REVIEW

Overview of the microbiota in the gut-liver axis in viral B and C hepatitis

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Abstract

Viral B and C hepatitis are a major current health issue, both diseases having a chronic damaging effect on the liver and its functions. Chronic liver disease can lead to even more severe and life-threatening conditions, such as liver cirrhosis and hepatocellular carcinoma. Recent years have uncovered an important interplay between the liver and the gut microbiome: the gut-liver axis. Hepatitis B and C infections often cause alterations in the gut microbiota by lowering the levels of 'protective' gut microorganisms and, by doing so, hinder the microbiota ability to boost the immune response. Treatments aimed at restoring the gut microbiota balance may provide a valuable addition to current practice therapies and may help limit the chronic changes observed in the liver of hepatitis B and C patients. This review aims to summarize the current knowledge on the anato-functional axis between the gut and liver and to highlight the influence that hepatitis B and C viruses have on the microbiota balance, as well as the influence of treatments aimed at restoring the gut microbiota on infected livers and disease progression.

Key Words: Viral B hepatitis; Viral C hepatitis; Gut-liver axis; Immunomodulation; Lipopolysaccharides; Short-chain fatty acids

Core Tip: We have provided an overview of the mechanisms involved in the immunomodulation of the gut-liver axis. We highlight the mechanisms by which hepatitis B virus and hepatitis C virus infections influence the microbiota and how in turn these changes affect the liver pathology. We have also looked at the current treatment options and their influence on the intestinal microflora.

INTRODUCTION

Viral B and C hepatitis are two types of infections with a high rate of morbidity and mortality[1]. Hepatitis B virus (HBV) is a DNA virus belonging to the Hepadna virus, and hepatitis C virus (HCV) is an RNA virus in the Flaviviridae family. These viruses have hepatic tropism, are non-cytopathic with the ability to cause chronic liver inflammation and even liver cirrhosis and hepatocellular carcinoma[2].

Both HBV and HCV may cause similar clinical manifestations. Some patients may be asymptomatic, while others may have mild signs and symptoms from general manifestations (fatigue, fever, loss of appetite) to gastrointestinal symptoms (abdominal pain, nausea, vomiting, jaundice)[3].

The microbiota represents the totality of microbes (bacteria, viruses, fungi, protozoans, and archaea) associated with the human microorganism, while the microbiome consists of all microbes and their genes[4]. The main part of the body colonized by microbes is the gastrointestinal tract, whereas other parts such as skin, airways, vaginal tract, *etc.* are also colonized, but to a lesser extent. Changes in the microbiota are continuous throughout our life and there are many influencing factors, from type of delivery and breastfeeding, to long-term dietary changes, frequent and prolonged antibiotic treatment or other medications, *etc.*[5]. There are six bacterial dominant phyla in the gut microbiota: *Firmicutes* and *Bacteroidetes* (90%), *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia*[6]. The intestinal microbiota is a cornerstone in maintaining the homeostasis of the human body. Firstly, this "organ" provides nutrients and energy from ingested food and, secondly, it is able to produce important metabolites that play a role in maintaining the host's metabolism [7].

The liver can be considered the largest immune organ in the body with a high ability to select and activate immune cells in response to metabolic products in the gut or to signals sent by various pathogens[8]. Recent years have seen advances in our understanding of the human microbiome and its interaction with us as hosts. The gut-liver axis is part of these new discoveries, integrating the microbiome modifications and dysbiosis in hepatic pathologies.

Our review will discuss part of the mechanisms by which the microbiome influences host immunity, as well as the gut-liver axis, with an accent on viral hepatitis B and C.

MICROBIOTA AND THE IMMUNE SYSTEM

Through its products, the human microbiota can influence both the local, enteric, and the systemic immune system, dysbiosis being correlated with several autoimmune, metabolic and neurodegenerative diseases (inflammatory bowel disease progression, rheumatoid arthritis, diabetes, asthma and bones homeostasis)[9-15]. This shows that the microbiota is not only involved in intestinal, but also in systemic and organ specific pathologies. This relationship is bidirectional; systemic modifications can trigger intestinal changes, but also intestinal dysbiosis can trigger and maintain organ dysfunctions. Gut-associated lymphoid tissue (GALT) is an important "immunological organ" of the body that belongs to the gut-mucosal immune system. GALT consists of Peyer's patches, intraepithelial lymphocytes, lamina propria lymphocytes (including dendritic cells) and mesenteric lymph nodes. Activation of this system has the ability

to produce various mediators with immunostimulatory or immunosuppressive effect [16].

