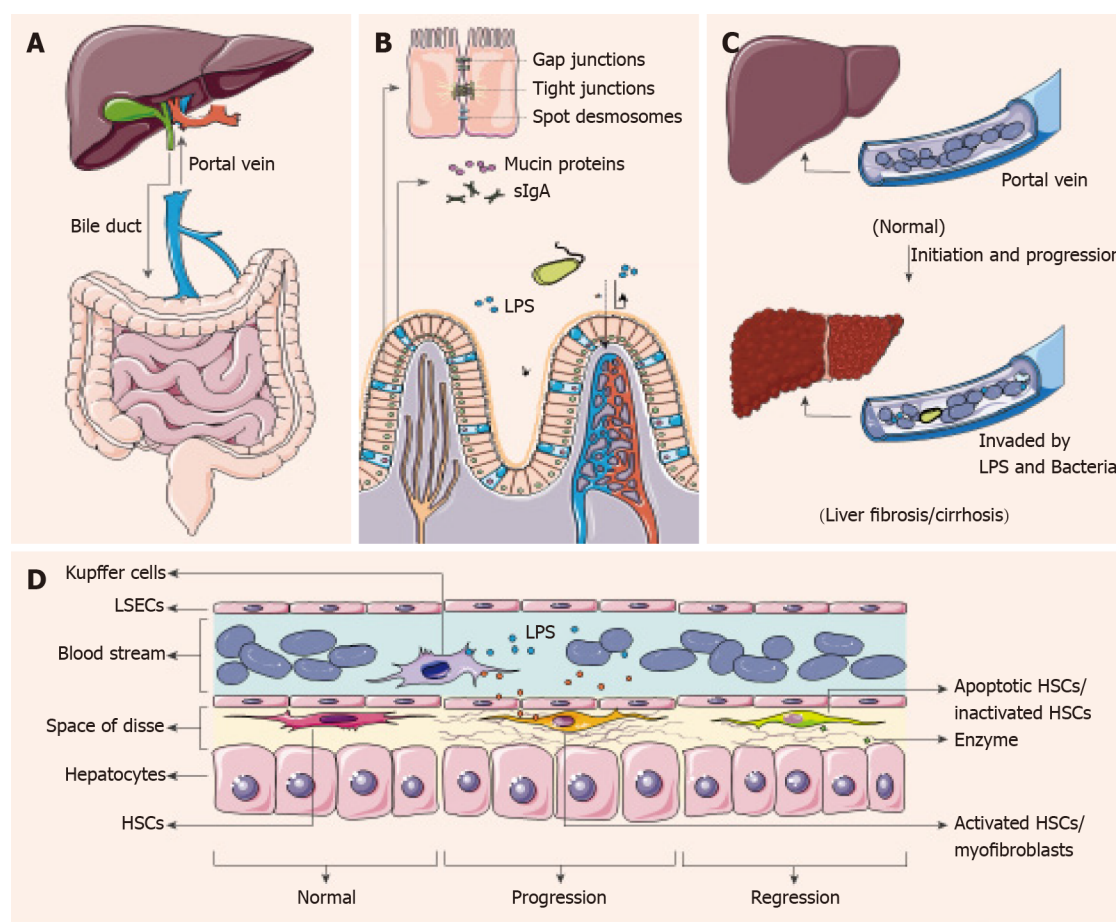
Liver fibrosis is fibrous scar caused by excess accumulation of ECM[41]. It is driven by the chronic and persistent occurrence of parenchymal injury and the activation of the inflammatory response, followed by a continuous repair reaction and liver fibrogenesis[42]. For HBV infection, liver infringement comes from not only HBV but also gut-derived microbe/antigen translocation and abnormal metabolites.

There is a close connection between the gut and liver through known organic pipelines (bile duct and portal vein)[43], and whether there are detours needs further study. The liver produces and sends primary bile acids (BAs) and immunologic active materials (some antimicrobial peptides) through the biliary tract to assist in intestinal digestion and immunity. Conversely, the portal vein carries secondary BAs, nutrients, gastrointestinal metabolites from the gut to the liver, to provide nutrients and get detoxification and biotransformation[17,44] (Figure 1A).

