



Research
Medical Engineering—Review

Gut Microbiota Modulation: A Viable Strategy to Address Medical Needs in Hepatocellular Carcinoma and Liver Transplantation



Ze Xiang^{a,b,c,#}, Jian Wu^{d,#}, Jiarui Li^{b,#}, Shusen Zheng^{e,f}, Xuyong Wei^{a,c,*}, Xiao Xu^{b,c,*}

^a Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China

^b Zhejiang University School of Medicine, Hangzhou 310058, China

^c Key Laboratory of Integrated Oncology and Intelligent Medicine of Zhejiang Province, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China

^d Department of Clinical Laboratory, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou 215008, China

^e Shulan (Hangzhou) Hospital, Zhejiang Shuren University School of Medicine, Hangzhou 310022, China

^f National Health Commission (NHC) Key Laboratory of Combined Multi-organ Transplantation, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

ARTICLE INFO

Article history:

Received 25 October 2022

Revised 18 December 2022

Accepted 30 December 2022

Available online 14 April 2023

Keywords:

Gut microbiota

Hepatocellular carcinoma (HCC)

Liver transplantation (LT)

Clinical value

Mediating mechanism

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver, posing a significant threat to public health. Although liver transplantation (LT) is an effective treatment for HCC, ischemia-reperfusion (I/R) injury, transplant rejection, and complications after LT can greatly reduce its effectiveness. In recent years, transplant oncology has come into being, a comprehensive discipline formed by the intersection and integration of surgery, oncology, immunology, and other related disciplines. Gut microbiota, an emerging field of research, also plays a crucial role. Through the microbiome–gut–liver axis, the gut microbiota has an impact on the onset and progression of HCC as well as LT. This review summarizes the mechanisms by which the gut microbiota affects HCC and its bidirectional interactions with chronic liver disease that can develop into HCC as well as the diagnostic and prognostic value of the gut microbiota in HCC. In addition, gut microbiota alterations after LT were reviewed, and the relationship between the gut microbiota and liver I/R injury, the efficacy of immunosuppressive drugs used, and complications after LT were discussed. In the era of LT oncology, the role of the gut microbiota in HCC and LT should be emphasized, which can provide new insights into the management of HCC and LT via gut microbiota modulation.

© 2023 THE AUTHORS. Published by Elsevier LTD on behalf of Chinese Academy of Engineering and Higher Education Press Limited Company. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Liver cancer is one of the most common malignancies worldwide and poses a huge medical burden. Liver cancer can be divided into two categories: primary and secondary. Primary liver cancer is a highly dangerous malignant tumor that accounts for the vast majority of liver cancer cases. Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for approximately 90% of all cases [1]. Despite progress in its prevention, diagnosis, prognosis, and treatment, the morbidity and mortality of HCC continue to increase [2]. Patients diagnosed with HCC are

often diagnosed at an advanced stage. Although they receive systemic therapy, their overall response rate is poor.

Orthotopic liver transplantation (OLT) is the best treatment option for patients with end-stage liver disease, especially for patients with decompensated liver function who are not suitable for surgical resection and local ablation. HCC can be cured by liver transplantation (LT). In 1996, Mazzaferro et al. [3] first proposed the selection of patients with small HCC with cirrhosis for LT, establishing the Milan criteria as a result. Transplant recipients who meet the Milan criteria have achieved long-term survival; however, due to the strictness of the criteria, many patients with HCC are deemed unsuitable for transplantation. In response to this, extensions of the Milan criteria, such as the Hangzhou, Valencia, University of California, and University Clinic of Navarra criteria, have been successively proposed [4–6]. With the continuous

* Corresponding authors.

E-mail addresses: 1315009@zju.edu.cn (X. Wei), zjxu@zju.edu.cn (X. Xu).

These authors contributed equally to this work.

strengthening of the concept of multidisciplinary comprehensive treatment, transplantation oncology has emerged over time. In 2014, Professor Hibi from Kumamoto University in Japan [7] proposed the concept of liver transplant oncology. The development of LT oncology brings together the strength of multiple disciplines, including surgery, oncology, immunology, pharmacology, and imaging [8,9]. Several studies have found that the gut microbiota plays an important role in transplantation oncology. In the era of LT oncology, the role of the gut microbiota cannot be ignored.

The gut microbiota is crucial for human health. As a “virtual metabolic organ,” the gut microbiota can interact with and influence various organs and different systems, including the brain, kidney, cardiovascular system, and skeletal system [10,11]. Although the liver does not interact directly with microbiota, it is anatomically connected to the gut. The discovery of the gut–liver axis has greatly improved our understanding of the role that the gut microbiota plays in the onset and progression of liver disease [12,13]. The gut microbiota can transfer microbial components and metabolites to the liver via the portal vein, thereby influencing liver function. For instance, short-chain fatty acids (SCFAs), the main microbial metabolites of dietary fibers in the intestine, can suppress hepatic inflammation by inducing regulatory T cells (Tregs) [14]. The gut microbiome-mediated 7α -dehydroxylation of primary bile acids (BAs) can produce secondary BAs, which induce DNA damage and regulate liver anti-tumor immune surveillance [15]. Other substances, such as lipopolysaccharide (LPS) and lipoteichoic acid, can also influence liver function [16]. Therefore, the gut microbiota is important for maintaining normal liver function. Furthermore, the gut microbiota has been found to not only serve as an emerging tool for the diagnosis and prognosis of HCC because of its operational simplicity and precision of analysis but has also been reported to exert pathological effects on HCC and LT by regulating metabolism and immunity [17,18].

In this review, the gut microbiota is briefly introduced. Then, the mechanisms by which the gut microbiota affects HCC and its bidirectional interaction with chronic liver disease, which can evolve into HCC, are summarized as well as the diagnostic and prognostic value of the gut microbiota in HCC. In addition, the role of the gut microbiota in LT is discussed. The objective of this review is to summarize achievements in the field and gain insights into the management of HCC and LT via the modulation of the gut microbiota.

2. Gut microbiota

The gastrointestinal tract is the largest microbial system in the human body, expanding over an area of 250–400 m² [19]. As many as 10–100 trillion microbes have been estimated to live in the human gastrointestinal tract [20]. The collective genome of the human gastrointestinal tract, known as the “microbiome,” is 150 times larger than the human genome [21]. A recent study compiled and analyzed 204 938 genomes and 170 602 708 genes from the human gut microbiome dataset and generated a Unified Human Gastrointestinal Genome and Protein catalog [22]. As the most complete catalog of human gut microbiota sequences available, this information provides an opportunity to enhance our understanding of the human gut microbiota.

The gut microbiota contains several types of microbes, including bacteria, fungi, archaea, and viruses [23]. Bacteria in the gut microenvironment are divided into seven major groups (Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria), with Bacteroidetes and Firmicutes accounting for over 90% [24]. Compared to bacteria, fungi and archaea have received less attention but have also formed a complete research system. Although fungi only account for 0.1%

of gut microbes, the crucial role of gut fungi cannot be ignored, especially *Candida* and *Saccharomyces* [25]. In addition, archaea are considered stable commensals in the gastrointestinal tract that can be involved in several physiological activities [26].

The gut microbiota connects various parts of the body into an organized system through pathways such as the gut–liver and gut–brain axes, which form a delicate symbiotic relationship in the human body. When the human body is in good condition, good and bad microbes depend on and restrict each other and can be found in a relatively balanced state, providing a natural defense system for the maintenance of human health. However, dysbiosis of the gut microbiota can cause damage to the body, which is closely related to the progression of a variety of metabolic, immune, and neurological diseases, including diabetes [27], hypertension and atherosclerosis [28], inflammatory bowel disease [29], and autism [30]. Therefore, the gut microbiota plays an important role in health and disease.

3. Gut microbiota and HCC

Despite a 2% annual decline in the incidence of liver cancer in recent decades, the mortality rate of liver cancer continues to rank second among the different types of cancer [2], with 412 216 deaths in China and 32 332 deaths in the United States [31], posing a huge threat to global public health. HCC is the most common type of primary liver cancer and one of the leading causes of cancer death worldwide. It is characterized by a poor prognosis, with a five-year survival rate of 18% [32,33]. Furthermore, there is increasing evidence of a strong link between HCC and the gut microbiota (Fig. 1).

3.1. Dysbiosis, leaky gut, and HCC

The intestinal tract serves as the primary site for the digestion and absorption of nutrients. It also functions as an immune barrier, and the intestinal immune system is divided into innate, adaptive, and mucosal immune systems [34]. The intestinal mucosa is directly connected to the outside world, coming into contact with various organic and inorganic substances in the intestine. This makes the intestinal mucosal epithelium the first protective barrier against pathogens. However, gut microbiota dysbiosis leads to increased intestinal permeability and the disruption of the intestinal mucosal barrier, with mucosal barrier disruption typically resulting in the breakdown of intestinal barrier tight junctions, known as leaky gut syndrome [35]. A strong link has been reported between gut microbiota imbalance and leaky gut. In addition, gut microbiota dysbiosis and leaky gut can lead to microbial translocation and increased liver exposure to microbiota-derived products and metabolites [36], which may cause liver cirrhosis. Liver cirrhosis is associated with the progression of early liver disease and can eventually cause HCC [37]. Therefore, dysbiosis of the gut microbiota, leaky gut, and HCC are closely related.

Gut microbiota dysbiosis, leaky gut, and HCC have a complex relationship with each other. Gut microbiota dysbiosis can cause leaky gut, which can aggravate the imbalance. In addition, intestinal leakage can also mediate the occurrence and development of HCC through the liver–intestine axis. Intestinal bacterial metabolites regulate intestinal permeability and inflammation through Toll-like receptor 4 (TLR4)-mediated pathways [38]. In a mouse model of diethylnitrosamine (DEN) plus carbon tetrachloride (CCl₄)-induced HCC, ligands derived from the bacterial gut microbiota were triggers that promoted TLR4-dependent tumors. TLR4-positive HCC cells have dramatically improved invasion and migratory capabilities [39]. Additionally, TLR4 signaling-induced leaky guts may enhance HCC progression. Moreover, LPS can cause

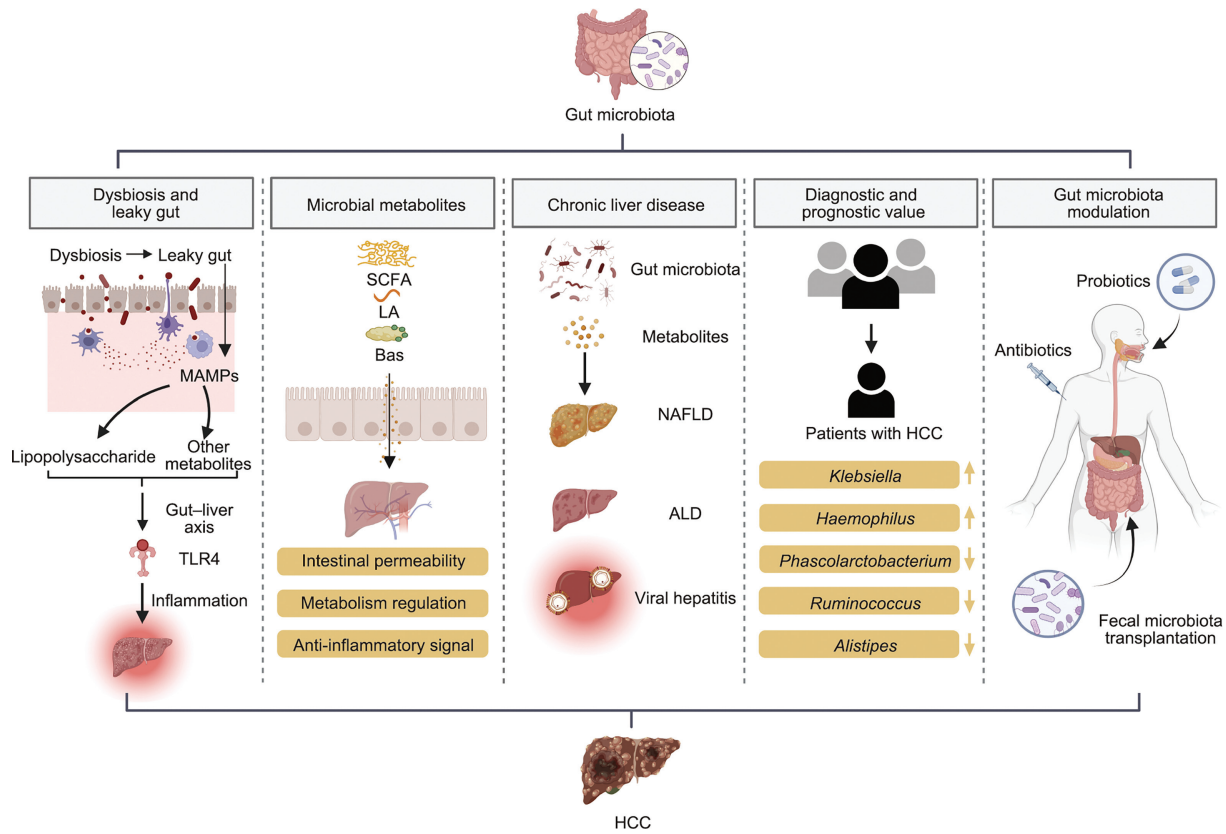


Fig. 1. Gut microbiota and HCC. MAMP: microbiota-associated molecular pattern; TLR4: Toll-like receptor 4; LA: lactic acid; NAFLD: non-alcoholic fatty liver disease; ALD: alcoholic liver disease.