Some of the products by which the intestinal microflora communicates with the rest of our organism are lipopolysaccharides (LPS), bacterial DNA and RNA, flagellin, short-chain fatty acids (SCFA) such as acetate, propionate and butyrate, tryptophan (Trp) and it's metabolites, teichoic acid and peptidoglycans and secondary bile acids (BA)[9,17]. These bacterial components and products of the bacterial metabolism are recognized by pattern recognition receptors, which particularly include the toll-like receptors (TLR) family. TLRs are expressed on epithelial and immune cells and are capable of recognizing specific bacterial molecules, triggering specific local protective and immunomodulatory (both pro- and anti-inflammatory) responses[18,19]. TLR activation is an essential element of the innate immune systems fight against the HBV and HCV infections[20,21]. Not all of these pathways were studied directly in connection with HBV and HCV. Therefore, more studies are needed to determine the exact relationship between the bacterial products, the immune system and hepatitis.

We will briefly mention some of the most important of the microbial-produced products and their interaction with the immune system (Figure 1).

LPS

In Gram-negative bacteria, LPS are an important pathogen-associated molecular pattern and a well-studied microbial marker in connection with bacterial translocation and host systemic responses[22,23]. The outer membrane of gram-negative bacteria consists of LPS, which possess a hydrophobic endotoxin, called lipid A[24]. This component is recognized by TLR4 and *via* this mechanism it further activates nuclear factor kappa B (NF-κB) and elicits pro-inflammatory effects[25,26]. One type of LPS is *Escherichia coli* (*E. coli*) produced LPS. This stimulates TLR4 receptors and triggers the release of pro-inflammatory cytokines. *E.coli* LPS also increases endotoxin tolerance and decreases the autoimmune activity, protecting against autoimmune diabetes[27]. However, some bacterial species produce LPS molecules with underacylated lipid A that exhibit an immuno-inhibitory effect[28]. These LPS molecules are produced especially by members of the *Bacteroidales* order and instead of stimulating TLR receptors, they silence the TLR4 signaling and the inflammatory process[29]. LPS induces the upregulation of cluster of differentiation 14 protein (CD14) *via* the TLR4 pathway, which decreases the relative epithelial resistance and increases its permeability. Increased intestinal permeability allows for more LPS to reach the general circulation, aiding it in reaching different organs and exhibiting a pro-inflammatory effect[30]. This is also true in cases of dysbiosis with an increase in LPS production that is correlated with an increase in tumor necrosis factor alpha (TNF-α), interleukin (IL) 6 and C-reactive protein levels[31,32]. Intestinal dysbiosis caused an LPS-induced inflammatory response in a mice model, while unaltered host microbiota reduced the inflammatory response to LPS in the liver[33]. LPS-induced monocyte activation has been shown to be increased in patients with HBV or HCV[34].

This underlines the ability of LPS and gut lipid metabolism to modulate both intestinal and organ-specific inflammatory response.

SCFA

In the gut, non-digestible carbohydrates are transformed by the microbiota into SCFA such as acetate, propionate and butyrate[35]. Acetate and propionate are produced mainly by *Bacteroidetes*, while butyrate, the main source of energy for colonocytes, by *Firmicutes*. A small portion of SCFA that is not metabolized can reach the liver through the portal vein, being used as energy substrates for hepatocytes[36,37]. Certain bacteria such as *Butyricimonas* and *Prevotella* have the ability to generate butyrate and propionate, SCFAs with anti-inflammatory effect[38].