In a non-disease state, intestinal physical and chemical barriers effectively block pathogens or toxic substances and decrease bacterial colonization. The barriers mainly include mucin proteins secreted by goblet cells, secretory IgA (sIgA) secreted by plasma cells in lymphoid follicles of the lamina propria and tight junctions between intestinal epithelial cells (IECs)[45] (Figure 1B). Disorders of these barriers can lead to increased intestinal permeability and translocation of microbial components or metabolites (LPS, microbial DNA) in CLD patients, allowing microbes and antigens to translocate into the portal vein[45], and subsequently induce chronic or acute inflammatory responses of different tissues and organs[46] (Figure 1C).

Intestinal barrier impairment

The gastrointestinal mucus layer is the first line of defense against microbes, and the mobility enables the layer to carry pathogens distally and reduce microbial colonization[47]. The experimental mouse models with liver cirrhosis [induced by bile-duct ligation (BDL) or tetrachloromethane (CCl₄)] show a reduced thickness of the mucus layer, with loss of goblet cells[48]. These cirrhotic mice show pathological bacterial translocation, which has not been found in healthy or pre-hepatic portal-hypertensive mice[48]. sIgA is the predominant contributor to mucosal immunity, recognizing and eliminating bacterial protein antigens, and it also participates in barrier layer limitation of microbe/antigen translocation[49]. Patients with HBV-induced decompensated cirrhosis have increased sIgA content in blood and stool[30], consistent with the increased bacterial migration. Simultaneously, intestinal tight junctions are weakened in patients with liver cirrhosis, and the expression of tight junction proteins is decreased[50,51]. Zonulin, an effective physiological regulator of tight junctions, is one of the markers of intestinal permeability[52]. Serum zonulin content is significantly increased in HBV-related liver cirrhosis and HCC patients and the levels are correlated with the stages[53].



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Figure 1 Mechanism of gut microbiota-related liver fibrosis/cirrhosis. A: Gut-liver axis. The close bidirectional connection between gut and liver is mainly through the portal vein and bile duct; B: Intestinal barriers. From the intestine lumen, intestinal barriers are mainly formed by mucin proteins, sIgA and intercellular junctions, especially tight junctions between intestinal epithelial cells. The asterisk means when the intestinal barriers are weakened or broken, microbe/antigen translocation ensues; C: Liver fibrosis/cirrhosis and gut microbe/antigen translocation. Compared with normal state, gut microbe/antigen translocation and liver fibrosis/cirrhosis may drive each other in chronic hepatitis B patients; D: Mechanisms of liver fibrosis/cirrhosis process and regression. Receiving the activation signal, hepatic stellate cells (HSCs) are activated into fibroblasts to form the fiber. As the activation signal ceases, the activated HSCs are inactivated or apoptotic. When fiber degradation predominated, fibrosis is reversed. HSCs: Hepatic stellate cells; LPS: Lipopolysaccharide; LSECs: Liver sinusoidal endothelial cells.

Gut-derived microbe/antigen translocation and metabolic dysbiosis

The impairment of the intestinal barrier greatly reduces the efficiency of blocking microbe/antigen translocation. Gut-derived microbes or fragments and metabolites enter the venous system, travel through the portal vein to invade the liver. Diversity of circulating bacteria in cirrhosis patients is consistent with the presence of dysbiosis[54]. Recent studies have also supported that the occurrence of intestinal bacterial overgrowth and bacterial translocation in cirrhosis using methods such as bacterial DNA sequencing[55] and fluorescence microscopy[21] and suggested that the mechanism is associated with antimicrobial host defense[56]. Simultaneously, LPS is one of the component of the outer membrane of Gram-negative bacteria, mainly from *Enterobacteriaceae*[57]. The dysbiosis of the gut microbiota in mice leads to endotoxemia, which may bring about Kupffer Cell (KC) IL-10 production and KC-mediated T cell suppression[57]. And endotoxemia is highly related to the severity in liver diseases and complications[58].

Additionally, abnormal composition of the gut microbiota results in metabolic disorders, among which the metabolism of BAs has aroused great concern[25]. The level of fecal total BAs decreased and the ratio of conjugated and primary BAs increased in CHB patients without liver cirrhosis, which may be the prelude of following changes[25]. And there is a trend that abundance of the bacteria genera responsible for BA metabolism is decreased in CHB patients with moderate/advanced fibrosis[59,60]. There is also a link between gut bacteria-controlled BA metabolism and liver antitumor immunosurveillance *via* natural killer T (NKT) cells[61].

