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REVIEW

Gut microbiota contribution to hepatocellular carcinoma manifestation in non-alcoholic steatohepatitis

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Abstract

Recently, the gut microbiota has been recognized as an obvious active player in addition to liver steatosis/steatohepatitis in the pathophysiological mechanisms of the development of hepatocellular carcinoma (HCC), even in the absence of cirrhosis. Evidence from clinical and experimental studies shows the association of specific changes in the gut microbiome and the direct contribution to maintaining liver inflammation and/or cancerogenesis in nonalcoholic fatty liver disease-induced HCC. The composition of the gut microbiota differs significantly in obese and lean individuals, especially in the abundance of pro-inflammatory lipopolysaccharide-producing phyla, and, after establishing steatohepatitis, it undergoes minor changes during the progression of the disease toward advanced fibrosis. Experimental studies proved that the microbiota of obese subjects can induce steatohepatitis in normally fed mice. On the contrary, the transplantation of healthy microbiota to obese mice relieves steatosis. However, further studies are needed to confirm these findings and the mechanisms involved. In this review, we have evaluated well-documented clinical and experimental research on the role of the gut microbiota in the manifestation and promotion of HCC in

nonalcoholic steatohepatitis (NASH). Furthermore, a literature review of microbiota alterations and consequences of dysbiosis for the promotion of NASH-induced HCC was performed, and the advantages and limitations of the microbiota as an early marker of the diagnosis of HCC were discussed.

Key Words: Gut microbiota; Hepatocellular carcinoma; Non-alcoholic steatohepatitis; Non-alcoholic fatty liver disease; Microbiome

Core Tip: Although the incidence of life-threatening cases of hepatocellular carcinoma (HCC) induced by nonalcoholic steatohepatitis (NASH) has recently increased due to the dramatic increase in steatohepatitis, the pathophysiological mechanisms of the manifestation of HCC nodules have not yet been fully elucidated. There is a lack of tools to diagnose HCC at an early stage, especially considering that HCC can occur in patients with NASH even in the absence of cirrhosis. In this review, we have evaluated the current state of research on the role of the gut microbiota in promoting NASH-induced HCC and the use of the microbiota for the early diagnosis of HCC.

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INTRODUCTION

In the different regions of the world, non-alcoholic fatty liver disease (NAFLD) affects 4%-55% of the population[1,2]. Subjects with NAFLD are constantly at risk of developing chronic liver inflammation leading to nonalcoholic steatohepatitis (NASH) and eventually progressing from liver fibrosis to cirrhosis. The latter has a higher risk of hepatocellular carcinoma (HCC) manifestation[3]. Although the risk of NAFLD progression to cirrhosis is less likely than in viral hepatitis (approximately 10% of NASH [4], and less than 1% of patients with NAFLD developed HCC within 8 years after initial diagnosis[5,6]), NASH alone can cause HCC even in the absence of cirrhosis, and this raises concerns[7-9]. Furthermore, it is estimated that HCC cases related to NASH may increase by up to 56% in the next 10 years[10].

In some cases, prolonged inflammation of the liver caused by steatosis appears to be a sufficient circumstance to cause the rise of the so-called compensatory proliferation of hepatocytes, which triggers the formation of HCC nodules[5], but the precise pathophysiological mechanism is still far from complete elucidation. To some extent, NAFLD/NASH mice models are helpful. However, translating animal studies into a human context is always difficult because only reliable mechanistic information comes from these studies[11].

In addition to liver steatosis / steatohepatitis, the gut microbiota has recently been recognized as an obvious active player in NAFLD-induced HCC. Experimental and clinical studies demonstrate a stimulating role of the intestinal microbiota in maintaining liver inflammation and an alteration of the microbiome composition toward a more pro-inflammatory state with the progression of liver disease from NAFLD to NASH at different stages of fibrosis and HCC[12,13]. It seems like this is a mutually supportive process. This has been confirmed by a study of germ-free mice transplanted with stool from genetically obese patients. Soon after the guts of these mice were colonized by the microbiota of obese subjects, a steatosis manifested in their livers despite a balanced diet[14]. On the contrary, fecal microbiota transplantation from healthy mice alleviated steatohepatitis in mice fed a high-fat diet[15].

The liver is closely related to the intestinal tract and serves as a vital metabolic center for digestion, detoxification, and clearance of microbial products[16]. Research on the gut-liver axis has greatly contributed to understanding the basic pathophysiology of liver diseases, including NAFLD of different severity and malignancy of the liver parenchyma[17,18].

In this review, we conducted a survey of the current state of research on the contribution of the gut microbiota to the manifestation and progression of HCC in patients with NASH.