inflammation through TLR4 and is the most commonly used marker of microbiota-associated molecular pattern (MAMP). After oral antibiotic mixtures were used to eradicate intestinal bacteria and lower LPS levels in mice, substantial tumor regression occurred [40]. Furthermore, calprotectin, which is mainly derived from neutrophils, has direct antibacterial effects and plays a role in the innate immune response. Calprotectin is present in various body fluids and is a useful surrogate marker for inflammatory responses [41]. Lower percentages of *Akkermansia* and *Bifidobacterium* were detected in the feces of HCC patients, whereas the concentration of calprotectin was significantly increased, which represents a more intense inflammatory reaction and hepatocyte injury [42]. Overall, it is speculated that, in the case of a leaky gut, bacteria can translocate to the upper gastrointestinal tract, from which the generated LPS enters the liver, thereby activating the corresponding immune response, resulting in the compensatory proliferation of hepatocytes, and ultimately inducing HCC.

3.2. Gut microbial metabolites and HCC

Through portal vein circulation, gut-derived metabolites, cellular components, hormones, and other substances enter the liver and interact with the immune cells [43]. The effects of compounds generated by microbes vary. Some contribute to inflammation, hepatitis, liver cirrhosis, fibrosis, and even cancer, while others maintain barrier integrity and prevent pathogen penetration. Currently, SCFAs, lactic acid (LA), and BAs are the main gut microbial metabolites that have been studied [44].

3.2.1. SCFAs

SCFAs, also known as volatile fatty acids, are the main products of the fermentation of undigested carbohydrates, such

as oligosaccharides, non-starch polysaccharides, and resistant starch, by anaerobic bacteria in the colon and include acetic acid, propionic acid, and butyric acid. In human metabolism, SCFAs are of great importance in maintaining the normal operation of the large intestine and the morphology and function of colonic epithelial cells [45].

Several studies have suggested that SCFAs can efficiently promote Tregs during active immune responses and control cancer progression by downregulating cancer related pathways. McBrearty et al. [46] found that SCFA-fed HBx transgenic mice exhibited normal liver tissue development and inhibited HCC growth. *Lactobacillus reuteri* plays an anticancer role by inhibiting the production of specific cytokines by type 3 congenital lymphocytes; however, the level of *Lactobacillus reuteri* is significantly reduced in patients with HCC, and SCFA supplementation can play a role similar to *Lactobacillus reuteri*, thus controlling the progression of HCC [47]. In contrast, SCFAs exceeding the threshold concentration and tolerated by the host have been shown to cause HCC [48,49]. Therefore, the specific mechanism by which SCFAs affect HCC needs to be further clarified, and further studies are urgently required.

3.2.2. Lactic acids

LA, a metabolic mediator, can determine the activity and function of immune cells. In the tumor microenvironment, the combined accelerated metabolism of tumor cells and cancer-associated fibroblasts creates an immunological environment that supports tumor development. Tumor tissues deplete local energy, forcing neighboring immune cells to process high concentrations of metabolites, such as LA, in the absence of nutrients, leading to immune suppression and tumor growth [50]. De la Cruz-López et al. [51] concluded that sodium lactate can inhibit several gly-

colytic enzymes of CD4⁺ T cells and reduce the expression of glucose flow, resulting in the accumulation of T cells at inflammatory sites. In addition, the level of LA increases significantly with the progression of liver disease and can be used as an effective tool for early HCC diagnosis [52]. Gu et al. [53] demonstrated that LA produced by over-glycolytic HCC cells can stimulate extracellular signal-regulated kinase (ERK) phosphorylation in the co-cultured human hepatic stellate cell line LX2 and the leukemic monocyte cell line THP1 non-tumor cells through NDRG3 and MCT1, which promotes HCC cell malignancy and stemness. As an important metabolite in cancer metabolic reprogramming, the question of how the gut microbial LA intervenes in HCC requires further investigation.

3.2.3. Bile acids

BAs are endogenous steroid molecules synthesized from cholesterol, which is the main component of bile. BAs can regulate the differentiation and function of T cells, including inflammatory T helper 17 (TH17) cells and anti-inflammatory Tregs [54]. Conde de la Rosa et al. [55] demonstrated that the level of total hepatic BAs in HCC patients is significantly increased, and BAs can stimulate the generation of tumor-initiating stem cells. Ma et al. also showed that the synthesis of BAs can mediate the upregulation of C-X-C motif ligand 16 (CXCL16) in mice, control the accumulation of wild-type natural killer T cells, regulate the expression of CXCL16 messenger RNA (mRNA) in human hepatic sinusoid endothelial cells, and play anti-HCC and cancer cell metastasis role [15]. Moreover, the metabolic regulator sirtuin 5 (SIRT5) has been reported to inhibit HCC immune escape by mediating the metabolism of BAs, which suggests a strategy for HCC treatment using BAs chelators [56]. Furthermore, deoxycholic acid, a secondary BA produced by the dihydroxylation of primary BAs produced by certain strains of the intestinal *Clostridium* cluster, can stimulate cellular functions related to inflammation and tumorigenesis through the senescence secretome, exacerbating the development of HCC [57]. Generally, the accumulation of BAs plays a key role in HCC development because it can cause cell damage. Thus, changing the type or amount of BAs in patients with HCC can reduce inflammation and represents a potential effective method for alleviating disease progression.

Overall, more studies are needed to investigate the precise mechanism by which gut microbial metabolites affect HCC as they may reveal two aspects of the control of HCC development. In addition, the effects of other gut microbial metabolites on HCC, such as choline metabolites, phenolic derivatives, and indole derivatives, should also be explored.

3.3. Gut microbiota and chronic liver disease

HCC usually develops as a result of chronic liver disease, with approximately 80–90% of HCC cases occurring alongside advanced liver fibrosis or cirrhosis; thus, cirrhosis is the greatest risk factor for the development of HCC [58]. The main causes of cirrhosis are non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and viral hepatitis, which are also closely associated with HCC [59]. The role of intrahepatic microbiota in liver diseases has been emphasized in pathogenesis and tumorigenesis. Liu et al. [60] found that the abundance of *Stenotrophomonas maltophilia* was higher in the intrahepatic microbiota of patients with HCC and cirrhosis, which can promote the progression of HCC by stimulating the senescence-associated secretory phenotype and inducing the secretion of inflammatory factors in the liver. Through the gut–liver axis, the gut microbiota can also interact with the host in the human body and function in the onset and progression of liver inflammation, fibrosis, and cirrhosis [61]. Understanding the alterations in the gut microbiota during cirrhosis and their

relationship with chronic liver disease will provide new strategies for the prevention and treatment of HCC (Table 1 [62–85]).

3.3.1. Non-alcoholic fatty liver disease

NAFLD includes a range of liver diseases, from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually HCC. The link between the gut microbiota and NAFLD was first revealed in the early 1880s. Drenick et al. [86] demonstrated that both liver steatosis and bacterial overgrowth were observed in patients with NAFLD and that the use of metronidazole significantly decreased steatosis, suggesting that intestinal bacteria are closely related to NAFLD. Wang et al. [62] found that compared with healthy controls (HCs), the levels of Bacteroidetes were higher but Firmicutes were lower in the feces of patients with NAFLD, and the ratio of Firmicutes to Bacteroidetes decreased significantly. Furthermore, Leung et al. [63] found that *Methanobrevibacter*, *Phascolarctobacterium*, *Slackia*, and *Dorea formicigenerans* may be risk factors for NAFLD. *Eubacterium rectale* and *Bacteroides vulgatus* were shown to be the most abundant organisms in mild/moderate NAFLD, whereas *Bacteroides vulgatus* and *Escherichia coli* were the most abundant in advanced fibrosis [64]. Yu et al. [65] also found that the abundance of *Veillonella*, *Collinsella*, *Latilactobacillus*, *Dialister*, and *Bifidobacterium* increased gradually with the progression of NAFLD. Rapid developments have enabled the relationship between the gut microbiota and NAFLD to be studied extensively.

Dysbiosis of the gut microbiota and NAFLD is closely linked. Bacterial toxic substances and metabolic mediators are generated in high doses during dysbiosis and accumulate in the intestinal tract, which may promote liver inflammation and NAFLD formation. Björkholm et al. [66] found that in the absence of the gut microbiota, high expression of constitutively active receptors can affect the levels of BAs, bilirubin, and steroid hormones, stimulating the development of NAFLD. In C57BL/J6 mice, high fructose consumption can lead to small intestinal bacteria overgrowth and increase intestinal endotoxin translocation, thereby resulting in the development of NAFLD [67]. Thuy et al. [68] regulated the gut microbiota and reduced intestinal permeability by controlling the intake of fructose and carbohydrates in NAFLD patients and concluded that dietary fructose intake can increase intestinal endotoxin translocation, which may contribute to the development of NAFLD. Additionally, the gut microbiota can regulate energy balance and affect NAFLD through intercommunication pathways. Two mechanisms have been found to stimulate fatty acid oxidation, reduce fat storage, and protect germ-free (GF) mice from diet-induced obesity, including elevated levels of fasting-induced adipose factor and increased 5'-adenosine monophosphate (AMP)-activated protein kinase activity [69].

The composition of the gut microbiota in patients with NAFLD differs from that in the healthy population. Furthermore, changes in energy and metabolites, endotoxin-mediated inflammation, and increased intestinal permeability are currently believed to be the main mechanisms by which the gut microbiota is involved in the pathogenesis and progression of NAFLD. Studying the role of the gut microbiota in NAFLD can better guide the prevention and treatment of HCC.

3.3.2. Alcoholic liver disease

Chronic alcohol consumption can cause damage to multiple organs, especially the liver, which is involved in alcohol metabolism [87]. The intestinal oxidation of alcohols results in an increase in acetaldehyde. Acetaldehyde can cause significant alterations in the quality and quantity of the gut microbiota. By detecting alterations in the gut microbiota, the connection between chronic ethanol feeding and the symbiotic bacterial microbiota was investigated in an ALD mouse model, showing that Bacteroidetes and Firmicutes decreased and Proteobacteria and Actinobacteria

Table 1
Gut microbiota and chronic liver disease.