Immune-mediated fibrosis and regression

Pattern recognition receptors (PRRs) are highly conserved host sensors that are able to recognize

exogenous and endogenous antigens, including pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs)[62]. PRRs are expressed by a plethora of immune cells, especially macrophages[63]. Macrophages could be at the center of innate immune regulation, linking microbe/antigen translocation and liver inflammation or fibrosis[64]. Recognition of PRRs sends the initial signal to active downstream adaptor proteins to undergo maturation and assemble transcription factors, such as nuclear factor (NF)- κ B[65,66]. The produced cytokines then recruit inflammatory cells, drive antimicrobial activities and promote myofibroblast formation[67].

Myofibroblasts, the collagen-producing cells, are not present in healthy livers[68]. In response to toxic liver injury, myofibroblasts are mainly transformed from activated hepatic stellate cells (HSCs)[69]. There are four different stages of HSCs, namely, quiescent, activated (equivalent to collagen type I-producing myofibroblasts), inactivated and senescent[41]. Under physiological conditions, quiescent HSCs stay in the space of Disse and function as the major vitamin A storage site[70]. Stimulated by several cytokines (especially transforming growth factor (TGF)- β)[71], quiescent HSCs modulate phenotypes and transform into activated HSCs, and the activated HSCs migrate and secrete ECM to produce a fibrous scar[41]. After removing the initial driver, there is a decrease in the levels of pro-inflammatory cytokines (interleukin-6, interleukin-1 β and tumor necrosis factor) and TGF- β , and a rapid decline of the counts of activated HSCs[41]. Activated HSCs can be transformed into inactivated or senescent cells, and stop producing type-I collagen fibers[72]. Later, when fiber degradation by matrix metalloproteinases overwhelms fiber formation, liver fibrosis can be controlled, regressed and even reversed[73].

In conclusion, increased microbe and endotoxin loads in the portal vein cause PRR activation on immune cells, especially on macrophages, which leads to the activation of quiescent HSCs into activated HSCs[44,66]. Later, activated HSCs proliferate in response to various cytokines, secrete type-I collagen fiber and make liver fibrotic[41]. Upon cessation of underlying injury, myofibroblasts undergo inactivation or apoptosis, and fibrosis can be discontinued or reversed[41] (Figure 1D). This is the mechanism of effective treatment to control and regress liver fibrosis.

GUT MICROBIOTA DYSFUNCTION IN LIVER FIBROSIS COMPLICATIONS

As mentioned above, gut microbiota alterations may drive immune-related inflammation and fibrosis in the liver. Due to the accumulation of collagen fiber, liver stiffness is increased, bloodstream transport is blocked, healthy liver parenchyma is replaced and liver biotransformation and detoxification abilities are weakened[74]. As the disease progresses into the decompensation stage, patients may experience deadly complications, such as portal hypertension, spontaneous bacterial peritonitis (SBP) and HE. The relationship among gut microbiota alteration, liver fibrosis and portal hypertension is similar to the question of the chicken and the egg, as they drive and affect each other[75]. Compared with compensated cirrhosis, gut microbiota composition is characterized by an increase in the abundance of potentially pathogenic bacteria in the decompensation stage, especially *Alcaligenaceae*, *Porphyrromonadaceae*, *Veillonellaceae* and *Enterobacteriaceae*[76].

SBP

SBP refers to the infection of ascites without an apparent intra-abdominal focus[77]. It is a severe infection and is often fatal in patients with cirrhosis and ascites[78]. The pathogen of SBP in liver cirrhosis patients is mainly from the intestinal tract.

More than two decades ago, DNA fragments of 30 bacterial isolated from ascites, mesenteric lymph nodes, portal blood, and ileal flora were compared[79]. The same bacterial strain was simultaneously isolated in ascites and in mesenteric lymph nodes and/or the ileum in 7/8 (87%) instances[79]. Intraperitoneal LPS increased TLR4 (Toll-like receptor 4, the canonical PRR for LPS) expression and amplified portal hypertension in rat liver fibrosis[80].

HE

HE is a fatal central nervous system complication caused by acute and chronic hepatitis or decompensated cirrhosis[81], which is considered consciousness disturbance after ammonia-related cerebral edema[82]. HE patients tend to have a poor prognosis and high mortality and recurrence rates, with greatly increasing economic and nursing burdens[83].

Currently, there is an increasing consensus that the gut microbiota and gastrointestinal metabolites play an important role in the initiation and progress of HE. On the basis of the gut-liver axis mentioned above, researchers proposed the concept of the gut-brain-liver axis to describe the role of the gut microbiota[84]. Cognitive dysfunction in cirrhosis is related to a decrease in the abundance of autochthonous families and an increase in *Alcaligenaceae* and *Porphyrromonadaceae*[85,86].

