Gut-Hepatic Relationship: From Disorders of the Gut Microbiota to Hepatocellular Carcinoma

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Abstract

Enterohepatic relationships reflect the integrity of homeostasis regulation in the human body. Anatomical and physiological connection through the portal vein of the intestine and liver ensures the transport of products derived from the intestine directly to the liver and through the liver ensures the connection of bile and the secretion of antibodies into the intestine. However, impairment of intestinal barrier integrity, endotoxemia, increase of lipopolysaccharides in hepatocytes, Kupffer and stellate cells with increasing content of pro-inflammatory cytokines and active oxygen forms creates inflammatory environment with sensitization of liver cells to injury and profibrotic processes. The goals of experimental and clinical research in this course are multifaceted, ranging from regulating human metabolism, immune and inflammatory reactions to preventing carcinogenesis, inhibition of liver cancer progression and improving the efficiency of liver cancer treatment. Here we will discuss epidemiological issues of hepatocellular carcinoma, the role of intestinal microbiota when enterohepatic relationships are impaired, and the intestinal-associated mechanisms of carcinogenesis in this form of liver cancer.

Keywords: Gut microbiota, Enterohepatic relationships, Hepatocellular carcinoma, Risk factors, Dysbiosis, Lipopolysaccharides, Pro-inflammatory cytokines, Bile acids, Short-chain bile acids, Choline deficiency, Ethanol, Acetaldehyde

Introduction

One of the leading causes of death worldwide is hepatocellular carcinoma. Research in recent years shows the important role of enterohepatic relationships in the pathophysiological mechanism responsible for the development and progression of HCC. The intestinal microflora is a positive factor of human homeostasis and immune reactions due to precise control and immunosensory ability to distinguish between commensal and pathogenic bacteria. Reciprocal enterohepatic relationships are established by means of a portal vein, which provides transport of products derived from the intestine directly to the liver and through the liver provides bile feedback and antibody secretion into the intestine. Liver products primarily affect the composition of the gut microbiome and the integrity of the intestinal barrier, while intestinal factors regulate the synthesis of bile acids, the metabolism of glucose and lipids in the liver.

Pro-inflammatory changes in the liver and intestines will mediate the formation of fibrosis, cirrhosis and, eventually, HCC. The exact contribution of microbiome to liver disease may vary depending on the etiology. Gut-associated mechanisms of carcinogenesis in HCC develop due to damage of the intestinal barrier integrity in the deficit of bile acids, short-chain bile acids and choline. Later, with the excess growth of microbes in the intestine, endotoxemia is progressed, inflammatory environment is formed with an increase in the content of lipopolysaccharides associated
with specific TLR4-receptors of hepatocytes, Kupffer and stellate cells, with subsequent release of pro-inflammatory cytokines and active oxygen forms. Ethanol also plays an essential role in the progression of HCC, its metabolism product – acetaldehyde, as well as increase of intestinal bacterial metabolite, deoxycholic acid. Research focused on understanding the functioning of the enterohepatic axis is aimed at improving the treatment of liver diseases, including hepatocellular carcinoma. The data from experimental studies on animals allow to find out the etiological mechanisms of HCC progression, however, well planned, large-scale clinical trials covering etiology of various liver diseases, as well as ethnicity of patients are required in clinical practice for effective interpretation and application of the results obtained in the experiment.

Hepatocellular Carcinoma: Epidemiology Issues

Hepatocellular carcinoma (HCC) is the most common primary carcinoma of the liver. Liver cancer is the sixth most frequently diagnosed and the fourth in the mortality rate due to cancer in the world after lung cancer, colorectal cancer, and stomach cancer [1]. HCC is one of many types of tumors that occur against the background of chronic inflammation. HCC, which accounts for 90% of all primary liver cancers [2,3].