Authors	Gut microbiota	Associated disease	Outcomes	Reference
Wang et al.	Bacteroidetes and Firmicutes	NAFLD	Higher levels of Bacteroidetes and lower levels of Firmicutes in the feces of NAFLD patients	[62]
Leung et al.	<i>Methanobrevibacter</i> , <i>Phascolarctobacterium</i> , <i>Slackia</i> , and <i>Dorea formicigenerans</i>	NAFLD	<i>Methanobrevibacter</i> , <i>Phascolarctobacterium</i> , <i>Slackia</i> , and <i>Dorea formicigenerans</i> may be risk characteristics of NAFLD	[63]
Lomba et al.	<i>Eubacterium rectale</i> , <i>Bacteroides vulgatus</i> , and <i>Escherichia coli</i>	NAFLD	Higher <i>Eubacterium rectale</i> and <i>Bacteroides vulgatus</i> abundance in mild/moderate NAFLD and <i>Bacteroides vulgatus</i> and <i>Escherichia coli</i> in advanced fibrosis	[64]
Yu et al.	<i>Veillonella</i> , <i>Collinsella</i> , <i>Latilactobacillus</i> , <i>Dialister</i> , and <i>Bifidobacterium</i>	NAFLD	The abundance of <i>Veillonella</i> , <i>Collinsella</i> , <i>Latilactobacillus</i> , <i>Dialister</i> , and <i>Bifidobacterium</i> increased gradually with the progress of NAFLD	[65]
Björkholm et al.	–	NAFLD	High expression of constitutive active receptors can affect stimulate the development of NAFLD in the absence of the gut microbiota	[66]
Bergheim et al.	–	NAFLD	Markedly reduced hepatic lipid accumulation after concomitant treatment with antibiotics, which may restrict the development of NAFLD	[67]
Thuy et al.	–	NAFLD	Dietary fructose intake can increase intestinal endotoxin translocation, which may contribute to the development of NAFLD	[68]
Bäckhed et al.	–	NAFLD	Increased fatty acid metabolism and phosphorylated AMP-activated protein kinase in GF mice	[69]
Bull-Ottersson et al.	Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria	ALD	Decreased Bacteroidetes and Firmicutes, and increased Proteobacteria and Actinobacteria were features of ALD	[70]
Llopis et al.	<i>Faecalibacterium</i>	ALD	Key deleterious species were associated with SAH while the <i>Faecalibacterium</i> genus was associated with noAH	[71]
Brandl et al.	–	ALD	ALD is associated with disturbance of BA homeostasis	[72]
Jiang et al.	Parvoviridae and Herpesviridae	ALD	Mammalian viruses increased in fecal samples from ALD patients	[73]
Hsu et al.	<i>Propionibacterium</i> , <i>Lactobacillus</i> , and <i>Leuconostoc</i> phages	ALD	ALD may be associated with intestinal virome	[74]
Yan et al.	Bacteroidetes and Verrucomicrobia	ALD	Bacterial translocation and overgrowth may contribute to the development and progression of ALD	[75]
Bode et al.	–	ALD	Gut-derived endotoxin can function in the development of ALD	[76]
Llorente et al.	<i>Enterococcus</i>	ALD	Gastric acid-induced <i>Enterococcus</i> overgrowth can aggravate the liver injury, steatosis, inflammation and fibrosis, thus leading to ALD	[77]
Duan et al.	<i>Enterococcus faecalis</i>	ALD	Bacteriophages targeting cytolytic <i>Enterococcus faecalis</i> can abrogate ethanol-induced liver injury and steatosis, thus alleviating ALD	[78]
Everard et al.	<i>Akkermansia muciniphila</i>	ALD	<i>Akkermansia muciniphila</i> can promote barrier function by improving mucus production, and protect against ALD	[79]
Grandier et al.	<i>Akkermansia muciniphila</i>	ALD	Treatment with <i>Akkermansia muciniphila</i> can protect against experimental ALD	[80]
Liu et al.	<i>Faecalibacterium</i> , <i>Ruminococcus</i> , and <i>Ruminoclostridium</i>	HBV	The species richness of fecal microbiota in B-HCC patients was much higher than NBNC-HCC patients and HCs	[81]
Wang et al.	–	HBV	Intestinal barrier disruption secondary to zonulin pathway disorder may contribute to the deterioration of HBV infection	[82]
Sultan et al.	<i>Prevotella</i> , <i>Succinivibrio</i> , <i>Catenibacterium</i> , <i>Megasphaera</i> , and Ruminococcaceae	HCV	Increase in the abundance of <i>Prevotella</i> , <i>Succinivibrio</i> , <i>Catenibacterium</i> , <i>Megasphaera</i> , and Ruminococcaceae was shown in treatment-naïve HCV	[83]
Pérez-Matute et al.	<i>Lachnospira</i>	HCV	The low abundance of <i>Lachnospira</i> may be another cause of persistent injury and inflammation in HCV-infected patients	[84]
Heidrich et al.	<i>Lactobacillus</i>	HCV	<i>Lactobacillus</i> increased in HCV-infected patients	[85]

AMP: 5'-adenosine monophosphate; GF: germ-free; SAH: severe alcoholic hepatitis; noAH: without alcoholic hepatitis; HBV: hepatitis B virus; B-HCC: HBV-related HCC; NCNB-HCC: non-HBV non-hepatitis C virus related HCC; HC: health control; HCV: hepatitis C virus.

increased significantly after chronic feeding with ethanol [70]. After transplanting GF mice with the gut microbiota of patients with or without alcoholic hepatitis (AH), liver inflammation in mice harboring the gut microbiota from an alcoholic with severe AH was found to be more severe than that in mice harboring the gut microbiota from a patient without AH (noAH), suggesting that the microbiota from noAH patients may reverse ALD [71]. In addition, patients with ALD have been shown to have reduced hepatic cholic acid synthesis and increased serum BAs, suggesting that ALD is associated with a disturbance of BA homeostasis [72]. Furthermore, Jiang et al. [73] reported that mammalian viruses, such as Parvoviridae and Herpesviridae, increased in fecal samples from ALD patients. Hsu et al. [74] also found that *Propionibacterium*, *Lactobacillus*, and *Leuconostoc* phages decreased in patients with alcohol use disorders, revealing that ALD may be associated with intestinal virome. Thus, there is a close correlation between the gut microbiota and ALD.

Recent evidence suggests a role for the gut microbiota and its metabolites in the pathophysiology of ALD. Alcohol abuse can lead

to intestinal bacterial overgrowth and translocation, which may be the result of reduced bactericidal c-type lectins, Reg3b and Reg3g. This suggests that bacterial translocation and overgrowth are the main contributors to the development and progression of alcoholic steatohepatitis [75]. Dysbiosis of the gut microbiota was also found to induce mucosal alterations and enhance intestinal permeability, resulting in endotoxemia [88]. The endotoxemia of patients with alcoholic cirrhosis was significantly higher than that of patients with non-alcoholic cirrhosis, which showed that gut-derived endotoxins play a role in the development of ALD [76]. In addition, hepatic macrophages and Kupffer cells can recognize *Enterococcus* and induce the secretion of interleukin (IL)-1 β , which leads to ethanol-induced liver inflammation and hepatocyte injury. Llorente et al. [77] found that inhibiting gastric acid-induced *Enterococcus* overgrowth could aggravate liver injury, steatosis, inflammation, and fibrosis in mice. The isolation of highly strain-specific *Enterococcus faecalis* bacteriophages may enable the direct editing of the gut microbiota. Bacteriophages targeting the cytolytic *Enterococcus faecalis* abrogate ethanol-induced liver injury and steatosis [78].

Furthermore, the gut microbiota and its metabolites can be used for the treatment of ALD. The administration of tributyrin or glycerol in mice receiving long-term intragastric ethanol administration was found to inhibit the decrease in the expression of tight junction proteins and the destruction of intestinal integrity, thus alleviating intestinal barrier damage [89]. *Akkermansia muciniphila* can promote barrier function by improving mucus production [79]. Grander et al. [80] found that patients with alcoholic steatohepatitis showed a decrease in *Akkermansia muciniphila* abundance, and *Akkermansia muciniphila* administration in ALD mice protected against steatosis, neutrophil infiltration, and liver injury. Therefore, *Akkermansia muciniphila* supplementation may be used for the treatment of ALD.

Dysbiosis of the gut microbiota increases the susceptibility of patients to ALD through intestinal barrier damage, toxins, and molecular metabolism, ultimately increasing the risk of developing HCC. Interventions targeting the gut microbiota and its metabolites can be used to treat ALD by introducing new strategies for the prevention of HCC.

3.3.3. Viral hepatitis

Dysbiosis of the gut microbiota is associated with viral hepatitis, represented by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Chronic HBV infection is a high-risk factor for HCC. HBV is believed to mediate chronic liver damage through abnormal immune attack, leading to chronic necroinflammation and hepatocellular regeneration, which are the main causes of HCC [90]. 16S ribosomal RNA (rRNA) analyses of HCs, HBV-related HCC (B-HCC) individuals, and non-HBV non-HCV-related HCC (NBNC-HCC) individuals showed that the species richness of fecal microbiota in B-HCC patients was much higher than that in the other two groups. However, the feces of patients with NBNC-HCC were found to contain more potential pro-inflammatory bacteria and decreased levels of *Faecalibacterium*, *Ruminococcus*, and *Ruminoclostridium*, which further reduced the levels of SCFAs [81]. Wang et al. [82] assessed zonulin levels in HCs, HBV-related cirrhosis patients, and HBV-associated HCC patients and found that the zonulin levels were significantly higher in patients with HBV-related cirrhosis and HBV-associated HCC, suggesting that intestinal barrier disruption secondary to zonulin pathway disorder may be a contributing factor to the deterioration of HBV infection.

HCV is also a major cause of HCC [91]. The carcinogenesis of the HCV-infected liver can be attributed to damage to hepatocytes carrying the virus, which can cause excessive cell proliferation. In addition, chronic inflammation and oxidative stress may lead to the accumulation of cancer-related gene mutations in hepatocytes [92]. The diversity of HCV microbiota also changes. For instance, Sultan et al. [83] found that treatment-naïve HCV showed an increase in the abundance of *Prevotella*, *Succinivibrio*, *Catenibacterium*, *Megasphaera*, and Ruminococcaceae, whereas Pérez-Matute et al. [84] showed that 15 bacterial genera differed in HCV patients, and the degree of liver fibrosis in HCV patients could lead to differences in the composition of the gut microbiota. Pérez-Matute et al. [84] also found that the low abundance of *Lachnospira* in HCV-infected patients may be another cause of persistent injury and inflammation. In addition, Heidrich et al. [85] found that *Lactobacillus* increased in HCV-infected patients.

HBV and HCV can induce liver injury through the gut–liver axis. The gut microbiota can mediate a persistent inflammatory response by regulating metabolism and aggravating or slowing the occurrence of viral hepatitis, thus affecting the development of HCC.

3.4. Diagnostic and prognostic value of the gut microbiota in HCC

HCC is highly recurrent and can develop into new HCC tumors after resection or ablation [93]. Clinically, most patients are already

in an advanced stage when diagnosed with HCC, and their prognosis is generally poor. Therefore, early detection and treatment are the major strategies for the treatment of HCC. The gut microbiota has the advantages of being non-invasive, highly efficient, and accurate in disease diagnosis. Alterations in the gut microbiota composition are prominent features of HCC and advanced liver disease that may evolve into HCC. Controlling the relationship between the gut microbiota and the stage of HCC lesions is an important breakthrough for the early prediction of HCC.

In the first global report on the characterization of the gut microbiota in patients with early HCC using MiSeq sequencing in a large cohort, the microbial diversity of early HCC was found to be significantly higher than that of cirrhosis, especially Actinobacteria. Thirteen genera, including *Gemmiger* and *Parabacteroides*, were enriched in early HCC and liver cirrhosis. Compared with the HCs, the beneficial bacteria (*Ruminococcus*, *Alistipes*, and *Phascolarctobacterium*) producing butyrate decreased in early HCC, whereas the harmful bacteria (*Klebsiella* and *Haemophilus*) producing LPS increased. The effectiveness of microbiota alterations in the diagnosis of HCC has been tested in clinical practice, with the results showing a high accuracy for patients with HCC in northwest and central China [17]. Deng et al. [94] showed that the abundance of Bacteroidetes decreased and that of Actinobacteria increased in patients with HCC compared with that in healthy controls and patients with cholangiocarcinoma. Albhaisi et al. [95] also found that the abundance of *Enterococcus*, *Salmonella*, *Clostridium XIVb*, *Clostridium IV*, *Lactonifactor*, and *Eggerthella* was lower in cirrhosis patients who developed HCC in the future. In addition, sex differences in the gut microbiota were also demonstrated in a spontaneous HCC mouse model. Alterations in the relative abundance of anaerobic and facultative anaerobic bacteria may be used as predictors of HCC in females, whereas *Paraprevotella*, *Paraprevotellaceae*, and *Prevotella* have the potential to predict HCC in males [96]. Furthermore, Liu et al. [97] found that the diversity of gut fungi changed in patients with HCC and that the abundance of *Candida albicans* was significantly increased. The abnormal colonization of *Candida albicans* is related to the development of HCC, which may provide new insights into the prediction and treatment of HCC. However, the clinical application of the gut microbiota in the prediction of HCC has not been fully investigated, and further studies are needed.

