

Host–Microbiota Interactions in Liver

Subjects: **Oncology** | **Microbiology**

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Hepatocellular carcinoma (HCC) is a difficult to treat liver cancer that generally arises in individuals suffering from alcoholic or non-alcoholic fatty liver diseases. Inflammation, tissue injury and fibrosis are important precursors of HCC. Translocation of microbial- and danger-associated molecular patterns (MAMPs and DAMPs) from the gut to the liver elicits profound chronic inflammation, leading to severe hepatic injury and eventually HCC progression.

microbiome

gut-liver axis

inflammation

obesity

alcoholic liver disease

metabolism

innate immunity

cirrhosis

1. Gut–Liver Communications

The liver is intimately linked to the gut and represents a critical metabolic hub involved in digestion, detoxification and clearance of microbial products. Its building blocks are the hepatic lobules organized around central veins and portal triads, consisting of a portal vein, a hepatic artery and a bile duct. The portal vein delivers 80% of the total liver blood supply, while the remaining 20%, i.e., the oxygenated blood, flows through the hepatic artery. Upon mixing, the blood flows across the lobule through the hepatic sinusoids and drains into the central veins, while the bile flows in the opposite direction via the bile canaliculi. Such an organization establishes gradients of oxygen and metabolites and creates a liver zonation. The hepatocytes, endothelial and immune cells of the liver are aligned along this vasculature, and their spatial distribution along the liver zonation dictates their phenotypes and functions.

The gut–liver communication axis involves multiple systems and messengers, namely (1) the biliary tract that delivers primary bile acids (BA) and antimicrobial molecules, including immunoglobulin A (IgA) to the intestine; (2) the portal vein that carries MAMPs and secondary BA to the liver; and (3) the systemic circulation that distributes dietary metabolites, free fatty acids, ethanol and choline metabolites to the intestine across blood capillaries (**Figure 1**). This gut–liver bi-directional connection regulates the intestinal microbiota composition and the integrity of intestinal epithelial and vascular barriers, as well as BA synthesis and composition and lipid metabolism in the liver.