On the one hand, gut microbiota alteration in the decompensation stage is consistent with the accumulation of microbe-derived products, including ammonia, mercaptans, benzodiazepine-like substances, and indoles[76]. These products can pass the blood-brain barrier and alter astrocyte function, resulting in osmotic or oxidative stress, mitochondrial dysfunction, neurotransmission

disorder, *etc.*[81]. On the other hand, neurotransmitters produced by the microbiota, including serotonin, dopamine, and aminobutyric acid, can act on specific receptors of exogenous primary afferent neuron cells, or cross the blood-brain barrier to act as active neurotransmitters[87]. The complex network among the enteric nervous system, the autonomic nervous system and the neuroendocrine and neuroimmunity systems of the central nervous system has a mutual impact on the gut microbiota, and the up-down or down-up regulation mechanisms need further exploration[84].

GUT MICROBIOTA-RELATED TREATMENT TOWARD HBV-RELATED FIBROSIS AND COMPLICATIONS

Based on the fibrosis regression theory mentioned above, removing the cause is the key to controlling and reversing liver fibrosis (Tables 2 and 3). For more than a decade, antiviral therapy has been recognized as an effective method to prevent, control and even reverse fibrosis and cirrhosis[88]. Rifaximin reduces the virulence of the overgrown gut microbiota[89]. With further understanding of the connection between the gut microbiota and HBV-related fibrosis, scientists have suggested that host health depends on the balance of the composition of the entire microbial community rather than one or a few dominant organisms[90]. New therapeutic strategies for HBV-related fibrosis, cirrhosis and complications have been broadened to regulate the gut microbiota through probiotic supplementation and microbiota transplantation from healthy donors.

Gut microbiota stabilization with antiviral treatment

At present, the main endpoint of all current treatment strategies is to maintain long-term suppression of HBV replication[2]. Two main options are nucleoside analogs (NAs) and interferon alpha[91]. NAs with a high barrier to HBV resistance, including entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), are believed to be favorably safe and long-acting[92]. Antiviral treatment (AVT) exerts a positive influence on survival rate and quality of life by preventing disease progression, reversing and degrading fibrosis and cirrhosis[93,94], and even reducing HCC incidence and mortality in CHB patients[95].

ETV therapy reverses gut microbiota dysbiosis induced by HBV infection in a mouse model[96]. And in a controlled cross-sectional and longitudinal real-world study, the species abundance of the gut microbiota increased markedly after ETV treatment[97]. After 8 wk of ETV treatment, the abundance of *Clostridium sensu stricto* 1, *Erysipelotrichaceae* UCG-007 and *Intestinibacter* increased significantly, and that of *Streptococcus*, *Atopobium* and *Murdochella* was markedly reduced[97]. Although the addition of *Clostridium butyricum* (CB) to ETV failed to improve the serum biochemical, immunologic and virologic variables, addition of CB affected the gut microbiota in CHB patients treated with ETV[98]. While there is a lack of dynamic and synergetic studies on liver fibrosis outcomes and gut microbiota alterations during AVT, collaborative microbes contributing the most to antiviral-intervened HBV-related fibrosis cannot be pinpointed definitively.

Rifaximin

Rifaximin is a rifamycin-based nonsystemic antibiotic with low gastrointestinal absorption and good antibacterial activity[89,99]. The gastrointestinal tract is the main therapeutic target of rifaximin, and it has been widely used in controlling HE with infrequent side effects and a favorable long-term safety profile[100,101].

Current ideas suggest that rifaximin may have positive implications for liver cirrhosis and complications by acting on the gut microbiota. However, according to a randomized trial, there seems to be a minor impact on the composition of the gut microbiota[102]. Enrolled patients with cirrhosis and ascites were divided into two groups to receive rifaximin or placebo for 4 wk. Rifaximin decreased gut bacterial abundance, while no effect on particular species was observed; blood bacterial richness was decreased and the difference in *Pseudomonadales* abundance was relatively obvious[102]. And there was no difference in circulating markers of inflammation between the two groups[102]. Two additional studies also supported that rifaximin has little influence on gut microbiota abundance[103], but the metabolite levels altered: after rifaximin application, endotoxemia was relieved, and serum saturated and unsaturated fatty acid levels were increased significantly[104]. The former conclusion agreed with a study on experimental mice[105]. Therefore, rather than having a bactericidal effect, rifaximin seems to have direct effects on bacterial function and virulence[89].