The clinical value of the gut microbiota in HCC is not only reflected in the diagnosis but also in the prognosis. According to clinicopathological characteristics, HCC can be divided into small HCC and non-small HCC, with the former showing a better prognosis. 16S rRNA sequencing was performed on fecal samples collected from patients with HCC associated with the HBV and HCs. *Bacteroides*, *Lachnospiraceae incertae sedis*, and *Clostridium XIVa* were found to be enriched in patients with small HCC, while the endotoxin activity produced by these strains was weak, also predicting moderate inflammatory response and controlled tumor development [18]. The gut microbiota can also influence the clinical response to immunotherapy in patients with HCC. Immune checkpoint inhibitors (ICIs) have been widely researched in the field of cancer treatment, and anti-programmed cell death protein-1 (PD-1) immunotherapy has shown encouraging effects in sorafenib-refractory HCC [98]. Studies have shown that the prevalence of Proteobacteria, especially *Escherichia coli*, may inhibit the effects of anti-PD-1 therapies. Patients with HCC who received ICI showed an association between gut microbiota diversity and response to treatment. A high abundance of *Faecalibacterium* was found to significantly prolong progression-free survival (PFS) after ICI treatment, whereas a high abundance of Bacteroidales had the opposite effect [99]. Moreover, the presence of probiotics, such as *Lactobacillus*, *Bifidobacterium dentium*, and *Streptococcus thermophilus*, can be beneficial for ICIs and inhibit the immune escape

of cancer cells, which may also have implications for HCC prognosis [100]. Thus, the gut microbiota can play a prognostic role in many aspects of HCC, ranging from distinguishing the prognosis of small and non-small HCC to influencing immunotherapy efficacy.

3.5. Gut microbiota modulation in HCC

With the development of studies on the gut microbiota and HCC, regulation of the gut microbiota may be a new and important adjunct to current anticancer treatments, and preventive approaches based on the gut microbiota and liver are promising research directions. Gut microbiota modulation has been explored, including via antibiotics, probiotics, and fecal microbiota transplantation (FMT).

3.5.1. Antibiotics

In 1928, the discovery of penicillin represented a breakthrough in medical history and catalyzed the development of antibiotics [101]. The regulation of the gut microbiota by antibiotics is a proven strategy that can suppress pro-inflammatory signals by eliminating bacteria with a high translocation capacity or eliminating cancer-promoting chemicals by reducing the number of bacteria producing specific metabolites. Vancomycin is a first-generation glycopeptide antibiotic that acts by inhibiting cell wall formation in gram-positive bacteria [102]. Singh et al. [103] revealed that vancomycin can suppress secondary BAs and SCFAs, which can halt the development of liver cancer in insulin-fed TLR5-deficient mice. However, its use in the treatment of HCC is not recommended because of its potential side effects. In addition, norfloxacin administration selectively eliminated aerobic gram-negative bacilli from fecal flora and significantly reduced the recurrence of spontaneous bacterial peritonitis in liver cirrhosis [104]. However, a major disadvantage of norfloxacin administration is that drug resistance can easily develop, making it difficult to meet the long-term demand for HCC prevention [105]. Furthermore, Fujinaga et al. [106] found that rifaximin can reduce intestinal permeability by reducing portal endotoxins and inhibiting the LPS–TLR4 signaling pathway, which can significantly reduce liver fibrosis. Rifaximin has the advantage of not having strong side effects on the gut microbiota. In contrast to norfloxacin, no clinically relevant drug resistance to rifaximin has been reported, suggesting that it may be suitable for long-term treatment [107]. However, the effects of norfloxacin and rifaximin on HCC development remain to be explored further.

3.5.2. Probiotics

Several studies have confirmed the efficacy and mechanism of probiotics in preventing HCC by regulating the composition of the gut microbiota, improving intestinal barrier function, and regulating local and systemic immunity. Probiotic VSL#3 has been shown to reduce the severity of liver disease and hospitalization in patients with cirrhosis and is widely commercialized [108]. Pro-hep, a probiotic mixture composed of *Lactobacillus rhamnosus* GG, *Escherichia coli* Nissle 1917, and VSL#3, can successfully inhibit angiogenesis, regulate the subpopulation of CD4⁺ T cells, and increase SCFA-producing bacteria, ultimately reducing tumor weight and size by 40% in mice [109]. Probiotics can also reduce HCC incidence by mediating epigenetic regulation in the host. Heydari et al. [110] demonstrated that *Lactobacillus acidophilus* and *Bifidobacterium bifidum* can negatively regulate the expression of oncogenic microRNAs in HCC cancer mice. Furthermore, Mihailović et al. [111] found that the probiotic *Lactobacillus paraplantarum* BGCG11 can reduce DNA damage and increase the activation of pro-survival protein kinase B (Akt), which may inhibit cell carcinogenesis. Probiotic supplementation can control HCC development by downregulating TLR-induced liver inflammation. In the DEN-

induced HCC model, probiotic supplementation restored intestinal homeostasis, reduced exotoxin levels, and inhibited tumor cell proliferation [112]. In addition, *Lactobacillus plantarum* can significantly decrease the expression of TLR4, CXCL9, and phosphatidylinositol 3, 4, 5 trisphosphate RAC exchanger 2 (PREX-2) and prevent carcinogenesis of liver cirrhosis [113]. Furthermore, several studies have shown that probiotics can prevent HBV and HCV infection and improve liver function during infection [114,115]. Interestingly, only high doses of probiotics were effective, suggesting that the adequate intake of probiotics may lead to the competitive exclusion of disease-promoting bacterial strains [116]. Overall, we can conclude that probiotics have the potential to be adjuncts in the treatment of HCC.

3.5.3. FMT

FMT is defined as the transfer of healthy gut bacteria via donor stool to a patient with the aim of obtaining therapeutic benefits by directly altering or normalizing the gut microbiota of recipients. Zhou et al. [117] showed that FMT not only increases the level of butyrate and reduces the level of endotoxin but also improves intrahepatic immunity in a NASH mouse model induced by a high-fat diet. Wang et al. [118] also suggested that FMT could prevent intestinal mucosal barrier damage and limit the systemic inflammatory response in mice with hepatic encephalopathy. Furthermore, no infections related to FMT were observed in immunocompromised patients with *Clostridium difficile* infection who received FMT, demonstrating the value of FMT in clinical practice [119].

FMT may delay the development of HCC and can reconstruct intestinal immune microecology, which may improve the efficacy of HCC immunotherapy. Nevertheless, one risk of FMT is the possibility of disease transmission, and the highly dynamic composition of living microorganisms is another major source of uncertainty. Additionally, FMT is susceptible to external factors, such as diet and drugs, and researchers should focus on manipulating the gut microbiota with greater precision. More studies are needed before FMT can be employed for the treatment of HCC.

4. Gut microbiota and LT

LT is a therapeutic option for patients with end-stage liver disease and acute liver failure (ALF), which can prolong the long-term survival rate and effectively improve the prognosis of patients [120,121]. In LT, allografts can bring donor immune cells into recipients, which leads to gut microbiota alterations in recipients [122]. Extensive research has shown that the gut microbiota and LT are closely correlated.

In this section, the alterations in the gut microbiota after LT are summarized, and the relationship between the gut microbiota and liver ischemia–reperfusion (I/R) injury, the efficacy of immunosuppressive drugs used, and complications after LT are also discussed (Fig. 2).

4.1. Gut microbiota alterations after LT

The gut microbiota and its alterations are crucial in LT. After rats received LT, researchers found that the number of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, significantly decreased, whereas the numbers of harmful bacteria, such as Enterobacteriaceae and *Enterococcus*, significantly increased [123]. Wu et al. [122] further found that the levels of the above strains, except for *Enterococcus*, returned to normal over time after LT. This change may be caused by the introduction of donor microorganisms into the recipient by the graft. In addition, Bajaj et al. [124] also showed alterations in gut microbial function after

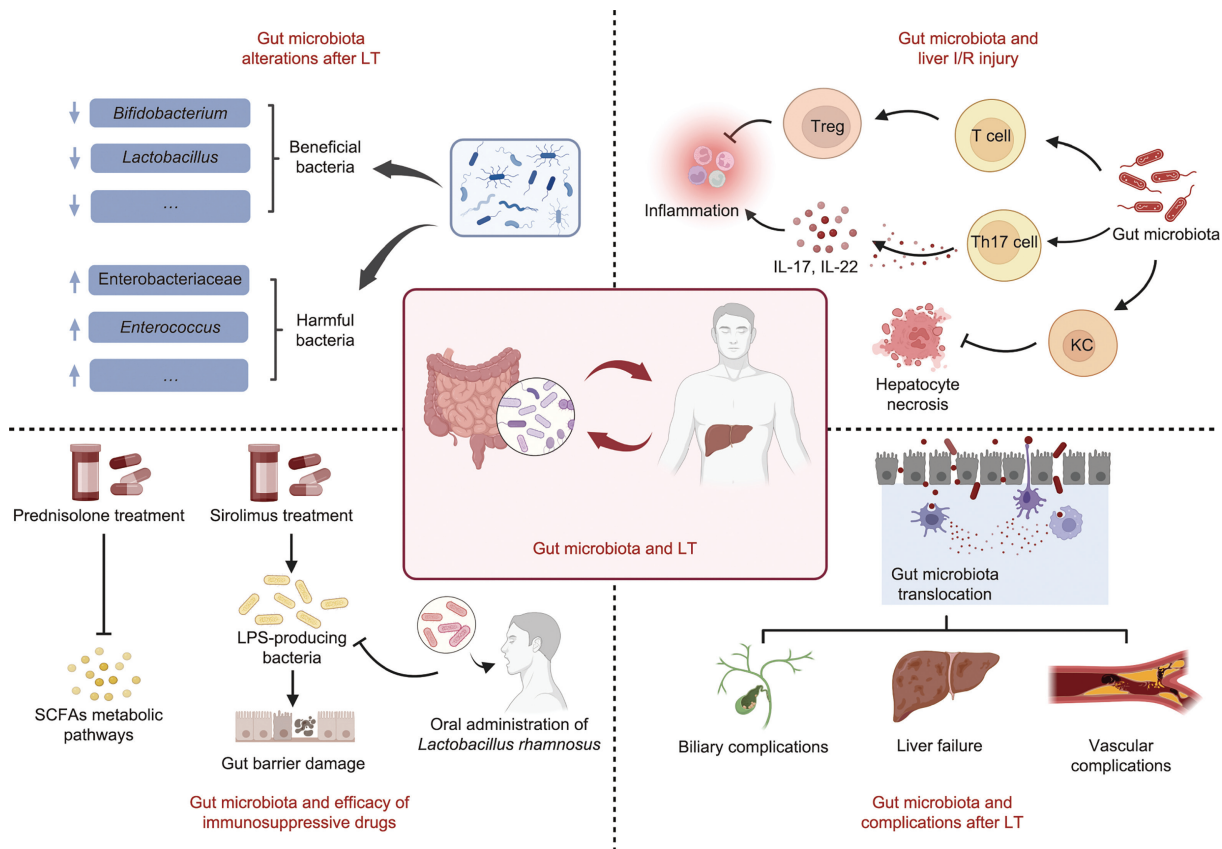


Fig. 2. Gut microbiota and LT. KC: Koffler cell.

LT. The relative abundance of Enterobacteriaceae was significantly reduced, whereas that of Ruminococcaceae and Lachnospiraceae increased after LT. They proved that endotoxin synthesis, ammonia, BA modulation, and methylamine metabolism were significantly improved, suggesting that the liver plays a central role in influencing the function of the gut microbiota.

The composition of the gut microbiota in patients before and after LT changes significantly, and improvement in liver function after LT is closely related to alterations in the gut microbiota.

4.2. Gut microbiota and liver I/R injury

Liver I/R injury is closely related to the gut microbiota [125]. Tregs can help improve the tolerance of liver allografts by modulating immune effects and preventing the development of I/R injury-induced acute cellular rejection [126,127]. It has been confirmed that intestinal *Bacteroides fragilis* and capsular polysaccharides induce CD4⁺ T cells to differentiate into Tregs after LT dysregulation, preventing increased inflammation and suppressing excessive immune responses [128]. As key mediators of autoimmune diseases, Th17 cells secrete IL-17, IL-22, and IL-26, which may trigger a strong inflammatory response and aggravate I/R injury [129]. The presence of segmented filamentous bacteria in the gastrointestinal tract of mice can specifically induce Th17 cell differentiation and inhibit the invasion of intestinal pathogens [130]. 3-oxolithocholic acid and isolithocholic acid can also regulate the Th17/IL-17 signaling axis, and there is a negative correlation between them [131]. Moreover, Corbitt et al. [132] found that the number of Koffler cells (KCs) is determined by gut bacteria and constitutive MAMP exposure through portal venous blood, and the depletion of gut bacteria can lead to KCs deficiency, which affects liver reperfusion injury. Inactivated KCs can abrogate I/R

injury and the gut microbiota can significantly affect the response of KCs to I/R injury [133]. Furthermore, Nakamura et al. [134] reported that the levels of sinusoidal congestion, edema/vacuolization, and hepatocellular necrosis were reduced in mice with gut microbiota modified with antibiotics after liver allotransplantation, indicating a decrease in I/R injury. *Clostridium* and *Bacteroides* can produce SCFAs, which induce the expression of IL-10 and downregulate the expression of claudin-2 in the small intestine, thereby preventing I/R injury, intestinal apoptosis, and inflammation in intestinal TLR9-deficient mice [135,136].