LITERATURE SEARCH AND ANALYSIS OF CLINICAL AND EXPERIMENTAL STUDIES SELECTED

An electronic search of the literature on the microbiota in NASH-induced HCC was performed. Articles available in the PubMed, Medline, Cochrane, and Web of Science databases were reviewed up to November 12, 2021. The search terms used were "nonalcoholic fatty liver disease AND hepatocellular carcinoma AND microbiome", "nonalcoholic fatty liver disease AND hepatocellular carcinoma AND microbiota", "nonalcoholic steatohepatitis AND hepatocellular carcinoma AND microbiota", "nonalcoholic steatohepatitis AND hepatocellular carcinoma AND microbiome", "nonalcoholic steatohepatitis AND liver cancer AND microbiota" and "nonalcoholic fatty liver disease AND liver cancer AND microbiota". No time restrictions were used for publications. A total of 1,073 articles and abstracts met the initial search criteria.

The titles, abstracts, and full papers were reviewed to identify full-text articles focusing on alterations in the gut microbiota in NASH/NAFLD - HCC compared to healthy controls, as well as animal model studies discussing changes in the gut microbiota in NASH/NAFLD - induced HCC (Supplementary Figure 1).

Inclusion criteria were: Well-documented full-text articles written in English, presence of the following study groups – NAFLD/NASH with/without cirrhosis, NAFLD/NASH-HCC with/without cirrhosis, control group of healthy subjects.

Exclusion criteria after abstract and full text reviews were: articles written in other languages than English, no presence of NAFLD/NASH - HCC, no evaluation of the NASH/NAFLD - HCC microbiota, no control group.

Following a comprehensive review of the current literature, we identified only six publications focusing on the gut microbiota in NASH/NAFLD induced HCC that were fully consistent with the inclusion criteria[12,13,19-22]. Three selected articles were clinical studies, in which the microbiota composition of 86 patients with HCC induced by NAFLD was analyzed among others with NAFLD of different severity (Table 1)[13,19,20]. The other three publications included animal model studies in which mice with NAFLD and HCC microbiota were analyzed (Table 2)[12,21,22]. The circumstantial analysis of the selected studies is presented below.

Human studies

All three identified clinical studies on NASH-induced HCC were cross-sectional. Two of them compared cirrhotic NAFLD with or without HCC with healthy controls[19,20], and one compared patients with NASH together, NASH-HCC with or without cirrhosis, and healthy controls[13]. In total, 168 patients with NAFLD and 70 controls were enrolled. The HCC had 72(55%) of 131 cirrhotic patients and 14(37.8%) of 37 without cirrhosis.

The α-diversity and bacterial richness were analyzed. Behary *et al*[19] confirmed dysbiosis in the NAFLD-HCC and NAFLD-cirrhosis groups compared to healthy controls. Patients in these following groups had reduced α-diversity (a measure of microbiome diversity applicable to a single sample) and the Chao-1 richness index. However, no other differences were observed in other alpha-diversity measures (Shannon's diversity index, Evenness index). A study by Sydor *et al*[13] showed that the rarity index increased in patients with NASH-HCC with cirrhosis compared to the control group. In the third study by Ponziani *et al*[20], α-diversity was reduced in the NAFLD-HCC group compared to healthy controls. However, diversity changes were not specified when comparing NAFLD-HCC with cirrhosis and NAFLD-HCC without cirrhosis.

There is a consistent amount of evidence that the gut-liver axis plays an important role in the progression of liver diseases[17,18]. In a study by Komiyama *et al*[23], the most common phyla of the gut microbiota (*Bacteroidetes, Firmicutes*, and *Proteobacteria*) were also dominant in HCC, suggesting that an increased abundance of these phyla is also found in subjects with HCC induced by NAFLD.

Ponziani *et al*[20] demonstrated an increased quantity of *Bacteroides* and *Lactobacillus* in cirrhotic patients with or without HCC. Furthermore, with deficiency of *Bifidobacterium* and *Blautia,* HCC patients had an even higher abundance of *Bacteroides* and R*uminococccaceae, Enterococcus, Phascolarctobacterium,* and *Oscillospira* than the NAFLD-non-HCC with cirrhosis patient group. A study by Behary *et al*[19] also showed a significant enrichment of *Bacteroides xylanisolvens* and *Ruminococcus gnavus* in both the NAFLD-HCC and NAFLD-cirrhosis groups compared to healthy controls. *Bacteroides caecimuris* and *Veillonella parvula* were specifically enriched in the NAFLD-HCC group compared to the control and NAFLD-cirrhosis groups[19]. However, Sydor *et al*[13] demonstrated a reduction in the abundance of *Bacteroidetes* along with Gram-positive *Actinobacteria* and *Bifidobacterium* and an increased abundance of *Proteobacteria* and *Lactobacillus* in patients with NASH-HCC.

In a previous study, the *Bacteroides* genera were also enriched in HCC *vs* patients with cirrhosis, suggesting that the enrichment of *Bacteroides* in the gut microbiota may be associated with the diagnosis of liver cancer[24].