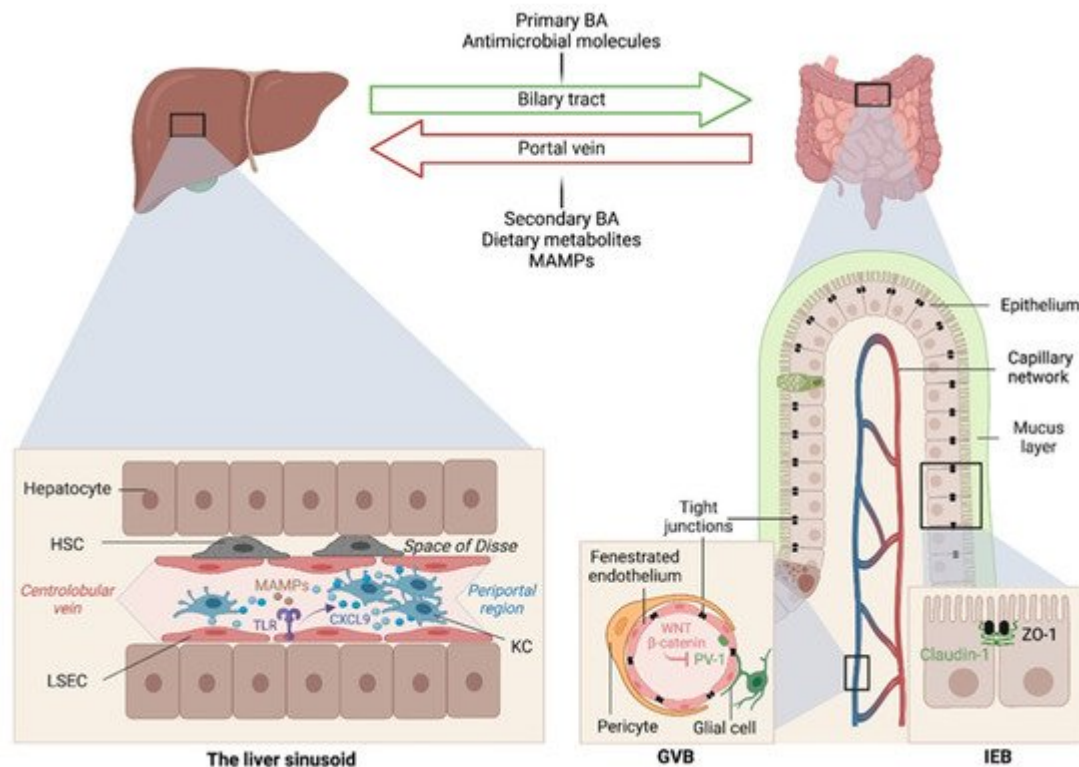


Figure 1. Gut–liver communication axes in health. The gut and liver are intricately connected through the portal vein and biliary circulations. Several messengers, including dietary metabolites, bile acids, antimicrobial peptides and microbial associated molecular patterns (MAMPs), are exchanged and required for intestinal and hepatic homeostasis, as well as host physiology in general. The intestinal microbiome also instructs liver zonation. Microbial sensing by toll-like receptors (TLR) on liver sinusoidal endothelial cells (LSECs) results in a CXCL9 chemokine gradient that attracts Kupffer cells closer to the periportal region to ensure immune surveillance and host defense from invading pathogens arriving through the portal vein circulation. GVB, gut-vascular barrier; IEB, intestinal epithelial barrier; ZO-1, zonula occludens-1; KC, Kupffer cell; HSC, hepatic stellate cell.

2. The Central Role of the Gut Microbiome in Liver Diseases

At birth, we are colonized by a collection of microorganisms, including bacteria, fungi, viruses and archaea, that outnumber our human cells by 10:1 and provide 100-fold as many genes as found in our human genome [1]. The gut microbiota provide essential functions for our digestion and nutrient absorption, including the breakdown of indigestible carbohydrates, the synthesis of vitamins and the deconjugation of primary BA, and in shaping our mucosal immune system.

Altered intestinal microbiota, accompanied by small intestinal bacterial overgrowth (SIBO), are observed in liver chronic inflammatory diseases [2][3][4], cirrhosis [5][6][7][8][9] and HCC [10], and gut microbiome metagenomic signatures have been identified in patients with NAFLD [11], cirrhosis [3] and HCC [12]. For instance, Boursier et al. reported that fecal *Bacteroides* and *Ruminococcus* were independently associated with NASH and fibrosis (stage 2 or higher), respectively, while *Prevotella* was depleted in these conditions [7]. Loomba and colleagues showed an

increased abundance of *Bacteroides vulgatus* and *Escherichia coli* in NAFLD patients with advanced fibrosis [11]. Of note, *E. coli* is the predominant bacterium detected by culture in NAFLD patients exhibiting SIBO [2]. In mice, prolonged high dietary cholesterol feeding caused spontaneous NAFLD and progression to HCC development, which was associated with gut-microbiota dysbiosis [13]. Importantly, treatment with a cholesterol-lowering drug restored the microbial ecology and prevented disease development in mice [13]. In mouse models of NASH or obesity-induced HCC, *Akkermansia* spp., *Prevotella* spp. and *Lactobacillus* spp. are decreased, while *Bacteroides* spp., *Clostridium* spp. and *Ruminococcus* spp. are elevated [14][15][16] (Figure 2). Last, besides bacteria, the intestinal microbiota diversity is reduced in patients with liver diseases, particularly ALD patients, in whom candida dominates [17]