Generally, the severity of I/R injury is directly related to the recovery and maintenance of organ function after LT, and the gut microbiota, as the core regulator of I/R injury, can provide a feasible way to improve the prognosis of LT.

4.3. Gut microbiota and efficacy of immunosuppressive drugs

Solid organ transplant recipients must take anti-rejection drugs after transplantation to prevent immune rejection [137]. The efficacy of immunosuppressive drugs and the composition of the gut microbiota can influence each other, with advances being made in this research field.

Sirolimus can inhibit the activation and proliferation of T lymphocytes stimulated by antigens and cytokines and is considered a promising immunosuppressive agent [138]. Compared to the control, the relative abundance of Proteobacteria significantly increased in mice treated with sirolimus, resulting in intestinal barrier damage and metabolic disorders after LT. Oral intervention with *Lactobacillus rhamnosus* HN001 alleviated sirolimus-induced adverse reactions [139]. In addition, combined immunosuppressive therapies, including prednisolone, mycophenolate mofetil, and tacrolimus, inhibit *Clostridium* and promote the proliferation

of *Escherichia coli* in the intestinal tract of mice [140]. Swarte et al. [141] demonstrated a strong correlation between immunosuppressive therapies and dysbiosis; they also showed that the more serious the extent of dysbiosis, the higher the mortality after transplantation.

Therefore, the dysbiosis observed in post-transplant recipients can be attributed to a complex interaction between anti-rejection drugs and the gut microbiota.

4.4. Gut microbiota and complications after LT

Although LT can effectively treat patients with end-stage liver disease and ALF, the occurrence of postoperative complications reduces the therapeutic effect [142,143]. The gut microbiota plays a role in the pathogenesis and development of complications after LT. There are differences in the gut microbiota and metabolites between patients with complications after LT and those without complications, suggesting that the gut microbiota and metabolites can be used to predict the occurrence of complications after LT. Moreover, several studies have revealed the mechanism by which the gut microbiota and metabolites mediate complications after LT. Therefore, early intervention of the gut microbiota and metabolites using probiotics after LT can prevent the occurrence of complications, which sheds new light on the therapeutic potential of gut microbiota modulation.

In this section, complications after LT, such as biliary complications, liver failure, and vascular complications, are introduced. Gut microbiota alterations, their mediating mechanisms, and potential preventive methods are presented (Table 2 [144–170]).

4.4.1. Biliary complications

Biliary complications are the most common complications after LT, with an incidence of 30%, and include bile leakage, bile duct stenosis, biliary sludge formation, and biliary tract infection [171]. Lichtman et al. [144] showed that rats with intestinal bacterial overgrowth displayed extrahepatic and intrahepatic bile duct injury. *Veillonella*, *Streptococcus*, and *Enterococcus* are enriched in patients with primary sclerosing cholangitis (PSC) [145]. Moreover, the analysis of intestinal fungi in patients with PSC revealed increased *Exophiala* and decreased *Saccharomyces cerevisiae* [146]. Gut dysbiosis was also observed in patients with primary biliary cholangitis (PBC) [147]. The gut microbiota and metabolites may be used to predict complications after LT. This suggests that biliary complications after LT can be regulated by the gut microbiota, showing a close relationship.

A bidirectional regulatory relationship exists between the gut microbiota and BAs, which may reveal the triggering mechanism of biliary complications. After LT, bile is released into the intestine, which alters the pH of the intestinal environment and inhibits the growth of harmful microorganisms. However, the gut microbiota, which is associated with the onset and development of cholestatic liver disease, can modulate the action of BA-activated receptors and mold the BA pool. By directly inducing the production of mitochondrial reactive oxygen species and subsequent mitochondrial oxidative stress, hydrophobic BAs can initiate apoptosis, which is a key mechanism in cholestatic liver disease following LT [148]. In addition, bacterial dysregulation can promote BA-induced cell death in mouse hepatocytes, increase intestinal permeability, activate inflammation, and induce cholestatic liver disease [149].

Ursodeoxycholic acid (UDCA) treatment may be used to prevent biliary complications after LT. Tabibian et al. [150] revealed that UDCA, a commensal microbial metabolite, can abrogate cholangiocyte senescence, suggesting the significance of commensal microbiota and its metabolites in biliary injury. Gut dysbiosis caused by PBC can also be partially ameliorated by UDCA treatment [147].

4.4.2. Liver failure

ALF, chronic liver failure, and acute-on-chronic liver failure (ACLF) are all significant side effects of LT. Previous research has established that gut microbiota translocation is a key factor in the development of systemic inflammation and liver failure [172].

The severe hepatotoxicity caused by acetaminophen (APAP) is one of the main causes of ALF. Several studies have shown that APAP-induced acute liver injury exhibits diurnal changes as well as changes in the composition and function of the gut microbiota, suggesting that ALF is associated with the gut microbiota [151,152]. Furthermore, gut microbiota modulation may effectively prevent the occurrence of ALF after LT. 1-phenyl-1,2-propanedione generated by *Escherichia coli*, *Citrobacter freundii*, *Clostridium difficile*, and *Enterococcus faecalis* can synergistically improve APAP-induced ALF, while yeast can protect the liver against such damage [153]. *Bifidobacterium adolescentis* CGMCC 15058 and *Bifidobacterium longum* R0175 were also found to inhibit bacterial translocation and inflammation during ALF and maintain intestinal mucosa integrity, which can effectively reduce or prevent ALF symptoms [154,155]. In addition, the use of probiotic bacteria, such as *Saccharomyces boulardii*, significantly improved gut dysbiosis and alleviated ALF in a D-galactosamine-induced liver injury mouse model [156].

The gut microbiota and metabolites may predict the complications of ACLF after LT. The analysis of the gut microbiota in liver cirrhosis patients with and without ACLF revealed that the intestinal ecology in ACLF patients was severely dysregulated, and dysbiosis of the gut microbiota on admission may predict an increased risk of extrahepatic organ failure, ACLF, and death [157]. Chen et al. [158] demonstrated that patients with ACLF also had gut dysbiosis. The abundance of Bacteroidaceae, Ruminococcaceae, and Lachnospiraceae was lower, while that of Pasteurellaceae, Streptococcaceae, and Enterobacteriaceae was higher. They also found that the relative abundance of Pasteurellaceae could be used to predict the mortality rate of ACLF patients [158]. In addition, the relationship between the gut microbiota and ACLF can provide guidance on how to prevent the occurrence of complications after LT through the modulation of the gut microbiota. Moreau et al. [159] revealed the relationship between the accumulation of blood metabolites and alterations in major metabolic pathways, intense systemic inflammation, and organ failure in patients with ACLF. Moreover, intestinal bacterial infection and alcohol abuse are the main causes of hepatocyte injury in patients with ACLF. Alcohol abuse can exacerbate intestinal barrier disruption, and bacteria trigger a strong inflammatory response through pathogen-related molecular patterning, ultimately leading to ACLF [160].

In summary, the gut microbiota and metabolites may be used to predict the complications of liver failure after LT, and specific interventions on the gut microbiota will promote or inhibit ALF and ACLF.

4.4.3. Vascular complications

Hepatic artery thrombosis is a LT complication that can terminate liver graft dysfunction or even ischemic necrosis. In addition to governing the gut barrier, several metabolites from the gut microbiota can reach distant regions in the body [173,174], and the gut microbiota is closely associated with vascular complications after LT.

Thrombosis of the arterial system is based on atherosclerotic plaque rupture. Ott et al. [161] found bacterial DNA in atherosclerotic plaques, supporting the hypothesis of multiple bacterial colonization in arterial lesions. Furthermore, *Acinetobacter*, *Acidovorax*, and *Neisseria polysaccharea* were found to be most prevalent in symptomatic atherosclerotic plaques, and asymptomatic plaques had a higher abundance of Porphyromonadaceae, Bacteroidaceae, Micrococ-

Table 2
Gut Microbiota and Complications after LT.

Authors	Gut microbiota	Associated complications	Outcomes	Reference
Lichtman et al.	–	Biliary complications	Intestinal bacterial overgrowth displayed extrahepatic and intrahepatic bile duct injury	[144]
Little et al.	<i>Veillonella</i> , <i>Streptococcus</i> , and <i>Enterococcus</i>	Biliary complications	<i>Veillonella</i> , <i>Streptococcus</i> , and <i>Enterococcus</i> were considered to be enriched in PSC patients	[145]
Lemoine et al.	<i>Exophiala</i> and <i>Saccharomyces cerevisiae</i>	Biliary complications	PSC patients revealed increased <i>Exophiala</i> and decreased <i>Saccharomyces cerevisiae</i>	[146]
Tang et al.	<i>Faecalibacterium</i> and Enterobacteriaceae	Biliary complications	Gut dysbiosis was found in PBC patients and partially relieved by treatment with UDCA	[147]
Li et al.	–	Biliary complications	Hydrophobic BAs can start apoptosis, which is a key mechanism of cholestatic liver disease following LT	[148]
Isaacs-Ten et al.	–	Biliary complications	Absence of the gut microbiota can protect mice from cholestatic-mediated liver injury and inflammation.	[149]
Tabibian et al.	–	Biliary complications	UDCA can abrogate cholangiocyte senescence	[150]
Kim et al.	–	Liver failure	ALF is associated with the gut microbiota	[151]
Thaiss et al.	–	Liver failure	ALF is associated with the gut microbiota	[152]
Gong et al.	–	Liver failure	<i>Saccharomyces cerevisiae</i> can reduce intestinal 1-phenyl-1,2-propanedione levels and markedly alleviate APAP-induced liver damage and ACLF	[153]
Li et al.	<i>Bifidobacterium adolescentis</i> CGMCC 15058	Liver failure	<i>Bifidobacterium adolescentis</i> CGMCC 15058 can effectively reduce or prevent ALF symptoms	[154]
Wang et al.	<i>Bifidobacterium longum</i> R0175	Liver failure	<i>Bifidobacterium longum</i> R0175 can effectively reduce or prevent ALF symptoms	[155]
Yu et al.	<i>Saccharomyces boulardii</i>	Liver failure	<i>Saccharomyces boulardii</i> significantly improved gut dysbiosis and alleviated ALF	[156]
Bajaj et al.	Proteobacteria and Firmicutes	Liver failure	Taxa belonging to phylum Proteobacteria (Enterobacteriaceae, Campylobacteriaceae, and Pasteurellaceae) and Firmicutes (Enterococcaceae and Streptococcaceae) may related to ACLF	[157]
Chen et al.	Bacteroidaceae, Ruminococcaceae, Lachnospiraceae, Pasteurellaceae, Streptococcaceae, and Entereococcaceae	Liver failure	The abundance of Bacteroidaceae, Ruminococcaceae, and Lachnospiraceae was lower, while that of Pasteurellaceae, Streptococcaceae, and Entereococcaceae was higher	[158]
Moreau et al.	–	Liver failure	The relationship between blood metabolite accumulation and metabolic pathway alteration and intense systemic inflammation in ACLF was revealed	[159]
Moreau et al.	–	Liver failure	Patients with ACLF had more associated bacterial infections than patients without ACLF	[160]
Ott et al.	–	Vascular complications	Bacterial DNA was present in atherosclerotic plaques	[161]
Mitra et al.	<i>Acinetobacter</i> , <i>Acidovorax</i> , <i>Neisseria polysacchara</i> , Porphyromonadaceae, Bacteroidaceae, Micrococcaceae, and Streptococcaceae	Vascular complications	Distinct groups of microbial agents might play different roles during the development of atherosclerotic plaques	[162]
Bennett et al.	–	Vascular complications	Gut microbial TMAO can cause atherosclerosis	[163]
Carnevale et al.	<i>Escherichia coli</i>	Vascular complications	LPS from <i>Escherichia coli</i> localizes in human atherosclerotic plaque and may trigger atherosclerotic damage	[164]
Zhu et al.	–	Vascular complications	TMAO can promote the formation of thrombosis by directly enhancing the activity of platelets	[165]
Duerschmied et al.	–	Vascular complications	Serotonin can promote the formation of thrombosis by directly enhancing the activity of platelets	[166]
Jäckel et al.	–	Vascular complications	The gut microbiota can regulate hepatic von Willebrand factor synthesis and arterial thrombus formation	[167]
Li et al.	<i>Akkermansia muciniphila</i>	Vascular complications	<i>Akkermansia muciniphila</i> can reverse the progression of atherosclerotic lesions	[168]
Wu et al.	–	Vascular complications	The inhibition of LPS is considered an effective way of treating thrombosis	[169]
Mathew et al.	–	Vascular complications	Butyrate plays a certain therapeutic role in atherosclerosis	[170]

PSC: primary sclerosing cholangitis; PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid; APAP: acetaminophen; ACLF: acute-on-chronic liver failure; TMAO: metabolite trimethylamine N-oxide.

caceae, and Streptococcaceae [162]. In animal models, Bennett et al. [163] demonstrated that the gut microbial metabolite trimethylamine N-oxide (TMAO) can cause atherosclerosis. LPS can translocate from the gut microbiota to atherosclerotic plaques, and the level of LPS is positively correlated with the degree of atherosclerosis [164]. Therefore, the gut microbiota and metabolites may serve as predictive markers for vascular complications after LT.