Animal studies

We identified 3 animal studies (mice) investigating changes in the gut microbiome in NAFLD-induced

Table 1 Clinical studies investigating gut microbiota composition in patients with nonalcoholic fatty liver disease - induced hepatocellular carcinoma

Ref.	Participants (groups)	Exclusion criteria	Main findings	Other metabolites investigated
Behary *et al*[19]	Patients with NAFLD-HCC-cirrhosis *n* = 32; Patients with NAFLD-cirrhosis *n* = 28; Control group (non-NAFLD) *n* = 30.	Unspecified	Subjects with NAFLD-HCC and NAFLD-cirrhosis had reduced α-diversity indices compared to non-NAFLD controls; NAFLD-HCC was characterized by expansion of *Proteobacteria* compared to a non-NAFLD group; Expansion of *Enterobacteriaceae* in NAFLD-HCC compared to NAFLD-cirrhosis and controls; NAFLD-HCC was characterized by a reduction in *Oscillospiraceae* and *Erysipelotrichaceae* compared to non-NAFLD; NAFLD-cirrhosis was characterized by an expansion of *Eubacteriaceae* compared to both NAFLD-HCC and controls; *Bacteroides caecimuris* and *Veillonella parvula*, were both significantly enriched in NAFLD-HCC, compared to NAFLD cirrhosis and controls	Pyruvate carboxylase (pycA), responsible for the production of oxaloacetate from pyruvate, was overexpressed in NAFLD-HCC compared to NAFLD-cirrhosis and non-NAFLD control; Genes related to acetate synthesis (phosphate acetyltransferase) and butyrate/acetyl phosphate synthesis (phosphate butyryltransferase) were both overexpressed in NAFLD-HCC compared to NAFLD cirrhosis and non-NAFLD controls; The feces of NAFLD-HCC subjects were enriched in acetate, butyrate and formate compared to NAFLD-cirrhosis and controls; Fecal SCFA was NAFLD-HCC specific
Sydor *et al*[13]	Patients with NASH-non-HCC without cirrhosis *n* = 23; Patients with NASH-non-HCC with cirrhosis *n* = 11; Patients with NASH-HCC without cirrhosis *n* = 14; Patients with NASH-HCC with cirrhosis *n* = 19; Control group *n* = 20.	Unspecified	B*acteroidetes* and, to a lesser extent, *Actinobacteria* were gradually decreased in abundance from controls to NASH-non-HCC to NASH-HCC; The abundance of *Proteobacteria* was significantly increased in NASH-HCC with cirrhosis; The abundances of *Bacteroides* and *Bifidobacterium* were decreased in NASH-non-HCC and NASH-HCC compared with controls; *Lactobacillus* showed a progressive increase in abundance from controls to NASH-HCC with cirrhosis; Abundance of *Clostridium* and *Escherichia/Shigella* remained unchanged; *Lactobacillus*-related ranks showed a progressive increase in abundance from controls to NASH-HCC with cirrhosis	Significant increase of BA associated with disease severity between healthy, NASH-non- HCC, and NASH-HCC; Individual and conjugated serum BA were associated with the abundance of *Lactobacillus*
Ponziani *et al*[20]	Patients with NAFLD-HCC with cirrhosis *n* = 21; Patients with NAFLD-non-HCC with cirrhosis *n* = 20; Control group *n* = 20.	Patients with CVH, AH, cholestatic disorders such as PBC or PSC, and inherited liver disorders leading to cirrhosis such as hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency; Patients who were taking drugs such as antibiotics, probiotics, prebiotics, PPIs, and laxatives during the last 6 mo; affected by diseases potentially influencing the gut microbiota composition; Patients with a history of cancer.	α-diversity was less diverse in patients with cirrhosis compared to controls; Cirrhosis patients showed enriched *Proteobacteria*, *Bacteroidetes* and *Cyanobacteria* compared to healthy controls; The gut microbiota of the HCC group was enriched with *Bacteroides*, *Ruminococcaceae*, *Enterococcus*, *Phascolarctobacterium*, and *Oscillospira* compared to patients with cirrhosis but without HCC and controls; Reduced abundance of *Verrucomicrobiaceae*, *Bifidobacteriaceae*, *Akkermansia*, *Bifidobacterium*, *Dialister*, *Collinsella*, and *Adlercreutzia* were seen in NAFLD-HCC compared with NAFLD-non-HCC.	Intestinal permeability was increased in all patients with liver cirrhosis, who had higher levels of plasma ZO1 and LPS compared to controls

AH: Autoimmune hepatitis; BA: Bile acids; CVH: Chronic viral hepatitis; HCC: Hepatocellular carcinoma; LPS: Lipopolysaccharides; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cholangitis; PPI: Proton pump inhibitors; PSC: Primary sclerosing cholangitis; SCFA: Short-chain fatty acid.

HCC, summarized in Table 2[12,21,22]. To induce HCC, mice were fed a high-fat diet (high-fat/high-cholesterol (HFHC) and high-fat/low-cholesterol (HFLC). In one study, additional intraperitoneal injections of CCl4 were administered once a week to induce HCC[21].