According to Singal AG and co-authors (2020), the prevalence of HCC is not homogenous around the world due to different prevalence of major risk factors. It is estimated that 72% of progression cases occur in Asia (over 50% in China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% in Latin America and 0.5% in Oceania [1]. Singal AG et al. (2020), highlighting new trends in the epidemiology and epidemiological surveillance of HCC, note that the highest estimated age standardized incidence rate (ASIR) for liver cancer in the world in 2018 per 100,000 people is found in East Asia (17.7), with the highest ASIR in the region and the world recorded in Mongolia (93.4), followed by Southeast Asia (13.3) and Africa (8.4), with Egypt (32.2) and Gambia (23.9) having the highest ASIR in Africa. The lowest ASIR was observed in South and Central Asia (2.5), followed by Central and Eastern Europe and Western Asia (approximately 4.0) [1]. Moreover, age standardized mortality rates (ASMR) due to HCC in 2018 are also the highest in East Asia (16.0) and North Africa (13.9), followed by Southeast Asia (13.2). The lowest ASMR is observed in South and Central Asia (2.3), followed by Central, Northern and Eastern Europe and Western Asia (about 3.8-4.0). Mongolia and Egypt have the highest ASMRs, and the lowest ASMRs are in Morocco and Nepal, the countries with low ASIR [1]. Liver cancer is a tumor with high mortality, with most cases being detected at late stages and the morbidity-to-mortality ratio approaching 1. It is important to note that HCC is the result of many etiological factors, such as viral infections of hepatitis B and C, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), autoimmune hepatitis and several genetic disorders. Hepatitis B virus (HBV) is the main cause of liver cancer and mortality in the world (33%), followed by alcohol (30%), hepatitis C virus (HCV) (21%) and other causes (16%) [1]. The main risk factors for HCC, including infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), lead to the formation and progression of liver cirrhosis (LC), which is observed in 80-90% of patients with HCC. The five-year cumulative risk of HCC progression in patients with liver cancer varies from 5 to 30% [2]. With the introduction of vaccination programs against hepatitis B and treatment of hepatitis C worldwide, the epidemiology of HCC shifts from a disease in which viral hepatitis prevails to the hepatic component of metabolic syndrome – NAFLD [3], where about 10-30% of cases of NAFLD progress to liver cancer. More than 65 million Americans are affected by NAFLD, which costs 103 billion dollars a year in the United States itself [1]. There are data on the influence of lipid reduction strategy, including ezetimibe, and its combination with other hypolipidemic agents on atherogenic dyslipidemia, glycemic profile, and morphological changes in liver steatosis [5].

The progression of HCC in NASH occurs in the absence of LC [6] in more than 25%, which is significantly higher than the frequency observed in other liver diseases [7]. HCC has a strong prevalence of men in morbidity and mortality, with a ratio of men to women exceeding 2.5 for both epidemiological indicators [8]. It is believed that this differential distribution by gender is due to the clustering of risk factors among men, as well as the potential impact of androgens on the risk of HCC. There are also essential environmental risk factors for HCC. For example, in some parts of Africa and Asia, an important factor for the progression of HCC is the consumption of Aflatoxin B1 with food, which occurs due to fungal contamination of staple foods. The impact of Aflatoxin B1 is closely related to the mutations of TR53 (codon 249) and the progression of HCC in people infected with HBV [9]. Several epidemiological studies have identified an increased risk of HCC progression among smokers, with meta-analysis reporting an adjusted OR 1.5 (95% of CI 1.37-1.67) compared to non-smokers [10]. Study of HCC prevention in the general population and in patients with chronic liver disease, coffee consumption, aspirin intake and metformin treatment consistently reduce the incidence of HCC in diabetics [11-13].

Gut Microbiota and Its Role When Enterohepatic Relationships are Impaired

The intestines and liver interact through close bi-directional connections through the bile paths, portal vein and systemic circulation. The liver binds to the intestine, releasing bile acids and many biologically active mediators in the biliary tract and the systemic circulation. In the intestine, the host and microbes metabolize endogenous (bile acids, amino acids), as well as exogenous substrates (against diet and environmental influences),
which products are transported to the liver through the portal vein and affect liver function [14,15]. An important factor in liver injury is disturbance of the gut microbiota (GM) system. The human gastrointestinal tract (GI tract) colonizes a large number of microbial microflora, forms a system of metabolism of the microbiota with the macroorganism, participating in various metabolic processes of the body, and plays an essential role in the human immune response. More than 2,000 different types of bacteria live in the intestines, and their number exceeds 100 trillion microorganisms, which is 10 times more than the total number of human cells [16]. Gut microbiome, which refers to the collective genomes of all microorganisms that make up the gut microflora, contains 150 times more genes than the human genome [17]. The number of different microorganisms is gradually increased during the intestine. This can be explained by the presence of a more aggressive environment in the upper parts of the intestine due to the incoming acidic content of the stomach, the action of digestive enzymes, rapid progression of chyme. The density of microbes increases from proximal to distal end of the intestine and includes a biomass of 1.5-2.0 kg, which is dominated by strictly anaerobic bacteria [18]. Aerobia predominating in the small intestine, as they progress down the GI tract, are replaced by facultative and then strict anaerobes. These microorganisms are collectively referred to as gut microbiota (IM), which consists of commensals, beneficial bacteria, and opportunistic pathogenic bacteria and pathogenic bacteria in a complex and dense microenvironment [19,20].