In addition, the destruction of liver vascular endothelial function and increased platelet activity are associated with the possibility of thrombosis [175]. TMAO, serotonin, and other metabolites can promote thrombosis by directly enhancing the

activity of platelets [165,166]. Extensive bidirectional interactions exist between the inflammatory and clotting systems. The inflammatory mechanism can increase platelet activity, trigger coagulation activation, and cause thrombosis [176]. The gut microbiota can regulate liver endothelial cell homeostasis in a TLR2-dependent manner, thus regulating von Willebrand factor and ultimately affecting platelet deposition in the extracellular matrix [167]. These findings explain the mechanisms of the gut microbiota, platelet function, and thrombosis risk and provide insights into the connection between the gut microbiota and vascular complications after LT.

Gut microbiota modulation may also play a role in the prevention of vascular complications after LT. Li et al. [168] indicated that *Akkermansia muciniphila* could reverse the progression of atherosclerotic lesions. Furthermore, LPS can induce inflammation and oxidative stress, which can affect the function of vascular endothelial cells and have a direct impact on thrombosis; the inhibition of LPS is considered an effective way to treat thrombosis [169]. Butyrate plays a therapeutic role in atherosclerosis by inhibiting oxidative and inflammatory responses during vascular smooth muscle cell proliferation [170].

5. Conclusions

The liver and intestine are closely related to physiological functions. Nutrients and toxins originating from the intestine first enter the liver through the portal vein and are then transported to the entire body after removing harmful substances from the liver. Some gut-derived immune cells and released cytokines can also enter the liver through the portal vein to achieve a remote echo of gut–liver immunity. The liver transmits substances to the intestine by secreting BAs, regulating hormone levels and immune responses, and affecting intestinal homeostasis.

In recent years, an increasing number of studies have focused on the role of the gut microbiota in the balance between host health and disease. Gut microbiota imbalance is related to the occurrence and development of HCC. Intestinal leakage caused by alterations in the gut microbiota can aggravate the translocation of various bacterial and gut microbial metabolites to the liver, which affects the development of HCC. The gut microbiota also functions in chronic liver disease, which may evolve into HCC. Furthermore, alterations in the composition of the gut microbiota can be used as effective diagnostic and prognostic markers for HCC. In addition, gut microbiota modulation through antibiotics, probiotics, FMT, and other methods can significantly improve liver function, reduce liver injury, and prevent chronic liver disease and HCC. LT is an effective treatment for HCC and its technology is relatively mature, with the gut microbiota composition changing in patients after treatment. Although LT continues to be plagued by postoperative rejection and various complications, its prognosis may be improved via the modulation of the gut microbiota. However, studies on the gut microbiota of patients with HCC receiving LT remain scarce.

To summarize, gut microbiota modulation is a viable strategy to address the medical needs in HCC and LT, particularly now, in the era of liver transplant oncology. However, studies on the gut microbiota in HCC and LT remain scarce and need to be promoted further. Unremitting efforts should be made to apply preclinical research in clinical practice to truly benefit patients.

Acknowledgements

This research gained support from the National Key Research and Development Program of China (2021YFA1100500), the Major Research Plan of the National Natural Science Foundation of China (92159202), the National Natural Science Foundation of China (82272396 and 81930016), the Key Research & Development Plan of Zhejiang Province (2019C03050), and the Construction Fund of Key Medical Disciplines of Hangzhou (OO20200093).

Authors' contribution

Ze Xiang and Xuyong Wei had the idea for the article; Jian Wu and Jiarui Li performed the literature search and data analysis; Xiao Xu and Shusen Zheng drafted and critically revised the work.

Conflict of with ethics guidelines

Ze Xiang, Jian Wu, Jiarui Li, Shusen Zheng, Xuyong Wei, and Xiao Xu declare that they have no conflict of interest or financial conflicts to disclose.

References

- [1] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7(1):6.
- [2] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72(1):7–33.
- [3] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334(11):693–9.
- [4] Tsimigras DI, Bagante F, Moris D, Merath K, Paredes AZ, Sahara K, et al. Defining the chance of cure after resection for hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer guidelines: a multi-institutional analysis of 1,010 patients. *Surgery* 2019;166(6):967–74.
- [5] Mirza DF. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria (Br J Surg 2011; 98: 1201–1208). *Br J Surg* 2011;98(9):1209.
- [6] Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016;65(6):1035–41.
- [7] Hibi T, Shinoda M, Itano O, Kitagawa Y. Current status of the organ replacement approach for malignancies and an overture for organ bioengineering and regenerative medicine. *Organogenesis* 2014;10(2):241–9.
- [8] Hibi T, Itano O, Shinoda M, Kitagawa Y. Liver transplantation for hepatobiliary malignancies: a new era of “Transplant Oncology” has begun. *Surg Today* 2017;47(4):403–15.
- [9] Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS Transplant Oncology Consensus Conference. *Transplantation* 2020;104(6):1136–42.
- [10] Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med* 2016;22(10):1079–89.
- [11] Kazemian N, Mahmoudi M, Halperin F, Wu JC, Pakpour S. Gut microbiota and cardiovascular disease: opportunities and challenges. *Microbiome* 2020;8(1):36.
- [12] Konturek PC, Harsch IA, Konturek K, Schink M, Konturek T, Neurath MF, et al. Gut–liver axis: how do gut bacteria influence the liver? *Med Sci* 2018;6(3):79.
- [13] Yang X, Lu D, Zhuo J, Lin Z, Yang M, Xu X. The gut–liver axis in immune remodeling: new insight into liver diseases. *Int J Biol Sci* 2020;16(13):2357–66.
- [14] Deng M, Qu F, Chen L, Liu C, Zhang M, Ren F, et al. SCFAs alleviated steatosis and inflammation in mice with NASH induced by MCD. *J Endocrinol* 2020;245(3):425–37.
- [15] Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* 2018;360(6391):eaan5931.
- [16] Ohtani N, Hara E. Gut–liver axis-mediated mechanism of liver cancer: a special focus on the role of gut microbiota. *Cancer Sci* 2021;112(11):4433–43.
- [17] Ren Z, Li A, Jiang J, Zhou L, Yu Z, Lu H, et al. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. *Gut* 2019;68(6):1014–23.
- [18] Huang H, Ren Z, Gao X, Hu X, Zhou Y, Jiang J, et al. Integrated analysis of microbiome and host transcriptome reveals correlations between gut microbiota and clinical outcomes in HBV-related hepatocellular carcinoma. *Genome Med* 2020;12(1):102.
- [19] Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017;474(11):1823–36.
- [20] Tian X, Yang Z, Luo F, Zheng S. Gut microbial balance and liver transplantation: alteration, management, and prediction. *Front Med* 2018;12(2):123–9.
- [21] Zhu B, Wang X, Li L. Human gut microbiome: the second genome of human body. *Protein Cell* 2010;1(8):718–25.
- [22] Almeida A, Nayfach S, Boland M, Strozzi F, Beracochea M, Shi ZJ, et al. A unified catalog of 204,938 reference genomes from the human gut microbiome. *Nat Biotechnol* 2021;39(1):105–14.
- [23] Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012;489(7415):220–30.
- [24] Adak A, Khan MR. An insight into gut microbiota and its functionalities. *Cell Mol Life Sci* 2019;76(3):473–93.
- [25] Zhang F, Aschenbrenner D, Yoo JY, Zuo T. The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly. *Lancet Microbe* 2022;3(12):e969–83.
- [26] Coker OO, Wu WKK, Wong SH, Sung JJ, Yu J. Altered gut archaea composition and interaction with bacteria are associated with colorectal cancer. *Gastroenterology* 2020;159(4):1459–70.e5.
- [27] Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 2020;51:102590.