Animal studies demonstrated the same results regarding α-diversity in the gut microbiome in HCC induced by NAFLD. In all studies, α-diversity was reduced in HCC mice compared to the control group. A study by Zhang *et al*[22] also showed that mice fed the HFHC diet had lower bacterial diversity than mice fed the HFLC diet. HFHC-fed mice also had a higher association with the development of HCC.

Increased LPS across the intestinal barrier in mice with NAFLD-induced HCC

Some studies in humans observed increased serum lipopolysaccharide (LPS) levels in HCC patients[25,26]. It indicated an increase in permeability of the intestinal epithelial barrier[23].

Thus, it was no surprise that higher serum LPS levels were observed in three reviewed animal studies [12,21,22]. Mice fed a high-fat streptozocin diet (STZ) and developed HCC had a higher abundance of *Bacteroides* and *Desulfovibrio* in their gut microbiome[12]. Since most *Bacteroides* and *Desulfovibrio* species

Table 2 Animal models investigating gut microbiota composition in nonalcoholic fatty liver disease induced hepatocellular carcinoma

Ref.	Experimental animal	Participants (groups)	Main findings
Xie *et al*[12]	Mice	Mice with STZ-HFD induced NASH-HCC; Control group	STZ-HFD group exhibited lower α-diversity than controls; The most abundant species in both control group and STZ-HFD group were primarily from the *Bacteroides* genus; The most decreased in abundance in the STZ-HFD group were *Parasutterella spp., Bacteroides acidofaciens, Odoribacter spp., Barnesiella spp., Moryella spp., Paraprevotella spp., Lactobacillus intestinalis, and Akkermansia spp*; *Atopobium spp., Bacteroides acidifaciens, Bacteroides spp., Bacteroides uniformis, Bacteroides vulgatus, Clostridium cocleatum, Clostridium xylanolyticum*, and *Desulfovibrio spp.* were significantly positively correlated with LPS in plasma, liver and feces; As most *Bacteroides* and *Desulfovibrio* were LPS-producers, LPS concentration was significantly increased in the STZ-HFD group.
Carter *et al* [21]	Mice	Western diet only (high fat and fructose diet, no CCl4 injection); CCl4 only (CCl4 injection intraperitoneal once a week and normal diet); NASH-HCC (Western diet and CCl4 injection intraperitoneally once a week); Control group (normal diet, no CCl4 injection);	NASH mice display impaired intestinal barrier function, leading to increased leakage of bacterial byproducts such as LPS into the circulation; NASH mice had reduced alpha diversity; Expansion of *Erysipelotrichales* was only observed in NASH mice
Zhang *et al* [22]	Mice	HFHC-fed mice (NAFLD-HCC group); HFHC-fed mice; Normal diet-fed mice (control group).	The microbiota composition changed during NAFLD-HCC formation: *Mucispirillum, Desulfovibrio, Anaerotuncus* were sequentially increased; Gut bacterial metabolites alteration like TCA and IPA were increased in NAFLD-HCC mice; Lower bacterial diversity and increased bacterial richness were observed in HFHC-fed mice with HCC than HFLC diet-fed mice with only steatosis; LPS concentration was elevated in HFHC-fed mice compared to HFLC-fed mice.

HCC: Hepatocellular carcinoma; HFHC: High-fat/high-cholesterol; HFLC: High-fat/low-cholesterol; IPA: Indole-3-propionic acid; LPS: Lipopolysaccharides; NAFLD: Non-alcoholic fatty liver disease; STZ-HFD: Streptozocin-high-fat diet; TCA: Trichloroacetic acid.

are producers of LPS, higher LPS concentrations were found in HCC mice' blood. In a study by Carter *et al*[21], NASH-induced HCC mice had increased gut permeability, which also resulted in elevated serum LPS.

Recent studies showed that circulating LPS was significantly elevated in patients with colorectal cancer compared to healthy controls. Furthermore, the authors concluded that serum LPS can cause chronic inflammation and activate the coagulation system, leading to cancerogenesis[27]. New studies show that elevated levels of circulating LPS may be highly associated with many chronic liver diseases, including liver fibrosis and HCC[28,29].

NASH-INDUCED HCC PATHOGENESIS ASSOCIATIONS WITH GUT MICROBIOTA

The accumulation of lipid droplets alone does not cause liver damage or inflammation. Hepatosteatosis (a.k.a. "bland steatosis") requires a necro-inflammatory mechanism characterized by ballooning hepatocytes, liver injury, and fibrosis[5]. The inflammation of the liver could be triggered by provocative factors, such as oxidative stress, stress of the endoplasmic reticulum, and/or the presence of infectious or commensal organisms[30]. This so-called two-hit hypothesis was first formulated by Day and James[31].

The specific mechanism that links the gut microbiota with the progression of NAFLD is still unclear. However, bacterial overgrowth, translocation of microorganisms, increased endotoxin absorption, and enterohepatic secondary bile acids may be possible explanations[32].