The GI tract, which functions as an effective barrier against endotoxin and intestinal bacteria, can protect the body [21]. In addition, the liver also plays an essential physiological role in detoxification of lipopolysaccharides (LPS) and hepatocytes participate in intestinal endotoxin clearance [22]. The process of endotoxin degradation can be disrupted if the liver is damaged, and the increase in endotoxin, in turn, exacerbates the damage to the liver. GM is involved in the metabolism of bile acids (BA), the synthesis of vitamins, the assimilation of complex polysaccharides and the production of short-chain BA (SCBA) [23]. SCBAs are a vital energy source for enterocytes, which are an integral part of maintaining intestinal barrier integrity. In addition, GM is also involved in the development of local and congenital immunity, providing protection not only against pathogenic invasion but also against systemic infection [24]. Thus, the gut microbiome is now considered an organ system that is central to maintaining metabolic and immunological homeostasis. It is involved in the production of compounds necessary for life, for the metabolism of many compounds that enter the body, and on the one hand, stimulates innate and adaptive immunity, and on the other hand, softens the immune response. Changes in the composition of bacteria (and other microbes) in the intestines in a state known as dysbacteriosis are associated with a growing and significant number of diseases characterized by chronic inflammation affecting various organ systems, including the liver [24-29].

3.3. Gut-Associated Carcinogenesis Mechanisms in Hepatocellular Carcinoma

On the experimental model of dysbiosis the link between intestinal colonization of H. hepaticus and development of HCC was proposed [30-32]. Huang Y et al. reported the presence of Helicobacter ssp DNA in liver biopsies from patients with HCC while being virtually absent from control samples [32]. Of note, the representatives of this kind are known to promote tumor development by activating the transmission of intracellular NF-κB and WNT signals that regulate cell differentiation and the development of malignant tumors, as well as suppressing antitumor immunity, which may play a potential role in the development of HCC [30,33]. On the other hand, Rocha et al. (2005) confirmed an association between the presence of Helicobacter ssp DNA and liver cirrhosis, but not a correlation between the presence of Helicobacter ssp DNA and HCC [34]. However, there is evidence of a correlation between the presence of helicobacter DNA in patients’ stool and development of HCC in patients with viral hepatitis [35]. Elevated intestinal level of Clostridium microbial species has been found in experimental models of HCC induced by obesity in mice [36,37], but clinical studies involving patients with HCC found excessive Escherichia coli growth [38]. Patients with liver cirrhosis and liver cancer frequently develop an intestinal dysbiosis which is also found in mice after DEN-administration, which show an increase growth rate of the E. coli and Atopobium cluster – gram-positive anaerobic microorganisms belonging to the Coriobacteriaceae family, which are associated with the development of bacterial vaginosis and inflammatory diseases of the small pelvis, while the percentages of benign bacteria (Lactobacillus group, Bifidobacterium group, and Enterococcus group) are significantly decreased [39].