Probiotics and synthetic probiotics

Probiotics are living nonpathogenic microorganisms, and treatment doses (at least 10⁶ viable CFU/g) may help temper the gut microbiota[106]. *Lactobacillus* and *Bifidobacterium* genera are widely reported as clinically available probiotics[107]. In recent studies, probiotics have been broadly used to regulate the gut microbiota for further positive influences on primary diseases, such as gastrointestinal dysfunctions [108,109], metabolic diseases[110,111] and psychoneurotic disorders[112,113].

Table 2 Gut microbiota-related treatment toward hepatitis B virus-related fibrosis and complications (studies in animal models)

Ref.	Study populations (n)	Treatment and grouping (n)	Conclusions
Antiviral therapy			
Li <i>et al</i> [96]	AAV-mediated persistent HBV infection (AAV-HBV) mice (n = 10)	35 d after HBV infection, 4 wk of daily ETV treatment. ETV (n = 5)	Gut microbiota dysbiosis of the AAV-HBV mice was reversed by ETV treatment with restored α diversity and changed proportion of <i>Akkermansia</i> , <i>Lactospiraceae</i> and <i>Marvinbryantia</i>
Rifaximin			
Kang <i>et al</i> [105]	Germ-free mice (n = 16)	15 d of rifaximin 100 mg/(kg·d), or humanized with stools from a HCV-induced cirrhotic patient with MHE. Rifaximin (n = 4); Humanized (n = 4); Rifaximin + humanized (n = 4)	Rifaximin beneficially altered intestinal ammonia generation by regulating intestinal glutaminase expression independent of gut microbiota. MHE-associated fecal colonization resulted in intestinal and systemic inflammation. It was ameliorated with rifaximin
Engineered probiotics			
Nicaise <i>et al</i> [120]	Ornithine transcarbamoylase-deficient Sparse-fur mice; Carbon tetrachloride rats; Thioacetamide-induced acute liver failure mice	NCIMB8826 (wild-type strain <i>Lactobacillus plantarum</i>), or EV101 (engineered <i>Lactobacillus plantarum</i> , LDH ⁺ /AlaD ⁺) oral and intrarectal administration	EV101 administration was effective in controlling hyperammonemia in constitutive animal models with a significant effect on survival, which might be involved with direct ammonia consumption in the gut
Kurtz <i>et al</i> [121]	Ornithine transcarbamoylase-deficient <i>spfash</i> mice; Thioacetamide-induced acute liver failure mice; Healthy volunteers (n = 52)	Non-modified <i>Escherichia coli</i> Nissle 1917 (EcN), SYNBI020 (engineered EcN, Δ argR, Δ thyA, malEK:PfnrS-argA ^{tr}) administration	SYNBI020 converted NH ₃ to L-arginine in vitro, and reduced systemic hyperammonemia, improved survival in mouse models. SYNBI020 was well tolerated in healthy volunteers
Ochoa-Sanchez <i>et al</i> [122]	Bile-duct ligated rats	Non-modified EcN, S-ARG, or S-ARG + BUT administration	S-ARG converted ammonia to arginine, it was further modified to additionally synthesize butyrate, which had the potential to prevent HE
FMT			
Liu <i>et al</i> [134]	Germ-free mice	Sterile supernatant or entire stool from pre-FMT and post-FMT cirrhotic patients with HE was transplanted to Germ-free mice	Transferred microbiota mediated neuroinflammation. Cirrhosis-associated dysregulation of gut microbiota was related with frontal cortical inflammation

AAV: Adeno-associated virus; HBV: Hepatitis B virus; ETV: Entecavir; HCV: Hepatitis C virus; MHE: Minimal hepatic encephalopathy; HE: Hepatic encephalopathy; FMT: Fecal microbiota transplantation.