- [28] Verhaar BJH, Prodan A, Nieuwdorp M, Muller M. Gut microbiota in hypertension and atherosclerosis: a review. *Nutrients* 2020;12(10):2982.
- [29] Sugihara K, Kamada N. Diet–microbiota interactions in inflammatory bowel disease. *Nutrients* 2021;13(5):1533.
- [30] Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 2013;155(7):1451–63.
- [31] Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J* 2022;135(5):584–90.
- [32] Temraz S, Nassar F, Kreidieh F, Mukherji D, Shamseddine A, Nasr R. Hepatocellular carcinoma immunotherapy and the potential influence of gut microbiome. *Int J Mol Sci* 2021;22(15):7800.
- [33] Ling S, Shan Q, Zhan Q, Ye Q, Liu P, Xu S, et al. USP22 promotes hypoxia-induced hepatocellular carcinoma stemness by a HIF1 α /USP22 positive feedback loop upon TP53 inactivation. *Gut* 2020;69(7):1322–34.
- [34] Doe WF. The intestinal immune system. *Gut* 1989;30(12):1679–85.
- [35] Ahmad R, Sorrell MF, Batra SK, Dhawan P, Singh AB. Gut permeability and mucosal inflammation: bad, good or context dependent. *Mucosal Immunol* 2017;10(2):307–17.
- [36] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010;140(6):805–20.
- [37] Wang L, Llorente C, Hartmann P, Yang AM, Chen P, Schnabl B. Methods to determine intestinal permeability and bacterial translocation during liver disease. *J Immunol Methods* 2015;421:44–53.
- [38] Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benchet AP, et al. Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity* 2014;41(2):296–310.
- [39] Liu WT, Jing YY, Yu GF, Han ZP, Yu DD, Fan QM, et al. Toll like receptor 4 facilitates invasion and migration as a cancer stem cell marker in hepatocellular carcinoma. *Cancer Lett* 2015;358(2):136–43.
- [40] Dapito DH, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. *Cancer Cell* 2012;21(4):504–16.
- [41] Ayling RM, Kok K. Fecal calprotectin. *Adv Clin Chem* 2018;87:161–90.
- [42] Ponziani FR, Bhoori S, Castelli C, Putignano L, Rivoltini L, Del Chierico F, et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. *Hepatology* 2019;69(1):107–20.
- [43] Bi C, Xiao G, Liu C, Yan J, Chen J, Si W, et al. Molecular immune mechanism of intestinal microbiota and their metabolites in the occurrence and development of liver cancer. *Front Cell Dev Biol* 2021;9:702414.
- [44] Visekruna A, Luu M. The role of short-chain fatty acids and bile acids in intestinal and liver function, inflammation, and carcinogenesis. *Front Cell Dev Biol* 2021;9:703218.
- [45] Luu M, Pautz S, Kohl V, Singh R, Romero R, Lucas S, et al. The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes. *Nat Commun* 2019;10(1):760.
- [46] McBrearty N, Arzumanyan A, Bichenkov E, Merali S, Merali C, Feitelson M. Short chain fatty acids delay the development of hepatocellular carcinoma in HBx transgenic mice. *Neoplasia* 2021;23(5):529–38.
- [47] Hu C, Xu B, Wang X, Wan W-H, Lu J, Kong D, et al. Gut microbiota-derived short-chain fatty acids regulate group 3 innate lymphoid cells in HCC. *Hepatology* 2023;77(1):48–64.
- [48] Singh V, San Yeoh B, Chassaing B, Xiao X, Saha P, Olvera RA, et al. Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. *Cell* 2018;175(3):679–94.e22.
- [49] Mirzaei R, Afaghi A, Babakhani S, Sohrabi MR, Hosseini-Fard SR, Babolhavaeji K, et al. Role of microbiota-derived short-chain fatty acids in cancer development and prevention. *Biomed Pharmacother* 2021;139:111619.
- [50] Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? *Trends Biochem Sci* 2016;41(3):211–8.
- [51] De la Cruz-López KG, Castro-Muñoz LJ, Reyes-Hernández DO, García-Carrancá A, Manzo-Merino J. Lactate in the regulation of tumor microenvironment and therapeutic approaches. *Front Oncol* 2019;9:1143.
- [52] Zhang W, Chen Z, Xue C, Zhang Y, Wu L, Zhu J, et al. The applicability of ADA, AFU, and LAC in the early diagnosis and disease risk assessment of hepatitis B-associated liver cirrhosis and hepatocellular carcinoma. *Front Med* 2021;8:740029.
- [53] Gu Y, Ji F, Liu N, Zhao Y, Wei X, Hu S, et al. Loss of miR-192-5p initiates a hyperglycolysis and stemness positive feedback in hepatocellular carcinoma. *J Exp Clin Cancer Res* 2020;39(1):268.
- [54] Cao W, Kayama H, Chen ML, Delmas A, Sun A, Kim SY, et al. The xenobiotic transporter Mdr1 enforces T cell homeostasis in the presence of intestinal bile acids. *Immunity* 2017;47(6):1182–96.e10.
- [55] Conde de la Rosa L, García-Ruiz C, Vallejo C, Baulies A, Nuñez S, Monte MJ, et al. STARD1 promotes NASH-driven HCC by sustaining the generation of bile acids through the alternative mitochondrial pathway. *J Hepatol* 2021;74(6):1429–41.
- [56] Sun R, Zhang Z, Bao R, Guo X, Gu Y, Yang W, et al. Loss of SIRT5 promotes bile acid-induced immunosuppressive microenvironment and hepatocarcinogenesis. *J Hepatol* 2022;77(2):453–66.
- [57] Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* 2013;499(7456):97–101.
- [58] Bruix J, Sherman M; the American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53(3):1020–2.
- [59] El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011;365(12):1118–27.
- [60] Liu B, Zhou Z, Jin Y, Lu J, Feng D, Peng R, et al. Hepatic stellate cell activation and senescence induced by intrahepatic microbiota disturbances drive progression of liver cirrhosis toward hepatocellular carcinoma. *J Immunother Cancer* 2022;10(1):e003069.
- [61] Li S, Han W, He Q, Zhang W, Zhang Y. Relationship between intestinal microflora and hepatocellular cancer based on gut–liver axis theory. *Contrast Media Mol Imaging* 2022;2022:6533628.
- [62] Wang B, Jiang X, Cao M, Ge J, Bao Q, Tang L, et al. Altered fecal microbiota correlates with liver biochemistry in nonobese patients with non-alcoholic fatty liver disease. *Sci Rep* 2016;6(1):32002.
- [63] Leung H, Long X, Ni Y, Qian L, Nychas E, Siliceo SL, et al. Risk assessment with gut microbiome and metabolite markers in NAFLD development. *Sci Transl Med* 2022;14(648):eabk0855.
- [64] Looma R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metab* 2017;25(5):1054–62.e5.
- [65] Yu JS, Youn GS, Choi J, Kim CH, Kim BY, Yang SJ, et al. *Lactobacillus lactis* and *Pediococcus pentosaceus*-driven reprogramming of gut microbiome and metabolome ameliorates the progression of non-alcoholic fatty liver disease. *Clin Transl Med* 2021;11(12):e634.
- [66] Björkholm B, Bok CM, Lundin A, Raftar J, Hibberd ML, Pettersson S. Intestinal microbiota regulate xenobiotic metabolism in the liver. *PLoS One* 2009;4(9):e6958.
- [67] Bergheim I, Weber S, Vos M, Krämer S, Volynets V, Kaserouni S, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. *J Hepatol* 2008;48(6):983–92.
- [68] Thuy S, Ladurner R, Volynets V, Wagner S, Strahl S, Königsrainer A, et al. Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake. *J Nutr* 2008;138(8):1452–5.
- [69] Bäckhed F, Manchester JK, Semenkovich CF, Gordon JL. Mechanisms underlying the resistance to diet-induced obesity in Germ-free mice. *Proc Natl Acad Sci USA* 2007;104(3):979–84.
- [70] Bull-Otterson L, Feng W, Kirpich I, Wang Y, Qin X, Liu Y, et al. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of *Lactobacillus rhamnosus* GG treatment. *PLoS One* 2013;8(1):e53028.
- [71] Llopis M, Cassard AM, Wrzosek L, Boschat L, Bruneau A, Ferrere G, et al. Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. *Gut* 2016;65(5):830–9.
- [72] Brandl K, Hartmann P, Jih LJ, Pizzo DP, Argemi J, Ventura-Cots M, et al. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. *J Hepatol* 2018;69(2):396–405.
- [73] Jiang L, Lang S, Duan Y, Zhang X, Gao B, Chopyk J, et al. Intestinal virome in patients with alcoholic hepatitis. *Hepatology* 2020;72(6):2182–96.
- [74] Hsu CL, Zhang X, Jiang L, Lang S, Hartmann P, Pride D, et al. Intestinal virome in patients with alcohol use disorder and after abstinence. *Hepatology* 2022;74(8):2058–69.
- [75] Yan AW, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011;53(1):96–105.
- [76] Bode C, Kugler V, Bode JC. Endotoxemia in patients with alcoholic and non-alcoholic cirrhosis and in subjects with no evidence of chronic liver disease following acute alcohol excess. *J Hepatol* 1987;4(1):8–14.
- [77] Llorente C, Jeppen P, Inamine T, Wang L, Bluemel S, Wang HJ, et al. Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal *Enterococcus*. *Nat Commun* 2017;8(1):837.
- [78] Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* 2019;575(7783):505–11.
- [79] Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci USA* 2013;110(22):9066–71.
- [80] Grandt C, Adolph TE, Wieser V, Lowe P, Wrzosek L, Gyongyosi B, et al. Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease. *Gut* 2018;67(5):891–901.
- [81] Liu Q, Li F, Zhuang Y, Xu J, Wang J, Mao X, et al. Alteration in gut microbiota associated with hepatitis B and non-hepatitis virus related hepatocellular carcinoma. *Gut Pathog* 2019;11(1):1.
- [82] Wang X, Li MM, Ni Y, Zhang X, Yin JB, Zhao CJ, et al. Serum zonulin in HBV-associated chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. *Dis Markers* 2019;2019:5945721.
- [83] Sultan S, El-Mowafy M, Elgaml A, El-Mesery M, El Shabrawi A, Elegezy M, et al. Alterations of the treatment-naive gut microbiome in newly diagnosed hepatitis C virus infection. *ACS Infect Dis* 2021;7(5):1059–68.
- [84] Pérez-Matute P, Iñiguez M, Villanueva-Millán MJ, Recio-Fernández E, Vázquez AM, Sánchez SC, et al. Short-term effects of direct-acting antiviral agents on inflammation and gut microbiota in hepatitis C-infected patients. *Eur J Intern Med* 2019;67:47–58.

- [85] Heidrich B, Vital M, Plumeier I, Döschner N, Kahl S, Kirschner J, et al. Intestinal microbiota in patients with chronic hepatitis C with and without cirrhosis compared with healthy controls. *Liver Int* 2018;38(1):50–8.
- [86] Drenick EJ, Fislis J, Johnson D. Hepatic steatosis after intestinal bypass—prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. *Gastroenterology* 1982;82(3):535–48.
- [87] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol* 2013;59(1):160–8.
- [88] Meroni M, Longo M, Dongiovanni P. Alcohol or gut microbiota: who is the guilty? *Int J Mol Sci* 2019;20(18):4568.
- [89] Cresci GA, Glueck B, McMullen MR, Xin W, Allende D, Nagy LE. Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury. *J Gastroenterol Hepatol* 2017;32(9):1587–97.
- [90] Chen Y, Tian Z. HBV-induced immune imbalance in the development of HCC. *Front Immunol* 2019;10:2048.
- [91] Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: a narrative review. *J Clin Transl Hepatol* 2018;6(1):79–84.
- [92] McGivern DR, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. *Oncogene* 2011;30(17):1969–83.
- [93] Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol* 2018;68(3):526–49.
- [94] Deng T, Li J, He B, Chen B, Liu F, Chen Z, et al. Gut microbiome alteration as a diagnostic tool and associated with inflammatory response marker in primary liver cancer. *Hepatol Int* 2022;16(1):99–111.
- [95] Albhaisi S, Shamsaddini A, Fagan A, McGeorge S, Sikaroodi M, Gavis E, et al. Gut microbial signature of hepatocellular cancer in men with cirrhosis. *Liver Transpl* 2021;27(5):629–40.
- [96] Huang R, Li T, Ni J, Bai X, Gao Y, Li Y, et al. Different sex-based responses of gut microbiota during the development of hepatocellular carcinoma in liver-specific *Tsc1*-knockout mice. *Front Microbiol* 2018;9:1008.
- [97] Liu Z, Li Y, Li C, Lei G, Zhou L, Chen X, et al. Intestinal *Candida albicans* promotes hepatocarcinogenesis by up-regulating NLRP6. *Front Microbiol* 2022;13:812771.
- [98] Zhu AX, Finn RS, Edeline J, Cattani S, Ogasawara S, Palmer D, et al. the KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018;19(7):940–52.
- [99] Li L, Ye J. Characterization of gut microbiota in patients with primary hepatocellular carcinoma received immune checkpoint inhibitors: a Chinese population-based study. *Medicine* 2020;99(37):e21788.
- [100] Zheng Y, Wang T, Tu X, Huang Y, Zhang H, Tan D, et al. Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. *J Immunother Cancer* 2019;7(1):193.
- [101] Lobanovska M, Pilla G. Focus: drug development: penicillin's discovery and antibiotic resistance: lessons for the future? *Yale J Biol Med* 2017;90(1):135–45.
- [102] Loo TM, Kamachi F, Watanabe Y, Yoshimoto S, Kanda H, Arai Y, et al. Gut microbiota promotes obesity-associated liver cancer through PGE₂-mediated suppression of antitumor immunity. *Cancer Discov* 2017;7(5):522–38.
- [103] Singh V, Yeoh BS, Abokor AA, Golonka RM, Tian Y, Patterson AD, et al. Vancomycin prevents fermentable fiber-induced liver cancer in mice with dysbiotic gut microbiota. *Gut Microbes* 2020;11(4):1077–91.
- [104] Ginés P, Rimola A, Planas R, Vargas V, Marco F, Almela M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12(4 Pt 1):716–24.
- [105] Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012;10(11):1291–8.
- [106] Fujinaga Y, Kawaratani H, Kaya D, Tsuji Y, Ozutsumi T, Furukawa M, et al. Efficacy combination therapy of angiotensin-II receptor blocker and rifaximin for hepatic fibrosis in rat model of nonalcoholic steatohepatitis. *Int J Mol Sci* 2020;21(15):5589.
- [107] Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. *Nat Rev Gastroenterol Hepatol* 2017;14(9):527–39.
- [108] Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumberu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014;147(6):1327–37.e3.
- [109] Li J, Sung CYJ, Lee N, Ni Y, Pihlajamäki J, Panagiotou G, et al. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. *Proc Natl Acad Sci USA* 2016;113(9):E1306–15.
- [110] Heydari Z, Rahaie M, Alizadeh AM. Different anti-inflammatory effects of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* in hepatocellular carcinoma mouse through impact on microRNAs and their target genes. *J Nutr Intermed Metab* 2019;16:16100096.
- [111] Mihailović M, Živković M, Jovanović JA, Tolinački M, Rajčić J, et al. Oral administration of probiotic *Lactobacillus paraplantarum* BCGG11 attenuates diabetes-induced liver and kidney damage in rats. *J Funct Foods* 2017;38:38427–37.
- [112] Zhang HL, Yu LX, Yang W, Tang L, Lin Y, Wu H, et al. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. *J Hepatol* 2012;57(4):803–12.
- [113] Elshaer AM, El-Kharashi OA, Hamam GG, Nabih ES, Magdy YM, Abd El Samad AA. Involvement of TLR4/ CXCL9/ PREX-2 pathway in the development of hepatocellular carcinoma (HCC) and the promising role of early administration of lactobacillus plantarum in Wistar rats. *Tissue Cell* 2019;60:38–47.
- [114] Nanis GA, Mohamed LS, Hassan E, Maii MN. *Lactobacillus acidophilus* and *Bifidobacteria* spp having antibacterial and antiviral effects on chronic HCV infection. *Afr J Microbiol Res* 2019;13(5):77–90.
- [115] Lee DK, Kang JY, Shin HS, Park IH, Ha NJ. Antiviral activity of *Bifidobacterium adolescentis* SPM0212 against Hepatitis B virus. *Arch Pharm Res* 2013;36(12):1525–32.
- [116] Gorbach SL, Barza M, Giuliano M, Jacobus NV. Colonization resistance of the human intestinal microflora: testing the hypothesis in normal volunteers. *Eur J Clin Microbiol Infect Dis* 1988;7(1):98–102.
- [117] Zhou D, Pan Q, Shen F, Cao HX, Ding WJ, Chen YW, et al. Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota. *Sci Rep* 2017;7(1):1529.
- [118] Wang WW, Zhang Y, Huang XB, You N, Zheng L, Li J. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. *World J Gastroenterol* 2017;23(38):6983–94.
- [119] Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014;109(7):1065–71.
- [120] Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013;95(5):755–60.
- [121] Ling S, Zhan Q, Jiang G, Shan Q, Yin L, Wang R, et al. E2F7 promotes mammalian target of rapamycin inhibitor resistance in hepatocellular carcinoma after liver transplantation. *Am J Transplant* 2022;22(10):2323–36.
- [122] Wu ZW, Ling ZX, Lu HF, Zuo J, Sheng JF, Zheng SS, et al. Changes of gut bacteria and immune parameters in liver transplant recipients. *Hepatobiliary Pancreat Dis Int* 2012;11(1):40–50.
- [123] Yu MH, Yu XL, Chen CL, Gao LH, Mao WL, Yan D, et al. The change of intestinal microecology in rats after orthotopic liver transplantation. *Chin J Surg* 2008;46(15):1139–42. Chinese.
- [124] Bajaj JS, Kakiyama G, Cox IJ, Nittono H, Takei H, White M, et al. Alterations in gut microbial function following liver transplant. *Liver Transpl* 2018;24(6):752–61.
- [125] Xing HC, Li LJ, Xu KJ, Shen T, Chen YB, Sheng JF, et al. Intestinal microflora in rats with ischemia/reperfusion liver injury. *J Zhejiang Univ Sci B* 2005;6(1):14–21.
- [126] Yu J, Liu Z, Li C, Wei Q, Zheng S, Saeb-Parsy K, et al. Regulatory T cell therapy following liver transplantation. *Liver Transpl* 2021;27(2):264–80.
- [127] Zhou J, Chen J, Wei Q, Saeb-Parsy K, Xu X. The role of ischemia/reperfusion injury in early hepatic allograft dysfunction. *Liver Transpl* 2020;26(8):1034–48.
- [128] Wegorzewska MM, Glowacki RWP, Hsieh SA, Donermeyer DL, Hickey CA, Horvath SC, et al. Diet modulates colonic T cell responses by regulating the expression of a *Bacteroides thetaiotaomicron* antigen. *Sci Immunol* 2019;4(32):eaau9079.
- [129] Aujla SJ, Dubin PJ, Kolls JK. Th17 cells and mucosal host defense. *Semin Immunol* 2007;19(6):377–82.
- [130] Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 2009;139(3):485–98.
- [131] Paik D, Yao L, Zhang Y, Bae S, D'Agostino GD, Zhang M, et al. Human gut bacteria produce T_H17-modulating bile acid metabolites. *Nature* 2022;603(7903):907–12.
- [132] Corbitt N, Kimura S, Isse K, Specht S, Chedwick L, Rosborough BR, et al. Gut bacteria drive Kupffer cell expansion via MAMP-mediated ICAM-1 induction on sinusoidal endothelium and influence preservation-reperfusion injury after orthotopic liver transplantation. *Am J Pathol* 2013;182(1):180–91.
- [133] Kolios G, Valatas V, Kouroumalis E. Role of Kupffer cells in the pathogenesis of liver disease. *World J Gastroenterol* 2006;12(46):7413–20.
- [134] Nakamura K, Kageyama S, Ito T, Hirao H, Kadono K, Aziz A, et al. Antibiotic pretreatment alleviates liver transplant damage in mice and humans. *J Clin Invest* 2019;129(8):3420–34.
- [135] Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature* 2013;500(7461):232–6.
- [136] Han SJ, Kim M, Novitsky E, D'Agati V, Lee HT. Intestinal TLR9 deficiency exacerbates hepatic IR injury via altered intestinal inflammation and short-chain fatty acid synthesis. *FASEB J* 2020;34(9):12083–99.
- [137] Thomson AW, Vionnet J, Sanchez-Fueyo A. Understanding, predicting and achieving liver transplant tolerance: from bench to bedside. *Nat Rev Gastroenterol Hepatol* 2020;17(12):719–39.
- [138] Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc* 2003;35(3 Suppl):75–14S.
- [139] Han Y, Wu L, Ling Q, Wu P, Zhang C, Jia L, et al. Intestinal dysbiosis correlates with sirolimus-induced metabolic disorders in mice. *Transplantation* 2021;105(5):1017–29.
- [140] Tourret J, Willing BP, Dion S, MacPherson J, Denamur E, Finlay BB. Immunosuppressive treatment alters secretion of ileal antimicrobial peptides and gut microbiota, and favors subsequent colonization by uropathogenic *Escherichia coli*. *Transplantation* 2017;101(1):74–82.