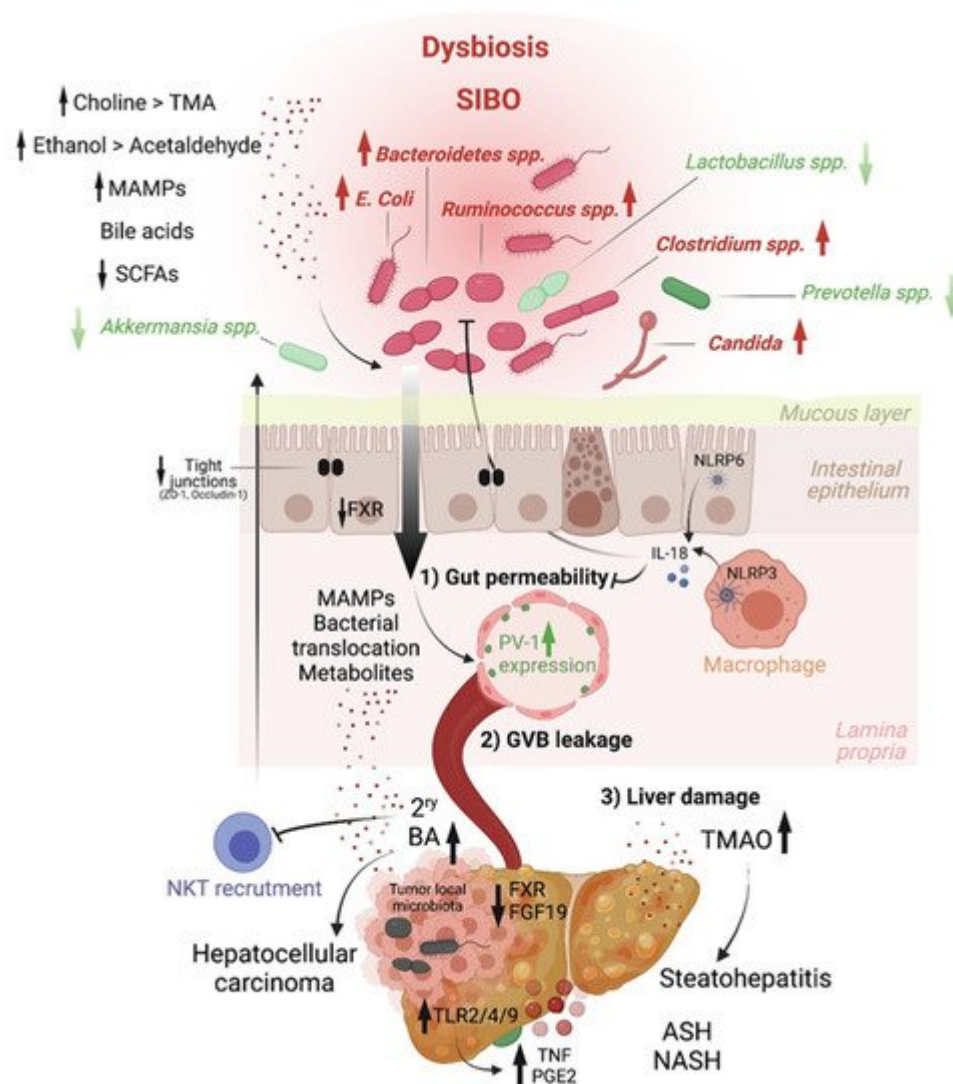


Figure 2. Host-microbiome molecular effectors driving liver inflammation and tumorigenesis. Chronic inflammatory diseases are well-established precursors of hepatocellular carcinoma. Intestinal microbial dysbiosis is associated with these conditions, in which beneficial bacteria (green) are depleted and pathobionts (red) expand. This results in disrupted gut-liver axis homeostasis. On the one hand, a reduction in short-chain fatty acids (SCFA) production leads to increased IEC layer permeability, a process normally countered by the activity of the NLRP3 and NLRP6 inflammasomes via interleukin-18 (IL-18). The integrity of the intestinal epithelial layer can also be