SCFA bind to the G-protein coupled free fatty acid receptors (FFA): GPR41 (FFA2) and GPR43 (FFA3)[39,40]. Enteroendocrine and pancreatic β-cells present both GPR41 and GPR43 receptors, while immune cells and adipocytes present mostly GPR41 and peripheral neurons GPR43[41]. This links SCFA production to a multitude of metabolic, neurological and inflammatory mechanisms. Thus, FFA receptors and SCFA production presents therapeutic targets in these diseases[41-43].

In immune cells (leukocytes and neutrophils) SCFA increase the intracellular calcium levels[39,44,45]. This reaction leads to an increased production of reactive oxygen species, as well as an increased neutrophil recruitment and a pro-inflammatory effect[46-48]. GPR41 activation by SCFAs in the gut promotes the function and size of regulatory T cells, protecting against intestinal inflammation[49]. Also, GPR43 was found to be a chemotactic receptor for neutrophils, stimulating their migration towards the source of SCFAs[50,51]. In a mouse model of gout, the intestinal
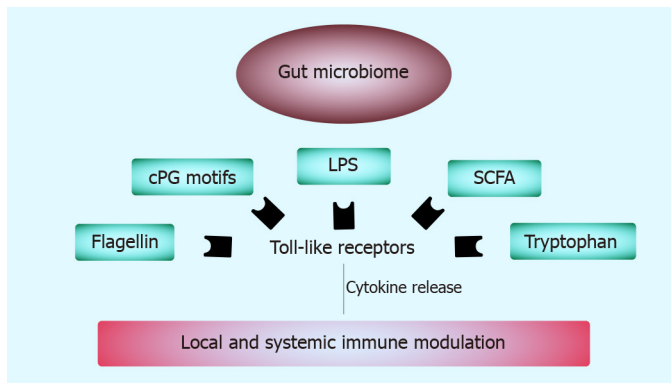
Figure 1 The mechanisms by which the gut microbiome influences the immune system. LPS: Lipopolysaccharides; SCFA: Short-chain fatty acids.

microbiota-produced SCFA determined inflammasome assembly, reactive oxygen species formation and IL-1b production and improved the inflammatory response[52]. Increased SCFA levels determined the production of macrophages and dendritic cells, protecting the lung against allergic inflammation[53]. Also, by activating another G-protein coupled receptor, GPR109A, the microbiota is involved in inflammatory suppression *via* the NF-κB pathway in normal and colon cancer cells[54].

Another SCFA mechanism involved the inhibition of histone deacetylases (HDAC). By non-competitively inhibiting the activity of HDAC 1 and 2, butyrate causes histone hyperacetylation. By this mechanism, butyrate and other SCFAs are thought to serve as a protective factor against colon cancer, dysbiosis being a risk factor for the development of this disease, as well as other chronic inflammatory diseases[55]. HDAC inhibition also promotes macrophage activity and CD8 T cells and improves anti-cancer therapy[56-59]. Furthermore, class 1 HDACs inhibition is proposed as a target in pulmonary inflammation, due to its contribution in the release of pro-inflammatory cytokines[60]. HDAC inhibition promotes effector and regulatory T-cell differentiation and the production of IL-17, interferon-γ (IFN-γ) and IL-10, contributing to an overall anti-inflammatory effect mediated by SCFAs[61,62].

By increasing acetyl-CoA activity and controlling gene expression, SCFA are involved in plasma B cells metabolism, activity, energy production boosting, and differentiation. During an infection, they support B cells antibody production, decreasing the host susceptibility to pathogens[63].

Therefore, SCFA present both a pro- and anti-inflammatory role[61]. There is still the need for more studies to fully understand the implications of SCFA in inflammatory and immune diseases and determine in which conditions they act as pro-inflammatory or as anti-inflammatory factors.

Trp

The microbiota is involved in the transformation of Trp in indole derivatives, serotonin (5-hydroxytryptamine) and kynurenine[64].

