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Review Article

Gut Microbiota Alterations in Liver Diseases

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Abstract

Liver disease is the fifth most common cause of death and poses a global health burden worldwide. The anatomical and functional relationship between the gut and the liver suggests an important role of the gut microbiota in liver disease. In the last decades, the association of the composition and function of gut microbiota with liver disease pathogenesis has attracted a great interest. The gut is colonized by trillions of microbes that assist digestion and modulate immune responses. The generation of a variety of products from those metabolic processes and from host-bacteria interactions can have profound effects on the liver. Qualitative changes such as increased proportions of harmful bacteria and reduced levels of beneficial bacteria have been associated with a number of liver diseases. This review aims to describe the main findings on the role of gut microbiota in the pathogenesis of NAFLD, NASH, alcoholic liver disease, cirrhosis, hepatic encephalopathy and hepatocellular carcinoma. Although, manipulation of the microbiota through the use of probiotics, prebiotics and fecal microbiota transfer is an attractive new approach to manage liver disease, clinical and experimental studies are lacking. Comprehension of the link between the pathophysiology of liver diseases and microbiota modifications will help in the development of innovative and effective therapies.

Keywords: *Gut Microbiota; Liver Disease; NAFLD; Cirrhosis; Alcoholic Liver Disease; Hepatic Encephalopathy; Hepatocellular Carcinoma*

Abbreviations

ALD: Alcoholic Liver Disease; HCC: Hepatocellular Carcinoma; CDR: Cirrhosis to Dysbiosis Ratio; CLA: c9, t11 Conjugated Linoleic Acid; HE: Hepatic Encephalopathy; LPL: Lipoprotein Lipase; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis

Introduction

Today almost 35 million people in the world die of liver diseases and the rates are steadily increasing over the years [1]. A growing number of studies associate gut microbiota with various human diseases including metabolic, gastroenterological and liver diseases. The anatomical and functional connection between the gut and the liver suggests that the liver is a target for gut microbes. Gut derived-toxins and microbial products continually enter the liver from the portal vein, which supplies about 70% of the liver's blood [2]. It is therefore not a surprise that the liver is greatly affected by the composition and function of gut microbes.

The gastrointestinal microbiota is a complex and dynamic community of trillions bacteria with diverse taxonomy, but it also consists archea, protozoa, and viruses. In physiologic conditions the intestinal microbiota has a symbiotic relationship with its human host providing metabolic, trophic and immunological functions. A balanced interaction between bacteria, epithelium and gut immune system is necessary for the proper function of a healthy gut, which is to absorb nutrients and to prevent the access of pathogens into the portal circulation and the liver. Human enzymes are not capable to digest complex carbohydrates and plant polysaccharides so gut microbiota ferment them in the colon to yield energy for microbial growth and end products such as short chain fatty acids. In this way the microbiota maximizes the energy efficiency from ingested food and influences both normal physiology and disease development.

Following birth, the human gut microbiota is characterized by low diversity and the dominance of *Proteobacteria* and *Actinobacteria*, followed by the emergence of *Firmicutes* and *Bacteroidetes* dominance in adulthood [3]. Then it is thought to remain relatively stable until the old age when *Bacteroidetes* predominate [2,4]. Gut microbiota homeostasis is tightly regulated by environmental and genetic factors as well as by the mucosal immune system. Immune tolerance to microbiota is shaped during the neonatal period when the immune system is too immature to attack intestinal microbes that regulate the host immune system. In the intestine, the mucosal immune system guarantees a beneficial microbiota composition by restricting the growth of pathogens, controlling bacterial overgrowth, and reacting to pathogens and bacteria that reach the intestinal barrier.

Composition of healthy microbiota can be compromised resulting in dysbiosis, gut barrier dysfunction, and liver disease. Under normal conditions when a small amount of bacteria reaches the liver most of them are eradicated by Kupffer cells. If there is intestinal inflammation or portal hypertension the gut-mucosal barrier is compromised allowing large amounts of bacteria to enter the liver inducing the activation of Kupffer and hepatic stellate cells. This leads, in turn, to the production of pro-inflammatory cytokines and liver damage.

Today evidence from a growing number of research groups implicates gut microbiota in the pathophysiology of liver diseases, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), cirrhosis, hepatic encephalopathy (HE) and hepatocellular carcinoma (HCC). Considering the composition of the gut microbiota and the complexity of its interactions with the immune system it is challenging to understand how disruption of microbial and intestinal homeostasis contributes to disease. This review aims to describe the main findings on gut microbiota in the development of liver diseases. Understanding the link between the pathophysiology of liver diseases and compositional and functional changes of the microbiota will help to develop innovative therapies.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a very common cause of liver disease ranging from hepatic steatosis with excessive hepatic fat deposition to NASH with steatosis and hepatic inflammation. NAFLD is the hepatic version of a metabolic disease and is associated with obesity and insulin resistance [5]. As gut microbiota is a key regulator of energy storage it is expected to have a profound influence on fat deposition. Indeed several mechanisms have associated microbiota to the NAFLD and NASH pathogenesis. Reduced *Bacteroidetes* and increased *Prevotella* and *Porphyromonas* levels have been observed in NAFLD patients [5].