compromised by ethanol metabolites. On the other hand, altered bile acids synthesis results in deregulated farnesoid X receptor (FXR)-mediated inhibition of gut-vascular barrier (GVB) leakage (induced by plasmalemma vesicle-associated protein 1 [PV-1]) and secondary bile acids retention in the liver. Last, enhanced choline metabolism to trimethylamine-N-oxide (TMAO) in the liver drives steatohepatitis. The leakage of the intestinal epithelial and gut-vascular barriers allows the translocation of microbial-associated molecular patterns (MAMPs) and microbial components into the liver, triggering Toll-like receptor (TLR)-mediated inflammation (e.g., via tumor necrosis factor (TNF)) and a senescence-associated secretory phenotype (in which prostaglandin E2 (PGE2) is notable), well-known promoters of liver cancer.

The key role of the microbiota in HCC was functionally demonstrated with the use of antibiotics, which reduce liver inflammation and tumor development in mouse models [14][18]. Besides promoting hepatic inflammation, the microbiota could also impact antitumor immunity. Notably, some species, including *A. muciniphila* and *Ruminococcaceae* spp., were found to be enriched in the gut of HCC patients that respond to anti-PD-1 immune-checkpoint blockade compared to non-responders [19].

Last, besides the gut microbiota, a local microbiome may also influence liver disease severity and tumor development [20].

3. Intestinal Permeability as a Precursor of Liver Diseases

Early studies have reported a link between liver diseases and disrupted intestinal epithelial cell (IEC) barrier integrity. For instance, NAFLD patients with no significant alcohol consumption were shown to exhibit disrupted IEC tight junctions and increased prevalence of SIBO, which correlated with the severity of steatosis [21]. Similarly, both in vitro and in vivo studies demonstrated the impact of alcohol on enhancing intestinal permeability by altering the expression of the tight junction proteins zonula occludens-1 (ZO-1) and claudin-1 [22][23]. Consistently, occludin deficiency in mice led to a more severe ALD phenotype [23]. Besides the IEC barrier, a gut vascular barrier (GVB), as described by the Rescigno lab [24], also restricts liver injury and the translocation of bacteria or bacterial products into the systemic circulation. The GVB is composed of intestinal endothelial cells closely associated with pericytes and enteric glial cells and is thought to provide an additional protective layer that shields the liver from microbial moieties and inflammatory damage [25]. The integrity of the GVB is sustained by the activation of the WNT/ β -catenin pathway, which inhibits the expression of the plasmalemma-vesicle-associated protein 1 (PV-1) [24], a membrane glycoprotein associated with the structure of fenestrated endothelia [26], and upregulated in leaky GVB [24] (Figure 1).

It is posited that gut microbiota dysbiosis results in reduced BA-mediated stimulation of the farnesoid X receptor (FXR) that drives β -catenin activation in endothelial cells. This has been demonstrated in mouse models of NASH induced by a HFD or a choline and methionine deficient (MCD) diet [27], and a mouse model of cirrhosis induced by bile duct ligation combined with carbon tetrachloride (CCL4)-mediated liver injury [28]. In both models, intestinal permeability led to microbial translocation from the gut to the liver, and FXR agonists, such as the BA analog

obeticholic acid (OCA), conferred protection against GVB disruption, limited bacterial translocation and ameliorated liver pathology^{[29][30]}.