Lactobacilli species can metabolize Trp into indole-3-aldehyde, a ligand for the aryl hydrocarbon receptor (AhR) that is involved in intestinal immunity and the production of IL-22[65,66]. There are only a few species such as *Peptostreptococcus russellii* and *Lactobacillus spp.* with the ability to produce AhR ligands[64]. In high fat diets IL-22 can act as an antioxidant and anti-inflammatory agent, protecting the intestinal mucosa and epithelial cells from oxidative and inflammatory stressors[67]. Also, IL-22 is involved in the intestinal mucosa immune response against exterior pathogens[68,69]. However, in patients with inflammatory bowel disease, Il-22 is considered a "two-headed cytokine": it acts as a mucosal producing and healing agent, but in the chronic form of the disease it is also involved in tumorigenesis, promoting tumoral growth[70-72].

The Trp microbiota metabolite AhR regulates the activation and transcription of several other pathways, including IL-6, cytochrome P450 1A1 (CYP1A1), and 1B1 (CYP1B1), vascular endothelial growth factor A, and prostaglandin G/H synthase 2 and also stimulates innate lymphoid cells and intraepithelial lymphocytes development, mediating their anti-inflammatory effects[73,74]. Other bacteria that interfere with Trp metabolism are *E. coli*, *Lactobacilli* and *Clostridium sporogenes*. The first two possess tryptophanase which converts Trp to indole, while the latter decarboxylates Trp and increases tryptamine production[64].

The microbiota influence on Trp provides intestinal anti-inflammatory effects, but it also poses potential research directions regarding systemic inflammation[75,76].

Flagellin

The locomotive bacterial flagella contain flagellin, which is recognized by the host TLR5. Via the TLR pathways, flagellin is involved in several immunological mechanisms, both locally, in the gut, but also systemic, inducing the release of pro-inflammatory molecules[77]. In a study administering purified flagellin in mice, there was a decreased microbial dysbiosis, as well as an amelioration of IL-10 deficiency-induced colitis[78]. This shows that flagellin presenting bacterial species could pose a beneficial effect in chronic inflammatory diseases. However, in patients with inflammatory bowel diseases there have been observed higher concentrations of flagellin, putting into question its supposed protective role[79]. Also, flagellin has been observed to be a potent TLR5/NF-κB activator, promoting inflammation in intestinal epithelial cells[80]. *Via* the same TLR5/NF-κB mechanism, flagellin could also promote the attachment and development of viral molecules, supporting viral infections *via* the intestine[81].

Bacterial CpG motifs

Bacterial DNA contains unmethylated CpG dinucleotides that are recognized by the immune system and produce an immunostimulatory effect[82,83]. These bacterial CpG motifs are recognized by TLR9 receptors and, depending on their localization, they exhibit several effects. Apical TLR9 activation inhibits NF-κB activation, while basolateral receptors stimulate NF-κB activation and the subsequent inflammatory pathways[84].

INFLAMMATION AND B AND C HEPATITIS

Many extrahepatic changes (metabolic, cardiovascular, autoimmune, renal) have been correlated with chronic HCV infection. This statement is supported by a prospective cohort study in which patients with chronic HCV infection (with HCV RNA detected in the serum) had a high risk of death due to liver or non-liver disease (cardiovascular and renal disease) compared to uninfected patients (without serum HCV RNA) or with patients presenting HCV antibodies[85].

Inflammatory cytokines are normally released in response to various stimuli, including viral infection. This limits cellular stress and cell damage[86]. HCV infection is associated with an immune activation status that can further influence the levels of inflammatory markers (Il-6, TNF-α, iNOS, COX-2, IL-1), which are correlated with various extrahepatic diseases[87,88]. In HBV-infected patients there is an increase in Il-8, IL-29 and COX-2. Under normal conditions, adult hepatocytes do not express COX-2, but in chronic inflammatory diseases, the expression of this isoenzyme increases. Furthermore, IL-8 activates the extracellular signal-regulated kinase and c-Jun N-terminal kinase signaling pathways, which are also involved in inflammatory processes[86].

In infected hepatocytes with HCV, the production of type 1 and 3 interferons is blocked by the action of the viral NS3/4A protease. This protease may also influence the innate immune adaptor molecules mitochondrial antiviral signaling proteins with an effect on the intracellular antiviral defense system. In an experimental study on hepatic macrophages the first activated factor in liver macrophages with HCV infection has been shown to be TNF-α that further activates NF-κB and increases IL-1β. Adding to this, the HCV core protein also activates the NLRP3 inflammasome. The hepatic inflammatory environment is ensured by the activity of the NLRP3 inflammasome, phospholipase-C and IL-1β. Thus, NLRP3 inflammasome and IL-1β can be considered as target of treatment in HCV-induced liver disease[89].