The microbiota has been shown to stimulate hepatic triglyceride production by suppressing lipoprotein lipase (LPL) inhibitor, fasting-induced adipose factor [6]. This in turn can result in the continued expression of LPL, which is a key regulator of fatty acid release from triglycerides in the liver and an active player on NAFLD development [6]. Furthermore, microbiota also regulates the systemic lipid metabolism by altering bile acid metabolic patterns. In this way it affects directly the emulsification properties of bile acids and indirectly the storage of fatty acids in the liver. Small intestinal bacterial overgrowth correlates with chronic liver disease severity and has been shown to predict severe hepatic steatosis [7]. Bacterial overgrowth can increase intestinal permeability, by disrupting intercellular tight junctions, and thereby increasing intestinal permeability as well as bacterial and endotoxin translocation, resulting in hepatic fat deposition. The role of microbiota in choline metabolism, as well as in activation of pro-inflammatory cytokines (e.g. TNF-α), is also relevant to the development of NAFLD and progression to NASH. Indeed, a correlation between choline bioavailability and hepatic steatosis has been demonstrated, through the metabolic activity of gut microbiota, which is affected by the diet [5]. Predisposition to NAFLD associates with the expression of Toll-Like receptors 4 or 9, or TNF-α that can be produced from activated Kupffer cells [8]. Endogenous production of ethanol from the microbiota also mediates hepatic fat accumulation and is involved in the progression from NAFLD to NASH [9]. Animal studies have shown that that defective inflammasome sensing and related dysbiosis result in an abnormal accumulation of bacterial products in the portal circulation and promote progression of NAFLD/NASH [9].

Probiotics are living beneficiary bacteria in the intestinal tract and are thought to have a therapeutic effect with no adverse effects. VSL#3 is the most-studied probiotic, and consists of a mixture of eight probiotic strains (*Streptococcus thermophilus, Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei* and *L. bulgaricus*) [10]. Administration of VSL#3 in NAFLD animal models had similar effects to anti-TNF-α antibody on inflammation and liver injury possibly through an NKT-dependent mechanism [11]. Xu., *et al*. concluded that *B. Longum* was more effective than *Lactobacillus acidophilus* in NAFLD and that these beneficial effects correlated to gut microbiota alterations [12]. Moreover, it was demonstrated that modulating enteric microbiota by linoleic acid and *Bifidobacterium* preparations resulted in an increase in of c9, t11 conjugated linoleic acid (CLA) and altered the liver fatty acid composition [13]. Notably, CLA is a microbial metabolite that positively correlates with NAFLD's improvement and the VSL#3 probiotic cocktail has been shown to induce its production *in vitro* [13]. Probiotics have been shown to reduce the impact of a variety of forms of acute liver injury [14], as well as the severity of more chronic forms of liver disease, such as that related to total parenteral nutrition TPN [15]. Prebiotic preparations have also been shown to ameliorate liver inflammation in obese mice through a glucagon-like peptide-2 (GLP-2)-dependent effect on the gut barrier [16] and hold promise for the management of NAFLD and related disorders. Two pilot non-randomized studies showed that probiotics can be well tolerated, improve conventional liver function tests and decrease markers of lipid peroxidation in NAFLD/NASH, reduced transaminases [17,18].

Alcoholic Liver Disease (ALD)

Chronic alcohol consumption is a leading cause of liver disease worldwide. ALD ranges from hepatic steatosis to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC). A number of studies have been shown the involvement the active participation of the microbiota in alcohol-related liver injury [19]. Decreased *Bacteroidaceae* and increased *Prevotellaceae* levels have been reported in the gut microbiota of alcoholic individuals [20]. A study by Tuomisto and his group examined the feces and ascites from patients with alcoholic cirrhosis and found that they contained higher levels of *Enterobacteriaceae* DNA compared to those of healthy individuals [21]. Alcohol promotes the growth of Gram-negative bacteria in the gut, which metabolize alcohol to acetaldehyde. As a consequence tight junctions are disrupted and gut permeability is compromised leading to the increased entry of LPS, endotoxins and bacterial DNA into the liver [19,21]. Activation of Kupffer cells through TLR4 or TLR9 follows resulting to pro-inflammatory cytokine production and liver damage [22].