Etiological factors of non-viral HCC lead to steatosis of the liver accompanied by oxidative stress, endoplasmic reticulum stress, intestinal dysbiosis and inflammation, which contributes to the final manifestation of cancer [40]. Yu LX et al. (2010) demonstrated that experimental depletion of host microflora suppresses tumor formation in a toxic model of hepatocarcinogenesis. Treatment of rats with polymyxin B and neomycin, which are bactericidal for most enteric gram-negative organisms, after DEN administration injection significantly reduced the number and size of HCC nodules [41]. These data were corroborated by findings of Dapito DH and colleagues demonstrating that gut sterilization protects from development of liver cancer when mice were subjected to a combination of diethyliltriamine (DEN) and hepatotoxin carbon tetrachloride (CC4), a model that features several characteristics of the cirrhotic environment of chronically injured livers in which HCC mostly arises, namely chronic injury, inflammation, fibrogenesis, and increased of endotoxin levels [42].
The antibiotic treatment led to a reduction of tumor number and size compared with mice that did not receive antibiotics. Moreover, mice that were grown in specific germ-free conditions demonstrated fewer and smaller tumors in this model compared with mice that were grown under non-germ free (SPF) conditions [42]. Human HCC is often associated with chronic inflammation of the liver and liver cirrhosis, pathophysiological processes that are the result of chronic viral infection, metabolic disorders or exposure to chemical toxins that can develop against the background of inflammatory environment in patients with advanced liver disease. Experimental data from rodent models as well as robust clinical data suggest a role of inflammation in the pathophysiology of HCC development. The liver is constantly exposed to microbial products from the enteric microflora, such as endotoxin, which activates proinflammatory signaling pathways and might contribute to the development of liver cancer as it has been previously demonstrated for liver cirrhosis [43]. Zhang HL et al. (2012) demonstrated that already the induction of such a dysbiosis is sufficient to promote hepatocarcinogenesis by enhanced portal lipopolysaccharide (LPS) levels [39]. Interestingly, in the above-mentioned study of Dapito DH and colleagues, chronic treatment of mice with a low, nontoxic dose of LPS during DEN/CCl4-induced hepatocarcinogenesis led to a significant increase in tumor number; tumor size in liver compared with control animals, thus further arguing for a direct influence of gut microbiota on hepatocarcinogenesis [42].

LPS connects to toll-like receptors type 4 (TLR4), which are present on hepatocytes, Kupffer and stellate cells, causing the release of pro-inflammatory cytokines and activation of proliferative and anti-apoptotic signals. LPS level in plasma is associated with excess intestinal bacteria growth, changes in microbiota composition and increased intestinal permeability [44]. The critical role in the maintenance and progression of the inflammatory component in the pathogenesis of hepatic injury is played by the translocation of endotoxins obtained from GM into the circulatory system with an increase in TLR4 expression, which leads to the activation of pro-inflammatory cytokines (tumor necrosis factor-alpha (TNF-a) and interleukin (IL)-6 [45], thus causing systemic inflammation. Inflammasomes, as a multi-protein oligomeric complex containing leucine and nucleotide binding domains, are responsible for the activation of the inflammatory response, controlling the splitting of pro-inflammatory cytokines. It was shown that dysbiosis leads to increased TNF-a expression [46]. The increased activation and production of TLR4 and pro-inflammatory cytokines in dysbiosis may also lead to the recruitment and activation of hepatic immune cells, and the pro-inflammatory transmission of TLR4 signals is involved in sensitizing cells to the profibrotic signaling pathways and thus leads to liver fibrosis [43] contributing to the progression of liver disease [46]. Kupffer cells (KC), as hepatic immunological cells, are critical components of the innate immune system located in the sinusoidal vascular space [47].

KC can be activated by a variety of endogenous and exogenous stimuli, including endotoxins in the impairment of GM [47]. KC activation triggers the production of inflammatory cytokines such as TNF-α as well as active oxygen forms [47], which may also lead to tissue damage, in duding liver damage. Bile acids (BAs) play a crucial role in the development and progression of liver diseases, including HCC. BAs are metabolites of cholesterol (CS) and perform several essential functions: emulsification of fats, elimination of cholesterol out of the body, detergent properties, impact on intestinal motility, etc. Bile acids synthesized from cholesterol in the liver are necessary for metabolism of cholesterol and digestion of lipids [48]. Bile acids are deposited in the gallbladder and excreted into the duodenum during digestion [49]. More than 95% of bile acids are reabsorbed in the terminal iliac and transported back to the liver through the portal vein. Bile acids contribute to the absorption of dietary fats, cholesterol, and fat-soluble vitamins [49]. In addition, bile acids also function as signal molecules that affect physiological processes [49], which include regulation of glucose and lipid metabolism through activation of the farnesoid X-receptor (FXR) and binding to the G-protein of the bile acid receptor [50-52]. Bile acids may also affect the gut microbiota, as they are directly related to the integrity of the intestinal mucosa and the synthesis of antibacterial peptides [53]. When bile acids bind to FXR, antimicrobial peptides such as angiogenin 1 are produced. These peptides can inhibit excess gut microbiota growth by increasing the potential of intestinal epithelial cells to prevent bacterial uptake, improving intestinal barrier function [53]. Gut microbiota in turn may affect the size and composition of the bile acid complex by converting primary bile acids to secondary ones [54,55]. This may subsequently change the metabolism of lipids and glucose, especially in NAPLD-predisposed people [54,55]. Another mechanism through which gut microbiota can contribute to liver disease is the production of short-chain fatty acids (SCFAs).