THE GUT-LIVER AXIS

The gut microbiome can interact tightly with the liver *via* the so-called gut-liver axis. Blood from the intestine, rich in microbiota-derived molecules, reaches the liver *via* the portal vein. In the liver, these molecules are recognized by TLRs pattern recognition receptors, mediating their effect on the liver tissue[90]. Related to liver pathologies, the gut microbiota is particularly involved in liver fibrosis and cirrhosis, hepatic cancers,

alcoholic and non-alcoholic fatty liver disease, autoimmune hepatitis, primary sclerosing and primary biliary cholangitis as well as viral hepatitis[91-96]. Some of the most studied components that affect liver pathologies are represented by LPS and SCFAs.

LPS produced by the microbiota are scarcely found in the normal liver, being cleared by Kupffer cells and not causing any damage[97]. However, in alcoholic liver disease, because of an increase intestinal permeability, an increased amount of LPS reached the liver[96]. LPS binds to TLR4, causing an excessive release of pro-inflammatory cytokines IL-1 and TNF-α[33,98]. Also, LPS can upregulate the expression of the cluster of differentiation 14 (CD14) receptor on Kupffer cells[99]. This could potentially make the liver more sensitive to LPS toxicity, as CD14 is vital for Kupffer cells LPS activation[100]. Kupffer cells activation produces a pro-inflammatory state, increasing the levels of NF-κB, TNF-α and IL-1. This leads to liver injury and disease progression, dysbiosis favoring the chronic inflammatory state[101].

SCFA such as acetate, propionate and butyrate may have a protective effect on liver diseases progression. High levels of butyrate restore the intestinal microbiota in cases of dysbiosis, reducing the intestinal permeability and thus the levels of endotoxins reaching the liver *via* the portal circulation. This attenuated the histological aspect of steatohepatitis livers, reducing the levels of TNF-α, IL-1, IL-6 and IFN-γ pro-inflammatory cytokines, as well as the expression of TLR4 receptors[102]. In an experimental study by Endo *et al*[103], administering probiotics, aimed at increasing butyrate levels, significantly improved non-alcoholic fatty liver disease progression, reducing the inflammation and oxidative stress. This clearly shows that intestinal-produced metabolites can influence the immune and inflammatory state of the liver. Dysbiosis and an increased intestinal permeability allows for the gut-liver balance to change, causing a pro-inflammatory state of the liver and contributing to disease progression [104,105]. Pathogen-associated molecular patterns (bacterial antigens and products) such as LPS and viral RNAs activate TLR4 on Kupffer cells and other immune cells. Thus, the innate immune response is induced.

The liver is influenced by the intestine through the portal circulation, while the intestine is influenced by the liver through the released mediators and hepatic bile flow. It is known that increased intestinal permeability contributes to systemic inflammation and disease progression[106]. BA and other mediators such as immunoglobulin A (IgA) regulate the gut-liver axis. IgA influences the homeostasis of the intestinal microbiota, preventing bacterial translocation. BA modulate the intestinal barrier and have antimicrobial activity. Several enzymes involved in BA synthesis are regulated by the microbiota. However, some secondary BA (*e.g.*, deoxycholic acid) resulting from intestinal biotransformation produce microbial dysbiosis and increase the intestinal permeability[107].