Many clinical trials and animal studies suggest that manipulating the gut microbiota through the use of probiotics, prebiotics or fecal microbiota transfer (FMT) may be an effective treatment for ALD. Treatment with *Lactobacillus rhamnosus* GG preparations has been shown to reduce liver inflammation, intestinal permeability and endotoxemia [23-25]. Administration of *Lactobacillus casei Shirota* probiotics has been shown to restore neutrophil phagocytic function by lowering endogenous levels of TLR4 and IL-10 in human alcoholic cirrhosis [26]. In an animal model, treatment with *Lactobacillus plantarum* reduced the levels of endotoxemia, AST and NF-κB, cytokines and improved liver and intestine histology [27]. Short-term treatment with *Bifidobacteria* and *Lactobacilli* in alcoholic patients appeared to increase their levels in the gut and reducing AST and ALT levels [28]. VSL#3 also improved liver lesions in ALD in humans and rodents [29]. Furthermore, *A. muciniphila* treatment also improved hepatic injury and neutrophil infiltration in already established ALD [30]. The use the prebiotic pectin has been shown to prevent completely liver injury in rodent models by restoring the levels of *Bacteroides*, and appears to be a promising therapeutic agent because it is a food product that can be safely used in humans [31]. FMT is the introduction of a fecal suspension derived from a healthy donor into the intestinal tract of a diseased individual. Altering microbiota composition in alcohol-sensitive mice by FMT also prevented alcohol-induced liver lesions [31]. Currently there is an-ongoing phase III trial taking place in India.

Liver cirrhosis

Liver cirrhosis is the end stage of different types of hepatic injury. Patients with liver cirrhosis have deranged hepatic structures, decreased bile acid secretions and portal hypertension that affect gut microbiota by increasing intestinal permeability and bacteria translocation. The gut microbiota in cirrhosis is characterized by an increase of potentially pathogenic bacteria, accompanied by reduced proportions of beneficial bacteria. More specifically, gut microbiota has been shown to have an overgrowth of the potentially pathogenic *Enterobacteriaceae*, *Veillonellaceae* and *Streptococcaceae* and reduced levels of beneficiary *Bifidobacteria*, *Bacteroidetes*, *Firmicutes*, *Lachnospiraceae* [32,33]. Fecal microbial communities are similar among patients with cirrhosis of different etiologies. Interestingly, the

severity of cirrhosis was positively correlated with the increased levels of Enterobacteriaceae and Streptococcaceae and negatively correlated with Lachnospiraceae levels [25,33]. Furthermore, alcoholic cirrhotics individuals had higher levels of *Enterobacteriaceae* and endotoxemia compared to non-alcoholic cirrhotic patients [25]. The ratio of cirrhosis to dysbiosis (CDR), which is the ratio between autochthonous and non-autochthonous taxa, negatively correlated with endotoxemia and was increased in healthy controls, lower in compensated cirrhotic patients and lowest in decompensated cirrhotic patients [25].

In addition another study analysed the microbiota of cirrhotic patients by quantitative metagenomics and showed reduced *Bacteroidetes* and *Firmicutes* levels and increased *Streptococcus* spp. and *Veillonella* spp. levels. Since both *Streptococcus* spp. and *Veillonella* spp. are bacteria of oral origin this suggests that an invasion of the oral microbiota in the gut may contribute to cirrhosis progression [34]. It was reported that gut microbiota plays a role in the progression of chronic hepatitis B to severe liver failure, including inflammation and pathogenic metabolic accumulation [35]. The importance of gut microbiota in cirrhosis has been also confirmed by a recent study that showed a significant improvement of cirrhotic patients gut microbiota diversity and symbiosis after liver transplantation [36]. Bajaj., *et al*. has recently shown that higher microbial diversity succeeded by diet associated with a lower risk for cirrhosis [37].

Hepatic Encephalopathy

HE is a potentially reversible neuropsychiatric complication in patients with acute or chronic liver injury. It is mainly caused by the accumulation of gut-derived neurotoxin ammonia in the central nervous system [35]. More specifically, urease-producing gut bacteria such as *Klebsiella* and *Proteus* increase the production of ammonia and endotoxins. Clearly, gut microbiota is a critical factor in HE development. Cirrhotic patients with HE are reported to have increased levels of *Enterobacteriaceae, Alcaligenaceae* and *Fusobacteriaceae* and lower levels of *Ruminococcaceae* and *Lachnospiraceae* in their fecal microbiota [38]. Bacterial translocation and increased intestinal permeability are common in HE patients. Bacterial translocation leads to the increased activation of TLR4 and TLR9 in the liver and positively correlates with pro-inflammatory IL-1β and TNF-α levels, arterial ammonia and HE severity [35]. It was reported by Bajaj., *et al.* that colon mucosal microbiomes of cirrhotic patients with HE consisted more *Enterococcus, Veillonella, Megasphaera*, and *Burkholderia* and less *Roseburia* than healthy individuals but there were no differences in the fecal microbiomes [38]. This finding indicates that colonic mucosal microbes may play an important role in HE development.