Leaky gut

Patients with exacerbated liver function have increased intestinal permeability and impaired mucosa due to the alternation of the tight epithelial junction[25,33]. This leads to the leakage of chemicals derived from the microbiota into the bloodstream of the portal vein. The more severe and long-lasting the liver disease, the higher the levels of different potentially pro-inflammatory and pro-oncogenic microbial products that might be detected in the blood of patients[25]. It should be noted that this state is often worse in the NASH population due to a high-fat/high-carbohydrate diet that maintains the pro-inflammatory alteration of the intestinal microbiota[34]. Improvement in liver function tests following dietary correction in clinical trials in patients with NASH / obesity is evidence of reduced parenchymal inflammation[35]. Mice experiments also confirmed the importance of diet for the healthy shape of the gut microbiota[15].

Bacterial overgrowth

There is a link between bacteria overgrowth and NAFLD/NASH. Approximately 50%-80% of patients with NAFLD/NASH have small intestine bacterial overgrowth (SIBO)[7]. SIBO, together with alteration of the intestinal microbial community, has been detected in NAFLD-induced chronic liver inflammation conditions of different stages[16].

In several clinical studies, an abundance of the *Veillonella* genus was found in the duodenum and colon of cirrhotic patients, along with the reduction of the genus *Akkermansia* and *Prevotella*[16,36]. Loomba *et al*[37] observed an increased quantity of *Bacteroides vulgatus* and *Escherichia coli* (*E. coli*) in patients with advanced NAFLD-induced fibrosis. *E. coli* was also predominant in patients with SIBO-affected NAFLD[38].

More studies are needed to show the prevalence of SIBO in patients with NASH-induced HCC.

Dysbiosis

Dysbiosis of the gut microbiota has been associated with a higher risk of certain cancers and has been shown to affect the body's reaction to various cancer treatments[39,40]. Furthermore, a reduction in the diversity of the intestinal microbiome has been reported in inflammatory bowel diseases, colorectal cancer, and gastric cancer[41-43]. The diversity of the gut microbiota is now considered an important environmental characteristic of NAFLD, since it can impact host metabolic processes, such as the extraction of energy from food. Through mechanisms such as altered hunger signaling, enhanced energy extraction from the diet, and altered regulation of gene expression involved in de novo lipogenesis or oxidation, the gut microbiota has the ability to increase intrahepatic fat[44].

It should be noted that researchers observed a larger difference in the abundance of bacteria at the levels of phylum, family, and genus levels between healthy and obese subjects, while relatively fewer differences were observed between obese and the NASH microbiome[45]. The only abundance of *Proteobacteria*, *Enterobacteria*, and *Escherichia* differed between obese and NASH[46]. Ezzaidi *et al*[32] found that patients with NASH have a lower abundance of *Faecalibacterium* and *Anaerosporobacter,* but a higher abundance of *Parabacteroides* and *Allisonella*. They also noted that the reduction in *Firmicutes* and the increase in *Bacteroidetes* were associated with an improvement in steatosis. However, *Bacteriodetes* are known as LPS-producing bacteria, which is why they are pro-inflammatory[32].

An elevated abundance of *Bacteroides vulgatus* and *E. coli* has been discovered in NAFLD patients with advanced fibrosis[37]. Fecal *Bacteroides* and *Ruminococcus* were independently related to NASH and fibrosis (stage 2 or above), while *Prevotella* decreased under the same circumstances[36].

The role of the microbiome in NAFLD-HCC is mainly unknown. The clinical studies summarized in Table 1 of this review agree on the decrease in the diversity of bacteria in patients with NASH-HCC, but demonstrate a discrepancy in the abundance of various representatives of the gut microbiota. Only changes at the phyla level toward LPS producers have been confirmed in all studies.

The gut microbiota produces a wide range of bioactive chemicals, including those from food substances [LPS, short-chain fatty acids (SCFA), deoxycholic acid (DCA)], resulting in a complex transgenomic metabolism between the microbiota and the host that significantly affects physiological and pathological states[47]. Through the gut-liver axis, intestinal microbial dysbiosis is linked to hepatic inflammation and HCC[32].

Dysbiosis of the intestinal microbiota appears to be a novel component that promotes the development of NALFD-induced HCC. The manifestation of HCC has been associated with increased *Bacteroides* and *Ruminococcaceae,* but lower *Bifidobacterium* in patients with NAFLD[20]**.**

The increase in *Bacteroides* and *Ruminococcaceae* in the HCC population is associated with higher levels of calprotectin and systemic inflammation[16,19,20,48,49]. In general, researchers agree that the gut bacteria of obese subjects promote HCC. However, the patterns of bacterial abundance were not consistent between studies. For example, some studies claimed an increase in *Bacteroidetes* in advanced NASH[19,20,37], , while other studies showed that patients with NASH possessed a lower abundance of *Bacterioidetes*[13].