The role of probiotics in complications of HBV-related fibrosis and cirrhosis has been validated, especially for HE. Probiotics can drive the gut microbiota, triggering emotional brain signatures[114]. For minimal HE, probiotic therapy (*Lactobacillus acidophilus*) can improve blood ammonia and psychometric tests and reduce the risk of overt encephalopathy deterioration[115]. Further studies confirmed that patients' cognition, venous ammonia level and intestinal mucosal barrier function were significantly improved after 3 mo of probiotic use (*Clostridium butyricum* combined with *Bifidobacterium infantis*), and the predominant bacteria (*Clostridium cluster I* and *Bifidobacterium*) were obviously enriched in the probiotic-treated group, while *Enterococcus* and *Enterobacteriaceae* were depleted[116]. The combination of probiotics and lactulose is effective for the secondary prophylaxis of HE patients with cirrhosis[117]. Simultaneously, probiotics may work by promoting the growth of beneficial microbes and preventing PAMP-mediated liver inflammation and the anti-proliferative, anti-angiogenic, and anti-metastatic effects of the antioxidant can block the progress of HCC[118].

Additionally, rapid progress in synthetic biology has brought more options, which makes engineered live biotherapeutics an available and promising strategy[119]. More than one decade ago, the genetically engineered ammonia-hyperconsuming strain NCIMB8826 was verified to exhibit a beneficial effect at a lower dose than its wild-type counterpart[120]. In recent years, more engineered bacteria have been constructed to accelerate ammonia metabolism, reduce blood ammonia concentration and reduce HE incidence[121,122]. One team from Synlogic Inc. engineered oral probiotic *Escherichia coli* Nissle 1917 (EcN) to create strain SYNBI020[121]. SYNBI020 is able to convert NH₃ to L-arginine *in vivo* and reduce hyperammonemia in two mouse models (ornithine transcarbamoylase-deficient *spfash* mice and thioacetamide-induced liver injury mice). Satisfyingly, it showed metabolic activity and good tolerance in a phase 1 clinical study of 52 healthy adult volunteers. Later, another group modified EcN to consume and convert ammonia to arginine, which was further modified to additionally synthesize butyrate[122]. Both of these studies showed that engineered probiotics have positive therapeutic significance for hyperammonemia and underlying potential for HE prevention. However, these strains have not progressed to clinical studies in hyperammonemia patients, and the clinical effects need further study.

Table 3 Gut microbiota-related treatment toward hepatitis B virus-related fibrosis and complications (studies in human)