TGR5 is a G-protein-coupled BA receptor involved in the anti-inflammatory immune response, energy homeostasis, metabolic pathways and in pathologies such as diabetes and obesity[108]. In the intestine, TGR5 is involved in regulating the colonic motility and the intestinal permeability *via* the farnesoid X receptor — cAMP pathway [109,110]. Moreover, TGR5 activation stimulates mucosal proliferation and protects against mucosal injuries[111]. In liver pathologies, the levels of BA are significantly decreased, leading to a reduced activation of TGR5 in the gut[112,113]. In a mouse model with TGR5 silencing, there was a significant reduction in gut epithelial cellularity, with histological abnormalities and distortions and an increased intestinal permeability[114]. BA and TGR5 activation are therefore necessary for a normal functioning of the intestine and the gut-blood barrier. BA administration is beneficial for viral hepatic diseases. In a HBV model, TGR5 agonists administration suppressed the infection[115]. BA and TGR5 agonists pose as potential treatment options for viral hepatitis[116].

Decreased BA quantities in virus hepatitis could be responsible for the increased intestinal permeability and the subsequent increase in LPS and other endotoxins. This in turn favors the progression of the liver pathology, creating a vicious circle where the liver pathology creates an environment that further promotes the liver pathology (Figure 2). Future studies should determine the exact mechanism by which liver diseases influence the intestinal permeability and lead to the production of dysbiosis.

THE GUT MICROBIOTA-VIRAL B AND C HEPATITIS

The presence of the HBV or HCV infection can lead to intestinal dysbiosis[117]. Some of the microbial changes present in patients with HBV and HCV-related liver diseases
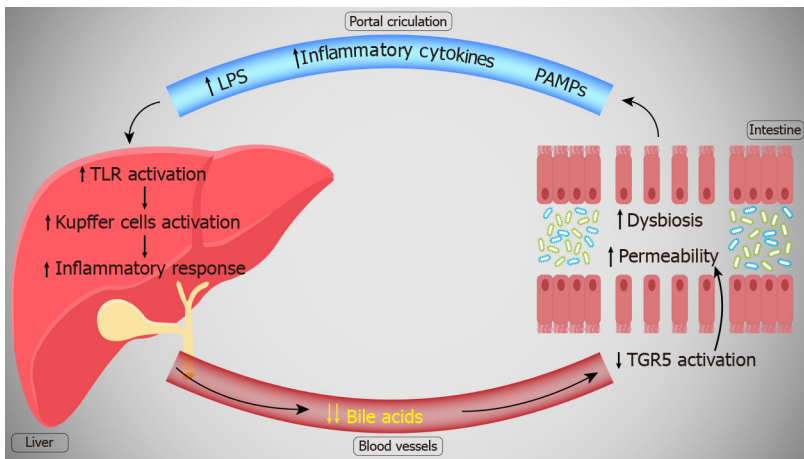
Figure 2 The gut-liver axis in liver diseases. TGR5: G-protein-coupled bile acid receptor; PAMPs: Pathogen-associated molecular patterns; LPS: Lipopolysaccharides; TLR: Toll-like receptor.

are shown in Table 1.

These studies showed significant differences in the composition of the intestinal microbiota between patients with B or C hepatitis with or without cirrhosis present. A healthy gut microbiota means a gut microbiota with great diversity and the ability to react to changes. Thus, B and C viruses can cause changes and can shape the gut microbiota in different directions[122].

Nowadays, the treatment of B and C hepatitis is well established by international guidelines[124-126]. The main question is: does the treatment of B or C hepatitis influence the diversity and abundance of the intestinal microbiota? And if so, are these changes helping in preventing or halting the evolution of the disease? A part of the studies looking into the microbial changes caused by HBV and HCV treatments are presented in Table 2.

Entecavir increases the abundance of the genus *Clostridium sensu stricto 1* which has been associated with large and extra-large HDL particles and also with a decreased risk of cardiovascular disease[131]. Increased lipid content in the liver and steatosis can result in the development of inflammation and, over time, cirrhosis, and can also increase oxidative stress[132]. Genus *Intestinibacter* along with genus *Escherichia, Shigella* can be considered as a major contributor to NAFLD progression. Increases in the abundance of *Intestinibacter* have been correlated with severe intestinal disorders in humans and are recognized as a biomarker of the onset of Crohn's disease[133].

In a study by Pérez-Matute *et al*[129], it was shown that the use of direct antiviral agents in patients with chronic HCV infection could only restore the intestinal bacterial changes in those patients with a lower degree of fibrosis (F0-1). The data highlight a strong relationship between the liver and the intestine and suggest that mild intestinal changes caused by liver damage could possibly be counteracted with the appropriate drugs.