MECHANISMS OF MICROBIOTA CONTRIBUTION TO PERSISTENT LIVER INFLAMMATION AND HEPATOCARCINOGENESIS

Since liver disease may be accompanied by SIBO and altered gut permeability, a correlation of the increased level of bacterial products in the portal blood can be expected with the severity of the disease. Due to the altered intestinal barrier, bacterial products derived from gut microbes (microbial-associated molecular patterns (MAMPs): LPS, peptidoglycan, and bacterial unmethylated cytosine–phosphate–guanine dinucleotides (CpG) DNA, DCA, and lipoteichoic acid (LTA), ethanol, acetone, butanoic acid, and many other molecules) can enter the liver and activate toll-like receptors (TLRs) in Kupffer cells, liver stellate cells, and hepatocytes, leading to an inflammatory response that promotes NASH[7,16,32]. In humans, TLR-2, TLR-4, and TLR-9 are known to be involved in the pathogenesis of NASH[50].

According to recent experimental and clinical studies, the intestinal microbiome can contribute to all histological components of NAFLD: liver steatosis, inflammation, and fibrosis[48]. As HCC in patients with NASH can occur in the absence of cirrhosis[8,9,51,52], chronic inflammation of the liver is the most important circumstance for its manifestation[53].

Several studies of NASH-induced HCC reported the correlation of *Bacteroides* and *Ruminococcaceae* expansion with systemic inflammation[19,20,48,49]. It is well known that after pro-inflammatory stimulation by nutrients metabolites or/and bacterial molecules that enter the liver, Kupffer cells, liver stellate cells, and infiltrating macrophages produce a variety of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL) -6, and IL-8, to establish the immune response. Increased levels of these cytokines have been detected in patients with NASH[54,55].

These cytokines contribute to the development of NASH and HCC by activating nuclear factor kappa-B (NF-κB) and STAT3 in initiated hepatocytes[30]. However, it is not yet clear how pro-inflammatory events trigger the development of HCC and how malignant hepatocytes escape the immune attack. Evidence from the experimental study elucidated a suppressive impact of immunoglobulin A+ plasma cells on cytotoxic T lymphocytes by expression of programmed death ligand 1 (PD-L1) that leads to the exhaustion of CD8 + T lymphocytes[56]. PD-L1 inhibitors appeared to be highly effective for HCC treatment[57]. The inflammatory cytokine profile and TNF-α activated NF-κB signaling, as well as the exhaustion of CD8+ T lymphocytes, are characteristic of HCC of non-NASH etiology[5].

LPS producing bacteria can induce liver inflammation and promote carcinogenesis

LPSs are active components of bacterial endotoxins released by Gram-negative bacteria after their death. LPS-specific TLR-4s are expressed by monocytes, mast cells, B cells, and the intestinal epithelium[1]. After release from the wall of the bacteria cell, LPS forms a complex with the lipopolysaccharide binding protein, CD14, and TRL4 and enters circulating blood due to increased intestinal permeability[58].

Hepatocytes, Kupffer cells, and liver stellate cells also express LPS-specific TLR-4. After activation of TRL-4 by LPS in Kupffer cells, an intracellular inflammatory cascade is triggered, inducing the production of pro-inflammatory cytokines (TNF-α, IL-6)[59,60].

TLR-4 activation also leads to overexpression of hepatomitogen epiregulin, which promotes mitosis of hepatocytes and, therefore, hepatocarcinogenesis. At the same time, LPS-activated liver stellate cells gain a pro-inflammatory state and start to secrete collagen, inducing liver fibrogenesis and vascular endothelial growth factor, which participates in hepatocarcinogenesis by promoting neoangiogenesis [47,61].

Furthermore, caspase-3 cleavage, responsible for cell apoptosis, appears in hepatocytes through the NF-κB-mediated mechanism[47]. All of the mentioned events lead to the survival of malicious hepatocytes and the formation of HCC nodules. In patients with liver cancer, the activated LPS-TLR-4 pathway is associated with increased invasiveness of tumor cells induced by NF-κB-mediated epithelial-mesenchymal transition and, consequently, metastasis and poor prognosis[62,63].

Other pro-inflammatory and pro-oncogenic impacts of the microbiota in NASH-induced HCC

Alongside TLR-4, Kupffer and hepatic stellate cells possess TLRs with specificity to other MAMPs. TLR-2 can be activated by components of Gram-positive bacterial cell walls, such as peptidoglycan and lipoteichoic acid. Through mitogen-activated protein kinases (MAPKs) induced by MyD88/MAL and NF-κB-mediated transcriptional programs, they promote liver tumorigenesis[16,64]. TLR-2, activated by lipoteichoic acid, along with secondary bile acid deoxycholate, promotes DNA damage, cell senescence, and apoptosis, and incites obesity-associated tumorigenesis through a pro-inflammatory and immunosuppressive pro-tumorigenic environment involving prostaglandin E2[65,66]. NASH progression and NASH-induced HCC have been prevented in an experimental model by treating mice with sequestrant bile acids[67].