Ref.	Study populations (n)	Treatment and grouping (n)	Conclusions
Antiviral therapy			
Lu <i>et al</i> [97]	Healthy volunteers (n = 30); CHB (n = 30)	8 wk of daily ETV treatment. ETV (n = 30)	After ETV treatment, gut microbiota abundance increased markedly, blood biochemical, immunological and virological responses improved significantly
Lu <i>et al</i> [98]	Healthy volunteers (n = 30); CHB patients (n = 60)	8 wk of daily ETV treatment, or with additional CB. ETV (n = 30); ETV + CB (n = 30)	Additional CB fail to improve blood biochemical, immunological and virological responses, but affects the gut microbiota in the CHB patients treated with ETV
Rifaximin			
Bajaj <i>et al</i> [104]	Decompensated LC patients with MHE (n = 20); CHB (NM)	8 wk of rifaximin 550-mg BD. Rifaximin (n = 20)	Rifaximin affected little on gut microbiota, there was just a modest decrease in <i>Veillonellaceae</i> and increase in <i>Eubacteriaceae</i> . Rifaximin significantly improved cognition and endotoxemia, it increased increase in serum saturated and unsaturated fatty acids post-rifaximin
Lutz <i>et al</i> [144]	Decompensated LC patients with ascites (n = 152); Viral hepatitis (n = 35)	Prophylactic antibiotic treatment before the time of paracentesis. Rifaximin (n = 27); Other systemic antibiotics (n = 17)	Prophylactic rifaximin did not reduce SBP occurrence. Prophylactic rifaximin was associated with the dominant bacteria in ascites: <i>Escherichia coli</i> and <i>enterococci</i> were dominant of patients without prophylaxis, <i>klebsiella</i> species were mostly recovered from the rifaximin group
Kimer <i>et al</i> [102]	Decompensated LC patients (n = 54); CHB (NM)	4 wk of rifaximin 550-mg BD or placebo BD. Rifaximin (n = 36); Placebo (n = 18)	Rifaximin had minor effects on bacteria translocation and gut microbiota. Rifaximin showed little impact on the inflammatory state (reflected as the level of TNF- α , IL-6, IL-10, IL-18, SDF-1 α , TGF-1 β , CRP)
Kaji <i>et al</i> [103]	Decompensated LC patients (n = 30); CHB (n = 4)	4 wk of rifaximin 1200 mg/d. Rifaximin (n = 30)	Rifaximin alleviated HE and endotoxemia with improved intestinal hyperpermeability, and it is involved in a gut microbial change. Rifaximin didn't affect serum proinflammatory cytokine levels (TNF- α , IL-6, IFN- γ , IL-10)
Probiotics			
Agrawal <i>et al</i> [117]	LC patients with recovered HE (n = 235); CHB (n = 49)	3 mo of lactulose 30–60 mL/d, or 3 capsules of probiotics per day, which contained 4 strains of <i>Lactobacillus</i> . Lactulose (n = 80); Probiotics (n = 77)	Lactulose and probiotics were effective for secondary prophylaxis of HE in cirrhotic patients
Ziada <i>et al</i> [115]	Decompensated LC patients with MHE (n = 90); CHB (NM)	4 wk of lactulose 30–60 mL/d, or 3 capsules of probiotics per day, which contained <i>Lactobacillus acidophilus</i> . Lactulose (n = 30); Probiotics (n = 30)	Probiotic was better tolerated than lactulose. Both of them can improve blood ammonia and psychometric tests and reduce the risk of developing overt HE. Magnetic resonance spectroscopy showed more improvement in the levels of brain neurometabolites in the probiotic group
Xia <i>et al</i> [116]	Decompensated HBV-LC patients with MHE (n = 67)	3 mo of probiotics 1500-mg TD, which contained <i>Clostridium butyricum</i> combined with <i>Bifidobacterium infantis</i> . Probiotics (n = 30)	After probiotics treatment, the therapeutic bacteria were significantly enriched, while <i>Enterococcus</i> and <i>Enterobacteriaceae</i> were decreased. Probiotics contributed to the improved cognition and the decreased ammonia levels
FMT			
Ren <i>et al</i> [132]	CHB with positive HBeAg, received over 3 yr of antiviral treatment (n = 18)	FMT was performed by gastroscopy every 4 wk until HBeAg clearance. FMT (n = 5)	FMT was effective on HBeAg-positive CHB, especially in patients who could not cease the oral antiviral treatment even after long-term treatment
Bajaj <i>et al</i> [135]	Decompensated LC patients with recurrent HE (n = 20). CHB (NM)	After 5 d of antibiotics, FMT was performed by enema, or standard of care (SOC, rifaximin/lactulose) was applied. FMT (n = 10); SOC (n = 10)	FMT increased diversity and beneficial taxa of gut microbiota, improved cognition and showed good tolerance, other than SOC
Bajaj <i>et al</i> [136]	Decompensated LC patients with recurrent HE (n = 20). CHB (NM)	FMT was performed by enema, or standard of care (SOC, rifaximin/lactulose) was applied. FMT (n = 10); SOC (n = 10)	Oral FMT capsules are safe and well tolerated. Post-FMT, duodenal mucosal diversity increased with higher <i>Ruminococcaceae</i> and <i>Bifidobacteriaceae</i> and lower <i>Streptococcaceae</i> and <i>Veillonellaceae</i> . Reduction in <i>Veillonellaceae</i> were noted post-FMT in sigmoid and stool
Chauhan <i>et al</i> [133]	CHB with positive HBeAg, received over 1 years of antiviral treatment (n = 18)	6 FMTs were performed by gastroscopy every 4 wk FMT (n = 12)	FMT appeared to be safe and effective on HBeAg-positive CHB in viral suppression and HBeAg clearance

CHB: Chronic hepatitis B; CB: *Clostridium butyricum*; CRP: C-reactive protein; EcN: *Escherichia coli* Nissle 1917; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HE: Hepatic encephalopathy; IFN: Interferon; IL: Interleukin; LC: Liver cirrhosis; MHE: Minimal hepatic encephalopathy; NM: Not mentioned; SBP: Spontaneous bacterial peritonitis; SDF-1 α : Stromal cell-derived factor 1- α ; TDF: Tenofovir disoproxil fumarate; TGF-1 β : Transforming growth factor β -1; TNF: Tumor necrosis factor; FMT: Faecal microbiota transplantation.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is an emerging treatment method that transfers the gut microbiota from a healthy donor to a patient[123]. Due to its ability to directly reshape or rebuild the recipient's gut microbial communities, FMT is one of the most promising therapies balancing and stabilizing the gut microbiota[76], and it has been applied to research-based treatment in animal models of a variety of diseases[124,125] and to study the mechanisms[126,127]. In recent years, FMT has been expanded to clinical treatment for human disease as a noninvasive strategy for conditions including recurrent *Clostridium difficile* infection[128], inflammatory bowel disease[129], severe obesity and metabolic syndrome[130]. Regarding the mechanism, the gut microbiota structure can be improved by FMT, and a clinical trial employing autologous FMT supported this point[131].