Gut microbiota splits non-digestible carbohydrates, releasing SCFAs in the human intestine [56]. The main SCFAs are acetate, propionate, and butyrate, which are metabolized by muscles, liver, and epithelium as such [56]. Studies on the role of SCFAs mainly focus on butyrate, the main energy source for colonocytes, which improves the barrier function of the large intestine [56] and therefore has a positive effect on intestinal permeability. Butyrate has been shown to improve intestinal barrier by induction of dense compound proteins and mucin mucin type 2 [57-59] and enhanced expression of daudin-1 [60]. Butyrate can induce apoptosis in the liver and inhibit cell proliferation in hepatocytes, suppressing the expression of type I airtuin, while increasing the expression of miR-22, as a tumor suppressor [61]. In other words, butyrate can inhibit liver cancer cells. It has also been shown that butyrate increases the feeling of satiety, reduces food intake, and delays gastric emptying.
by activating free fatty acid receptors type 2 and 3 [62]. Normal body weight and glucose homeostasis were more often found in mice with a deficit of free fatty acid receptors of type 2 and 3. Stimulation of intestinal hormones and inhibition of food ingestion by butyrate and propionate may represent a new mechanism by which gut microbiota regulates host metabolism. Finally, butyrate can also affect inflammation. Studies have shown that butyrate in the intestinal tract binds and activates the gamma receptor activated by the proliferator peroxisome (PPAR-y), which counteracts the transduction of nuclear factor-kappa B (NF-kB), thus causing an anti-inflammatory effect [63]. Therefore, the presence or excess of gut microbiota-produced butyrate can affect the pathogenesis of liver diseases through several mechanisms [63].

Choline deficiency also plays the most important role in liver injury with gut microbiota imbalance. Choline is an essential nutrient and phospholipid component of the cell membrane [64]. There are several mechanisms through which choline deficiency can affect the liver, including [64] the reduction of very low-density lipoprotein formation (VLDL), dysfunction, mitochondrion, and endoplasmic reticulum stress [64,65]. Phosphatidylcholine, which is a phospholipid, is a key component of the VLDL shell. Choline deficiency caused by a diet or gut microbiota metabolism disorder leads to a decrease formation of VLDL and the export of triglycerides from the liver, resulting in fatty hepatosis. Choline deficiency reduces the concentration of phosphatidyl ethanolamine and phosphatidylcholine in mitochondrial membrane, leads to a decrease in membrane potential, which in turn causes oxidative damage [64] of cell membrane. Gut microbiota can help reduce the bioavailability of choline [66] contained in eggs, milk, and red meat. This in turn increases the conversion of choline into trimethylamine (TMA) [67], which is absorbed into the blood, increasing the risk of cardiovascular disease [67]. TMA reaching the liver is further metabolized by flavin-containing monooxygenases of types 1 and 3 to form trimethylamine-N-oxide (TMAO) [67-69]. This can lead to an increase in the accumulation of hepatic triglycerides, as TMAO inhibits key enzymes and limits the enterohepatic circulation of bile acids [70-72]. In such a way the formation of choline deficiency either through diet or through conversion of choline into TMA in case of GM metabolism disorder may lead to liver injury through accumulation of fat in it. The next factor impairing the enterohepatic relationship is alcohol abuse. Studies in the United States and Italy have shown that alcohol is the main cause of HCC (ranging from 32% to 45% of HCC). The EPIC (The European Prospective Investigation into Cancer and Nutrition) multi-centre cohort study from 1992 to 2000 selected about 520,000 randomly selected men and women aged 35-70 from 10 European countries [73].