Probiotics have been shown to inhibit the activity of bacterial ureases, modulate intestinal pH values, and ultimately, reduce ammonia absorption in HE [26]. Administration of probiotic preparations with *Lactobacillus* and *Bifidobacterium*, non-pathogenic strains of *Escherichia coli, Clostridium butyricum, Streptococcus salivarius* and *Saccharomyces boulardii*, and VSL#3 has been shown to alter gut microbiota composition and improve HE [29]. A number of clinical trials using mainly *Lactobacillus* GG probiotic indicate that probiotics could be effective in preventing overt HE [8]. Wang., *et al.* and his group reported that FMT had potent protective effects in improving motor activity in a rat model of HE that was comparable to VSL#3 administration [35]. In the same study, FMT was superior to probiotics in ameliorating the intestinal mucosal barrier function. Adawi., *et al.* found that rectal administration of a number of *Lactobacillus* species suppressed bacterial translocation [39].

HCC

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide. The major risk factors for HCC occurrence include chronic hepatitis B and C, excess of alcohol consumption, obesity and NAFLD. However, the risk varies greatly among individuals suggesting that additional factors are implicated in hepatocarcinogenesis, including diet composition [40]. HCC patients have been reported to have high levels of *Escherichia coli* in their gut microbiota [41]. Metagenomic analysis has revealed an altered microbiota on the tongue of HCC patients with *Oribacterium* and *Fusobacterium* being microbial biomarkers of HCC [42]. Furthermore, the levels of microbial genes related to the energy-producing system, nickel/iron-transport, amino acid-transport and metabolism were significantly different between HCC and healthy control microbiomes [42]. In a clinical study with healthy donors, probiotics have been suggested contribute to the inhibition of aflatoxin B-induced hepatocarcinogenesis [22].

In chemically induced hepatocarcinogenesis in rodents the intestinal microbiota has been implicated in HCC development. Dapito., *et al*. showed that gut microbiota correlates with tumor promotion through the TLR4 activation on hepatic cells [43]. Another similar study examined the fecal and cecal microbiota and revealed reduced levels of *Lactobacillus* spp., *Bifidobacterium* spp. and *Enterococcus* spp. and increased gram-negative bacteria that paralleled LPS serum levels [44]. Notably, probiotic administration restored intestinal dysbiosis, lowered LPS levels and decreased tumor size [44]. In another HCC mouse model, the probiotic mixture prohep slowed down tumor growth and volume by up to 40% and had high levels of *Prevotella* and *Oscillibacter* in their fecal microbiota [45]. Moreover, gut bacterial metabolites have been reported to promote obesity-induced HCC development in mice and a similar pathway may also contribute to NASH-associated HCC development [46].

Conclusion

A central role for the microbiota in liver diseases and its complications has been established and evidence for a more fundamental role in the aetiology of certain liver diseases continues to accumulate. However, the mechanisms of the microbiota and its metabolic and immunological functions in various forms and stages of liver disease are still far from complete. Although clinical and experimental evidence supports the use of probiotics in the management of liver diseases, data is limited on how these interventions impact the microbiota-host interactions and on safety assessments. While probiotics are generally assumed to be safe, there are reservations regarding their use in immunosuppressed individuals, whether such preparations offer a greater risk of initiating septic complications. There is a sufficiently strong rationale for the use of strategies that involve microbiota manipulation in the management of liver-related diseases that urge further exploration.

Available data on gut microbiota in HCC development is mainly from chemically induced animal models, in which the microbiota associates with tumor development. However, one should note that there is a growing awareness of the limitations of animal research and its inability to make reliable predictions for human clinical trials. This is especially accurate for liver cancer, in which multiple factors contributing to its pathogenesis. Differences in physiology and variations in the homology of molecular targets between mice and humans can lead to translational limitations.

Our understanding of the clinical significance of microbiota in liver disease is starting to take shape. Without a doubt larger studies, incorporating liver biopsies, standardized dose administration and duration, and an analysis of the long-term impact on the intestinal membrane are required to confirm these encouraging results. It is also important to examine the involvement of host genetics and/or epigenetic factors on how microbiota influences liver disease. Further studies are needed, combining metagenomics, metatranscriptomics, and metabolomics with longitudinal studies to gain a better understanding on the relationship between gut microbiota and liver disease development and progression.

Conflict of Interest

I accept responsibility for the contents of the amended manuscript and I affirm that there is no conflict of interest.

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