Clinical trials have also aimed to determine whether CHB patients can benefit from FMT therapy. In a pilot study carried out in China, FMT showed the potential to induce HBeAg clearance in HBeAg-positive CHB patients after long-term AVT: There was a significant HBeAg level decline in the FMT group (FMT combined with AVT), while no decline in the control group (AVT only) was found[132]. The results were consistent with a nonrandomized controlled clinical trial carried out in India: after 1 year of FMT therapy for 6 terms, the FMT group (FMT + AVT) seemed to show potential effectiveness and safety compared with those of the AVT group (AVT only)[133]. Some researchers have also hypothesized that FMT of some potential beneficial bacteria can change the occurrence of disease, and HBV carriers might be the most suitable donors for slightly higher microbiota abundance[27]. However, due to the limitations of a small number of participants and a lack of randomized clinical trials, further well-designed clinical trials are needed to confirm the initial assumptions and promote clinical practicability.

Studies on FMT for HE animal models or patients show satisfactory results. In animal experiments, neuroinflammation alleviation was found in cirrhosis model mice receiving FMT[134]. In a randomized clinical trial, FMT from rationally selected donors helped reduce and improve hospitalizations and improve cognition and dysbiosis for cirrhosis with recurrent HE[135]. Later, the same team verified the safety of FMT capsules through a phase 1, randomized and placebo-controlled clinical trial[136]. In addition to integral inoculation, selective inoculation of specific strains also plays an ameliorating role. Transplanting low-urease altered Schaedler flora to mice prepared with a depleted microbiota led to durable reduction in fecal urease activity and ammonia production[137]. The symbiotic pair of *Lactobacillus reuteri* JBD400 and *Streptococcus rubneri* JBD420 cooperatively improved transplantation efficiency 2.3×10^3 times more than that of sole transplantation and significantly lowered blood ammonia levels [138].

CONCLUSION

Consequently, gut microbiota alteration has been observed to be related to HBV-related fibrosis initiation and progression, and it is a promising therapeutic target. According to current studies, HBV persistence and clearance show consistency with the maturity and health of the gut microbiota[19,21]. With an increase of Child-Pugh scores and the model for end-stage liver disease, the gut microbiota is characterized by a decrease in the ratio of "good" to "potentially pathogenic" bacteria, and species diversity tends to decrease[139,140]. However, it is difficult to clarify which is the initiating factor between gut microbiota alteration and HBV-related fibrosis progression. Existing studies tend to be descriptive and lack HBV-specific exploration. Gut microbiota-related mechanisms are based on the gut-liver axis and immune-mediated response, briefly including intestinal barrier impairment, PRR activation, cytokine production, HSC activation and transformation, and fiber secretion and formation [41]. When the driver is removed, activated HSCs are inhibited or become apoptotic, and fiber scars are degraded, resulting in fibrosis regression[41].

Beyond theory, quite a few studies have begun examining therapeutic inventions. AVT can effectively control or even reverse HBV-related liver fibrosis, during which the gut microbiota gradually returns to homeostasis[96,97]. Rifaximin may decrease the virulence of the overgrown gut microbiota[89]. Probiotics and FMT are the most popular gut microbiota targeted therapies, and they are moving from the laboratory to the clinic. In addition, synthetic probiotics and selective microbiota transplantation may make these therapies more precise, and bring fewer side effects.

However, current studies do have limitations. There is a lack of in-depth research on the specific molecular mechanisms of the gut microbiota. Further clinical studies are needed to determine its effectiveness in patients with HBV-induced liver cirrhosis in the real world[141]. We must also admit that age, host location, dietary habits have a great impact on the gut microbiota, which leads to the lack of consistency and comparability of the alterations in gut microbiota in different studies. Therefore, diagnosis potential of microbial markers should be considered the factors mentioned above. We are looking forward to more powerful studies to strengthen the theoretical foundation and promote clinical application.

FOOTNOTES

Author contributions: Ren ZG and Li A designed the study; Li YG, Yu ZJ, Li A and Ren ZG collected data and summary viewpoints; Li YG wrote the manuscript; Ren ZG and Li A revised the manuscript; and All authors reviewed and approved the manuscript.

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