Among men and women, 33% (11%-54%) and 18% (3%-38%) of the total number of HCC was due to past and present alcohol consumption [74]. The causal link between alcohol consumption and HCC development may be due to direct (hepotoxic) and indirect factors (cirrhosis development) [75]. Case-control studies from different countries report that chronic ethanol consumption is associated with approximately double increase in the odd ratio of HCC development. Obesity and alcohol synergistically contribute to the progression of ALD and development of HCC, although data in this regard are still contradictory [76-80]. Alcohol consumption causes significant changes in the quality and quantity of GM, changes in the mucous membrane, and increased intestinal permeability, which leads to endotoxia [81] due to lipoteichoic acid, flagellin, bacterial hypomethylated DNA, and other intestinal toxins. Intestinal hyperpermeability due to alcohol abuse leads to a higher concentration of LPS in the portal bloodstream, which binds to TLR4, releases pro-inflammatory cytokines, produces active oxygen forms, and activates oxidative stress. In addition, regardless of alcohol consumption, ethanol is produced endogenously in small amounts under normal intermediate metabolism and in the gastrointestinal tract through the formation of microbes. The concentrations caused by this process in human venous blood are approximately 0-50 µm [82]. Dense compounds of the intestinal epithelium are impaired by acetaldehyde by increasing intestinal permeability to endotoxins. All these events can cause the activation of macrophages, Kupffer and stellate cells of the liver, supporting inflammation and fibrosis in the liver [83,84].

Impairment of the intestinal barrier may also cause the bacteria to move into the mesenteric lymph nodes, which further confirms systemic inflammation [85]. Formation of a strong inflammatory environment caused by direct exposure of alcohol to nonparenchymatous cells of the liver or indirectly fed by intestinal hyperpermeability is a condition that enhances the process of liver injury and regeneration and certainly favors the formation and reproduction of liver tumor foci [86]. The main causes of alcohol-related oncogenesis are not yet fully understood though, various factors have been suggested that play a part: localized effects of alcohol, induction of cytochrome P4502E1 (CYP2E1) (conversion of various xenobiotics), acetaldehyde (isoenzyme polymorphism), malnutrition, interaction with retinoids, changes in methylation levels, immunological surveillance, and angiogenesis [87-89]. It was shown that the concentration of CYP2E1 in the liver may be associated with the formation of hydroxethyl radical and, consequently, with lipid peroxidation. Lipid peroxidation triggers the production of 4-hydroxynonenal, which can bind to the purine and pyrimidine bases of DNA, thus forming carcinogenic exocyclic etheno-DNA adducts. It has been shown that there is a significant relationship between the induction of CYP2E1 and the appearance of exocyclic etheno-DNA-adducts in hepatocytes [88,90]. As such, the abuse of ethanol causes qualitative and quantitative changes in the taxonomic composition of the intestinal flora, inflammation
of the mucous membrane and impairment of the intestinal barrier, with subsequent translocation of viable pathogenic bacteria, gram-negative microbial products and pro-inflammatory luminal metabolites into the bloodstream, which additionally confirms alcohol-induced liver injury.

Obesity and high fat diet have been identified as major risk factors for HCC [91,92]. In a prospective study of more than 900,000 adult American patients (404,576 males and 49,547 females) it was found that overweight and obesity have been accompanied by a significant increase in esophagus cancer, colorectal cancer, liver cancer, gall bladder cancer, pancreatic and kidney cancer mortality rates. For liver carcinoma, the odds ratio was 4.52 for men and 1.68 for women [93]. Yoshimoto S and colleagues demonstrated that administration of antibiotics and gut sterilization lead to a significant decrease in HCC development in an obesity related model of hepatocarcinogenesis in mice [36]. The authors demonstrated that obesity induced alterations of gut microbiota lead to elevated levels of deoxycholic acid (DCA), a gut bacterial metabolite, which induces the secretion of various inflammatory and procarcinogenic factors in the liver and thus facilitated HCC development. In this model eradication or modulation of the gut microflora blocked the DCA-inflammation-HCC axis, thus preventing obesity related liver tumors [36].

Conclusion

Thus, the data of the literature review indicate that disorders of enterohepatic relationships due to changes in gut microbiota with excess bacterial growth, intestinal barrier hyperpermeability increases the content of LPS, which when combined with TLR4-receptors on hepatocytes, Kupffer and stellate cells, cause the activation of pro-inflammatory cytokines, production of activated forms of oxygen, form a pro-inflammatory microenvironment of the liver that promotes the development of HCC. In the light of a lack of pharmacopreventive strategies and limited chemotherapeutic options for treatment of liver cancer, the therapeutic modulation study of the gut microbiota, Probiotics 

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