TLR-9 is an intracellular receptor that detects bacterial and viral DNA. It recognizes DNA containing unmethylated CpG motifs, which are common in bacteria[64,68]. The TLR-9 signaling pathway induces IL-1b production by Kupffer cells, leading to steatosis, inflammation, and fibrosis. IL-1b promotes lipid accumulation and cell death in hepatocytes[69,70].

Modifying bile acid metabolism and other small metabolites contribute to the development of HCC induced by NASH

Metabolites produced by the gut microbiota have received much attention in the scientific community, and they are helping us to understand the metabolic changes that contribute to the development of NAFLD and NAFLD-HCC. Liposomes (SCFA), glucose, amino acids, and bile acids are now being investigated to improve our understanding of the pathophysiology of NAFLD-HCC[32,71].

Bile acids and their metabolites play an important role in the regulation of hepatic glucose, cholesterol, and triglyceride balance, and their changes can cause NAFLD by affecting lipid and energy metabolism[7]. In addition, bile acids can directly affect the intestinal microbiome by altering bacterial membranes[72].

The colon microbiota, particularly Gram-positive bacteria belonging to *Clostridium* clusters, convert primary bile acids, which were not resorbed in the small intestine, into secondary bile acids,

deoxycholate and lithocholate, which are then transported back to the liver with portal blood[73]. Dysbiosis promotes the increase of levels of such secondary bile acids in the liver. Consequently, a senescence hepatic stellate cell phenotype appears, which is characterized by the overproduction of various pro-inflammatory and tumorigenic factors that promote the development of HCC[7,16]. Sydor *et al*[13] have determined the direct correlation of blood levels of conjugated bile acids with the severity of NAFLD, although independent of the occurrence of HCC. Enterohepatic DCA also promotes the development of HCC in mice[74].

On the other hand, liver inflammation has been shown to cause intrahepatic retention of bile acids, directly promoting the development of HCC[67].

By activating TGR5 (Takeda G protein receptor 5), secondary bile acids may participate in the regulation of insulin sensitivity[16,75]. Activation of FXR (Farnesoid X receptor) by the gut microbiota may also influence bile acid metabolism during the onset and progression of hepatic steatosis[16,76].

Other small bacterial metabolites generated by the gut microbiota are also attractive objects to study metabolic alterations that may play a role in the progression of NAFLD and NAFLD-HCC[32,77].

Branched chain amino acids (leucine, isoleucine, valine, and phenylalanine) and bile acids (glycocholic acid, taurocholic acid, glycochenodeoxycholate) were found to be strongly associated with progression of steatosis to NASH, NASH-cirrhosis, and HCC[78], while glutathione was inversely associated[79].

SCFAs (formate, acetate, propionate, and butyrate) can enter the portal vein and promote lipid build-up and glucogenesis in the liver and possibly promote inflammation and oncogenesis[19,80]. The feces of patients with NAFLD-induced HCC were enriched in those SCFs[19]. Although other researchers propagate the anti-inflammatory effects of aromatic amino acid metabolites, especially butyrate[81,82].

Intestinal bacteria can convert dietary choline to trimethylamine (TMA), which is then further metabolized in the liver to trimethylamine-N-oxide (TMAO). Contrary to the useful choline metabolite, phosphatidylcholine, TMAO promotes the accumulation of triglycerides leading to hepatic steatosis and, thus, contributes to inflammation[7].

The difference between bland and NASH steatosis is the accumulation of free non-sterified cholesterol in the latter[5]. Free cholesterol and its oxidized derivatives are cytotoxic and can cause liver damage[5,83].

NAFLD patients had higher serum alcohol concentrations than healthy controls and obese subjects, indicating the possible impact of ethanol-producing bacteria on the pathogenesis of NASH[7].

How the aforementioned bacterial metabolites contribute to the manifestation of HCC in subjects with NASH must be elucidated.

Modifying antitumor immunity

The multilayer immune components of the colon wall, together with the genetic diversity of the colon microbiota, create an ideal environment for intestinal microbe-human immunological interactions[84]**.** The gut microbiota and its metabolites alter host gene pathways implicated in immunological and metabolic diseases[85].

In addition to promoting inflammation, the gut microbiota can possibly affect antitumor immunity. *A. muciniphila* and *Ruminococcaceae spp*. were found to be enriched in the gut of HCC patients who respond to anti-PD-1 immune checkpoint inhibitor compared to nonresponders[86]. The gut microbiota of patients with unresectable HCC differs: Those with progressive HCC were characterized by the abundance of fecal *Prevotella*, while those with a good response to immune checkpoint inhibitors were distinguished in the amount of *Veillonella, Lachnospiraceae, Lachnoclostridium, Lactobacillales, Streptococcaceae,* and *Ruminococcaceae*[87].