- [141] Swarte JC, Li Y, Hu S, Björk JR, Gacesa R, Vich Vila A, et al. Gut microbiome dysbiosis is associated with increased mortality after solid organ transplantation. *Sci Transl Med* 2022;14(660):eabn7566.
- [142] Han CZ, Wei Q, Yang MF, Zhuang L, Xu X. The critical role of therapeutic plasma exchange in ABO-incompatible liver transplantation. *Hepatobiliary Pancreat Dis Int* 2022;21(6):538–42.
- [143] Wei RL, Fan GH, Zhang CZ, Chen KC, Zhang WH, Li CB, et al. Prognostic implication of early posttransplant hypercholesterolemia in liver transplantation for patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2022;S1499–3872(22):00123.
- [144] Lichtman SN, Keku J, Clark RL, Schwab JH, Sartor RB. Biliary tract disease in rats with experimental small bowel bacterial overgrowth. *Hepatology* 1991;13(4):766–72.
- [145] Little R, Wine E, Kamath BM, Griffiths AM, Ricciuto A. Gut microbiome in primary sclerosing cholangitis: a review. *World J Gastroenterol* 2020;26(21):2768–80.
- [146] Lemoinne S, Kemgang A, Ben Belkacem K, Straube M, Jegou S, Corpechot C, et al. Fungi participate in the dysbiosis of gut microbiota in patients with primary sclerosing cholangitis. *Gut* 2020;69(1):92–102.
- [147] Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. *Gut* 2018;67(3):534–41.
- [148] Li Y, Tang R, Leung PSC, Gershwin ME, Ma X. Bile acids and intestinal microbiota in autoimmune cholestatic liver diseases. *Autoimmun Rev* 2017;16(9):885–96.
- [149] Isaacs-Ten A, Echeandia M, Moreno-Gonzalez M, Brion A, Goldson A, Philo M, et al. Intestinal microbiome–macrophage crosstalk contributes to cholestatic liver disease by promoting intestinal permeability in mice. *Hepatology* 2020;72(6):2090–108.
- [150] Tabibian JH, O'Hara SP, Trussoni CE, Tietz PS, Splinter PL, Mounajjed T, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. *Hepatology* 2016;63(1):185–96.
- [151] Kim YC, Lee SJ. Temporal variation in hepatotoxicity and metabolism of acetaminophen in mice. *Toxicology* 1998;128(1):53–61.
- [152] Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 2014;159(3):514–29.
- [153] Gong S, Lan T, Zeng L, Luo H, Yang X, Li N, et al. Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice. *J Hepatol* 2018;69(1):51–9.
- [154] Li Y, Lv L, Ye J, Fang D, Shi D, Wu W, et al. *Bifidobacterium adolescentis* CGMCC 15058 alleviates liver injury, enhances the intestinal barrier and modifies the gut microbiota in *D*-galactosamine-treated rats. *Appl Microbiol Biotechnol* 2019;103(1):375–93.
- [155] Wang K, Lv L, Yan R, Wang Q, Jiang H, Wu W, et al. *Bifidobacterium longum* R0175 protects rats against *D*-galactosamine-induced acute liver failure. *MSphere* 2020;5(1):e00791–e19.
- [156] Yu L, Zhao XK, Cheng ML, Yang GZ, Wang B, Liu HJ, et al. *Saccharomyces boulardii* administration changes gut microbiota and attenuates *D*-galactosamine-induced liver injury. *Sci Rep* 2017;7(1):1359.
- [157] Bajaj JS, Vargas HE, Reddy KR, Lai JC, O'Leary JG, Tandon P, et al. Association between intestinal microbiota collected at hospital admission and outcomes of patients with cirrhosis. *Clin Gastroenterol Hepatol* 2019;17(4):756–65.e3.
- [158] Chen Y, Guo J, Qian G, Fang D, Shi D, Guo L, et al. Gut dysbiosis in acute-on-chronic liver failure and its predictive value for mortality. *J Gastroenterol Hepatol* 2015;30(9):1429–37.
- [159] Moreau R, Clària J, Aguilar F, Fenaille F, Lozano JJ, Junot C, et al. the CANONIC Study Investigators of the EASL Clif Consortium, the Grifols Chair, and the European Foundation for the Study of Chronic Liver Failure (EF Clif). Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. *J Hepatol* 2020;72(4):688–701.
- [160] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144(7):1426–37.1437.e1–9.
- [161] Ott SJ, El Mokhtari NE, Musfeldt M, Hellmig S, Freitag S, Rehman A, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. *Circulation* 2006;113(7):929–37.
- [162] Mitra S, Drautz-Moses DI, Alhede M, Maw MT, Liu Y, Purbojati RW, et al. *In silico* analyses of metagenomes from human atherosclerotic plaque samples. *Microbiome* 2015;3(1):38.
- [163] Bennett BJ, de Aguiar Vallim TQ, Wang Z, Shih DM, Meng Y, Gregory J, et al. Trimethylamine-*N*-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. *Cell Metab* 2013;17(1):49–60.
- [164] Carnevale R, Nocella C, Petrozza V, Cammisotto V, Pacini L, Sorrentino V, et al. Localization of lipopolysaccharide from *Escherichia coli* into human atherosclerotic plaque. *Sci Rep* 2018;8(1):3598.
- [165] Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell* 2016;165(1):111–24.
- [166] Duerschmied D, Canault M, Lievens D, Brill A, Cifuni SM, Bader M, et al. Serotonin stimulates platelet receptor shedding by tumor necrosis factor- α -converting enzyme (ADAM17). *J Thromb Haemost* 2009;7(7):1163–71.
- [167] Jäckel S, Kioptsis K, Lillich M, Hendriks T, Khandagale A, Kollar B, et al. Gut microbiota regulate hepatic von Willebrand factor synthesis and arterial thrombus formation via Toll-like receptor-2. *Blood* 2017;130(4):542–53.
- [168] Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in *Apoe*^{-/-} mice. *Circulation* 2016;133(24):2434–46.
- [169] Wu H, Wang Y, Zhang Y, Xu F, Chen J, Duan L, et al. Breaking the vicious loop between inflammation, oxidative stress and coagulation, a novel anti-thrombus insight of nattokinase by inhibiting LPS-induced inflammation and oxidative stress. *Redox Biol* 2020;32:101500.
- [170] Mathew OP, Ranganna K, Milton SG. Involvement of the antioxidant effect and anti-inflammatory response in butyrate-inhibited vascular smooth muscle cell proliferation. *Pharmaceuticals* 2014;7(11):1008–27.
- [171] Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. *World J Gastroenterol* 2013;19(19):2841–6.
- [172] Trebicka J, Bork P, Krag A, Arumugam M. Utilizing the gut microbiome in decompensated cirrhosis and acute-on-chronic liver failure. *Nat Rev Gastroenterol Hepatol* 2021;18(3):167–80.
- [173] Yang F, Chen H, Gao Y, An N, Li X, Pan X, et al. Gut microbiota-derived short-chain fatty acids and hypertension: mechanism and treatment. *Biomed Pharmacother* 2020;130:110503.
- [174] Trøseid M, Andersen GØ, Broch K, Hov JR. The gut microbiome in coronary artery disease and heart failure: current knowledge and future directions. *EBioMedicine* 2020;52:102649.
- [175] Kadri OE, Surblyte M, Chandran VD, Voronov RS. Is the endothelial cell responsible for the thrombus core and shell architecture? *Med Hypotheses* 2019;129:109244.
- [176] Esmon CT. The interactions between inflammation and coagulation. *Br J Haematol* 2005;131(4):417–30.