Blautia, Coprococcus, Dorea, Lachnospira, Oribacterium, Roseburia and *L-Ruminococcus* were detected in the human intestine as the main genera belonging to the *Lachnospiraceae* family[134]. *Lachnospiraceae* is considered a "good" family of bacteria, having a beneficial role in host homeostasis. The bacteria belonging to this family can convert carbohydrates into SCFA in the gut[135]. Decreasing the abundance of *Lachnospiraceae* leads to decreased SCFA production and thus increases the pH of the colon. This change increases the production of ammonia and its absorption in the intestine[136].

Direct-acting antivirals (DAA) treatment in cirrhotic patients appears to have a positive impact on changes in the intestinal microbiota, as well as fibrosis and inflammation, but without a positive impact on the function of the intestinal barrier. DAA has greatly reduced the abundance of *Enterobacteriaceae, Staphylococcus*, and *Veillonellaceae*[130]. The abundance of the *Enterobacteriaceae* family, belonging to the *Proteobacteria* phylum, depends on the amount of oxygen that crosses the intestinal barrier. The abundance of *Enterobacteriaceae* is elevated after the oxygen level increases and can aggravate intestinal inflammation. Members of this family cannot degrade complex carbohydrates (as *Clostridia* and *Bacteroidia* do); they are only involved in the passive transport of oligosaccharides. This disadvantage may explain the lower abundance of *Enterobacteriaceae* compared to *Clostridia* and *Bacteroidia* in the healthy distal intestine [137]. *Veillonellaceae* belonging to *Firmicutes* phylum, is one of the main microbial taxa

Table 1 Microbiota changes in different studies regarding hepatic B and C virus

	Changes of gut microbiota in patients *vs* healthy subjects	Ref.
Type of HBV infection		
Chronic HBV infection	↓ *Bacteroidetes* and *Firmicutes*; ↑ *Proteobacteria* and *Actinobacteria*	Chen *et al* [117]
	↑ *Bifidobacterium dentium*; ↓ *Bifidobacterium catenulatum* and *longum*	Xu *et al* [118]
	↑ *Veillonellaceae*; ↓ *Lachnospiraceae, Rikenellaceae, Ruminococcaceae*	Wang *et al* [119]
HBV liver cirrhosis	↓↓↓ *Bacteroidetes* and *Firmicutes*; ↑↑↑ *Proteobacteria* and *Actinobacteria*	Chen *et al* [117]
Decompensated HBV cirrhosis	↓ *Bifidobacteria/Enterobacteriaceae* ratio; ↑ *Enterobacteriaceae*; ↓ *Firmicutes* (*F.prausnitzii, Clostridium clusters XI* and *XIVab, Bifidobacterium*); ↓ *Bacteroidetes*	Lu *et al* [120]
HBV related hepatocellular carcinoma	↓ *Proteobacteria*; ↑ *Prevotella, Phascolarctobacterium, Anaerotruncus*; ↑ *Proteus, Veillonella, Prevotella 2, Barnesiella* and *Ruminococcaceae spp.*	Liu *et al* [121]
Type of HCV infection		
Chronic HCV infection without cirrhosis	↑ *Veillonella spp., Lactobacillus spp., Streptococcus spp.* and *Alloprevotella spp.*; ↓ *Bilophila spp., Clostridium IV spp., Clostridium XlVb spp., Mitsuokella spp.* and *Vampirovibrio spp.*; No changes: *Akkermansia spp., Bifidobacterium spp., Escherichia/Shigella spp., Haemophilus spp., Micrococcus spp.* and *Weissella spp.*	Heidrich *et al*[122]
Chronic HCV infection with cirrhosis	↑↑↑ *Veillonella spp., Lactobacillus spp., Streptococcus spp.* and *Alloprevotella spp.*; ↓↓↓ *Bilophila spp., Clostridium IV spp., Clostridium XlVb spp., Mitsuokella spp.* and *Vampirovibrio spp.*; ↑↑↑ *Akkermansia spp., Bifidobacterium spp., Escherichia/Shigella spp., Haemophilus spp., Micrococcus spp.* and *Weissella spp.*	Heidrich *et al*[122]
Stage 4 HCV infection (cirrhosis)	↓ *Firmicutes*; ↑ *Prevotella, Faecalibacterium* (*F. prausnitzii*); ↑ *Acinetobacter*; ↑ *Veillonella*	Aly *et al* [123]

HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Microbial changes as a result of several treatments in viral B and C hepatitis

Drug	Type of study	Changes in gut microbiota	Ref.
Entecavir	Experimental (mice)	↑ *Lachnospiraceae, Akkermansia, Alistipes, Escherichia, Shigella, Oscillibacter, Bilophila*	Li *et al*[127]
	Clinical	↑ *Clostridium sensu stricto 1, Erysipelotrichaceae UCG-007, Intestinibacter*; ↓ *Streptococcus, Atopobium*, and *Murdochiella*	Lu *et al*[128]
Direct antiviral agents in patients with HCV infection	Clinical	↑ *Phylum Firmicutes, genera Lachnospira*	Pérez-Matute *et al*[129]
Direct antiviral agents in patients with HCV-related liver cirrhosis	Clinical	↓ *Enterobacteriaceae, Staphylococcus* and *Veillonellaceae*	Ponziani *et al* [130]

HCV: Hepatitis C virus.

associated with the severity of fibrosis in non-obese patients. This family has the ability to produce propionate, one of the most important SCFAs and has been associated with chronic liver disease[138]. The LPS and SCFA metabolites produced by intestinal *Veillonella* stimulate the release of cytokines (Il-6, IL-10, TNF-α) in human peripheral blood mononuclear cells and thus have a negative impact on liver pathology and host inflammation[139].

GUT MICROBIOTA-TARGET OF TREATMENT

Although standard therapy for B and C viral hepatitis is well established and presented in clinical guidelines, many dietary supplements, including pre-, pro-, and symbiotic agents, are being studied to reduce the toxicity of standard therapy (side effects) or to increase their effect. Also, fecal microbiota transplantation (FMT) is one of the methods that can manipulate the composition of the intestinal microbiota. It has

the ability to strengthen the intestinal barrier, reduce intestinal permeability and also improve host immunity[140]. There are various routes of administration for FMT: nasogastric tube, upper endoscopy or colonoscopy, retention enema, *etc.* The route of administration depends on the characteristics of the disease. For example, good results have been obtained after duodenal administration in metabolic disease[141].

There are only a few studies that support the effect of certain probiotics in viral B or C hepatitis.

Oo *et al*[142] studied the long-term (36-mo) effect of probiotic heat-treated strain Enterococcus faecalis FK-23 in patients with HCV infection. This probiotic may change the microbiota in these patients and may have an important role of decreased ALT in serum.

In patients with HBV-induced liver cirrhosis, the role of a probiotic (*Clostridium butyricum* combined with *Bifidobacterium infantis*) has been studied in the treatment of minimal hepatic encephalopathy. The results claim that the probiotic modulates the intestinal barrier and thus can lower the level of ammonia and can improve cognition [143].

CONCLUSION

Most of the microbiota-derived components elicit an immunomodulatory effect, both pro- and anti-inflammatory. Alteration of the host microbiome produces an unbalance of these factors, leading to negative effects both locally in the intestine, as well as at distance in other organs. Therefore, we can conclude that by its factors, the host microbiota is an important determinant in the hosts immune response modulation. Future experimental and clinical studies are needed to determine the exact mechanisms of these changes, as well as the exact conditions in which the microbiota can serve as a protective factor.

Currently, the intestinal microbiota is a target of treatment for various diseases in humans. Future studies should focus on the effects and efficacy of treatments aimed at restoring the gut microbial environment (prebiotics, probiotics, symbiotics, fecal transplant) and their exact relationship with liver pathologies. By understanding the natural communication pathways between the liver and the gut, in both health and disease, we could potentially formulate better therapies aimed at reducing the effects of the chronic inflammatory response on the progression of liver diseases.

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