In several clinical studies of using an anti-CTLA-4 treatment for cancers of other etiology, the promoting effect for response to treatment by several species of the gut microbiota was also reported. However, the possible mechanism of such an impact is not very clear[84]. Furthermore, molecules born of the microbiota, including genomic material, the so-called bacterial signature, have been found in the liver parenchyma and the HCC nodules themselves[16]. These molecules could certainly play an active role in modulating the immune response in favor of more severe inflammation and hepatocarcinogenesis. A direct association of intrahepatic *Gamma-proteobacteria* abundance with liver disease progression from non-NAFLD to NAFLD and NASH of different severity was reported[88]. And finally, bile acids themselves possess immunomodulatory properties. Therefore, their modulation by the gut microbiota directly impacts host immunity.

LIMITATIONS AND FUTURE PERSPECTIVES

Most healthy individuals demonstrate relative stability of their gut microbiota with the transient effect of diet and the slightly longer effect of antibiotics[89-91]. For example, shared housing promotes the preservation of the same microbiota profiles[92]. On the contrary, discrepancies in the data on the composition of the gut microbiota are observed in clinical studies, including those of NASH-induced HCC. Due to the small number of subjects enrolled, the absence of control groups, different sample

collection techniques, and distinctive sequencing methods, the results of clinical studies are difficult to compare, and there are always doubts about their reproducibility.

Estimated differences between the composition of the gut microbiota of a healthy population, NAFLD, NASH, and those with NASH-induced HCC, even at the phyla level, can be considered as evidence of the participation of the microbiota in the pathogenesis of HCC, especially with a shift towards LPS-producing phyla. However, the collected data is not sufficient to draw reasonable conclusions so far.

Moreover, even in the generally pro-inflammatory LPS-producing phyla, there is a huge difference between the properties of bacteria depending on the species. Furthermore, bacterial strains belonging to the same species can also vary greatly in properties. Since affordable measures, such as a balanced diet and aerobic exercises, gradually shift the microbiota toward a healthy shape, it can be presumed that substantial changes are likely to occur at the species/strain level. Possibly, the research of some representative of the gut microbiota at the species/strain level in subjects with NASH-induced HCC in comparison with those without HCC will provide us with more definitive hepatocarcinogenesis provokers in the NASH population, or at least a noninvasive marker of early HCC will be confirmed. One such candidate – *Veillonella parvula* – has already been discovered. However, it is too early to draw conclusions about whether it was an incidental finding or a reliable HCC marker[93].

The microbiota as a potential noninvasive marker for the diagnosis of HCC, especially in the early stages, is intensively studied and might be promising since researchers determine some peculiarities distinguishing the microbiota composition in cirrhotic patients with HCC patients[48,49]. A more attentive study of comparing the gut microbiota of non-cirrhotic NAFLD-HCC patients with cirrhotic ones may prove useful in clarifying the most provocative representatives of liver oncogenicity. HCC of different stages can also be characterized using a dysbiosis index[49]. Although the cohorts of patients in such studies are too small to expect reproducibility of the results.

Experimental studies of the gut microbiota are characterized by another limiting aspect, different methodological approaches. These problems were perfectly elucidated in the Ponziani *et al*[94] review. However, the authors state that despite existing limitations, research on the impact of the gut microbiota on liver diseases has diagnostic, preventive and therapeutic potential, especially in patients with early stage HCC[94].

The therapeutic potential of the microbiota is currently intensively studied. In multiple clinical trials, fecal microbiota transplantation is applied with the expectation of reducing the progression of various etiology liver diseases, including NAFLD of different stages and NASH-induced HCC. Unfortunately, the published results are not promising so far[95]. More clinical trials are needed to better understand the efficacy of intestinal microbiota transplantation in NASH liver and HCC. Prebiotic and probiotic therapy appears to be more promising for the prevention and/or treatment of HCC, although it is necessary to determine its long-lasting effect[96,97].

The other members of the gut microbiome community, including fungi, viruses, and bacteriophages, are also worthy of consideration by researchers as possible participants in the pathogenesis of liver diseases, including NASH and HCC. They can also potentially contribute to the relief of liver disease. For example, Duan *et al*[98] presented experimental research on the beneficial effect on reducing liver disease of bacteriophages targeting *Enterococcus faecalis* that produces toxin cytolysin. Due to more affordable and powerful sequencing technologies, in addition to bacterial components, enteric fungal and viral species will certainly become objects of future research not only in connection with NASH-induced HCC, but also in elucidating the pathophysiological mechanisms of liver diseases of other etiologies[32]. Furthermore, a healthy lifestyle is an affordable approach that can be an effective measure in modulating the microbiota to a healthier shape, reducing obesity, and prophylaxis of NASH and NASH-induced HCC[2,99].

CONCLUSION

Current research claims that in the long run, steatohepatitis and the gut microbiota establish mutually maintaining pathological circuit that trigger liver inflammation. This can result in the manifestation of HCC and the growth of malignant nodules, even in the absence of obvious cirrhosis. However, a definite picture of that circuit treads remains blurred.

FOOTNOTES

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