4. MAMPs and PRR Activation Link Microbiota Dysbiosis to Liver Inflammation and HCC

MAMPs reaching the liver, including LPS, unmethylated cytosine–phosphate–guanine dinucleotides (CpG) DNA and lipoteichoic acid (LTA), have long been shown to elicit hepatic inflammation by stimulating Toll-like receptor (TLR)4^{[31][32]}, TLR9^[33] and TLR2^{[34][35]}, respectively. These PRR expressed by liver immune cells, including KCs^[32] and hepatic stellate cells (HSCs)^{[31][33][35]}, signal through the adaptor MYD88 to activate MAPKs and NF-κB transcriptional programs, leading to oxidative and endoplasmic reticulum stress; cellular senescence; and the secretion of inflammatory cytokines, chemokines, matrix-remodeling factors and growth factors that collectively promote liver tumorigenesis^{[14][35]}. Notably, while TLR4-mediated signaling was demonstrated to promote liver fibrosis and fibrosis-associated tumorigenesis^{[32][36]}, TLR2 stimulation by LTA, in conjunction with the action of the secondary BA deoxycholate (DCA; a reported inducer of DNA damage^[37] and apoptosis^[38], was implicated in obesity-associated HCC^[35]. TLR2 signaling in HSCs led to senescence and the establishment of a senescence-associated secretory phenotype (SASP), which promoted obesity-induced HCC through a pro-inflammatory and immunosuppressive pro-tumorigenic environment involving prostaglandin E (PGE)2 overproduction^[35]. Consequently, a BAs sequestrant that formed non-absorbable complexes in the intestine reversed liver injury and prevented NASH progression^[39], as well as NASH-HCC development in mice^[16] (Figure 2).

5. Host–Microbiome Metabolic Interactions in Liver Pathologies: A Focus on Bile Acids, Short Chain Fatty Acids, Choline and Ethanol Metabolites.

Bile acids. Primary BAs are synthesized in hepatocytes from cholesterol through the action of Cholesterol 7 alpha-hydroxylase, also known as cytochrome P450 or CYP7A1^[40]. In humans, the main primary BAs are cholic acid (CA) and chenodeoxycholic acid (CDCA), while CDCA is further metabolized into beta-muricholic acid (betaMCA) in mice^[41]. Primary BAs are conjugated mainly to glycine or taurine before getting secreted in the gall bladder, along with phospholipids, to form bile salts. These are released in the duodenum to facilitate emulsification and absorption of lipids and fat-soluble vitamins. BAs are de-conjugated by microbial bile salt hydrolases (BSH) before getting reabsorbed in the terminal ileum and recirculated back to the liver. Around 5% of primary BAs escape reabsorption and transit to the colon, where anaerobic bacteria, particularly Gram-positive bacteria belonging to the Clostridium cluster XI and XIVa, convert them through 7alpha-dehydroxylation into secondary BAs, namely DCA and lithocholate (LCA), which are transported back to the liver via the enterohepatic circulation^[42]. BAs are considered hormones that regulate host metabolism and contribute to the shaping of host immunity^[43]. Their production is tightly regulated by BA receptors, FXR and TGR-5 (Takeda G protein Receptor 5)^{[44][45]}. For instance, through endocrine production of fibroblast growth factor (FGF19 and FGF15 in mice), FXR limits de novo BA synthesis in the liver through suppression of CYP7A1 transcription in hepatocytes^[46]. Several studies have

reported dysregulated BA metabolism associated with microbiota dysbiosis in liver diseases [47] and HCC [16]. By reducing the expression of BA transporters, liver inflammation was shown to result in intrahepatic retention of BAs that directly promote HCC proliferation [16]. In an ethanol-induced mouse model of ASH, reduced FXR activity and FGF15-mediated inhibition of Cyp7a1 promoted liver injury [48]. Similarly, in a murine model of NASH, antibiotics treatment suppressed HCC and reduced the levels of secondary BAs in the liver, implicating these in tumorigenesis, potentially through mTOR activation in hepatocytes [18]. In addition, secondary BAs were shown to impair antitumor immunity mediated by NKT cells, by decreasing the production of the NKT chemokine CXCL16 by LSECs [49] (**Figure 2**). Different strategies aimed at restoring BA homeostasis, such as treatment with FXR agonists or FGF19 [48] or BA sequestrants [39], have shown efficacy in improving liver diseases in mouse models. More recently, the role of this biliary network in regulating the Th17-Treg balance in the gut has been described [50][51].

Short Chain Fatty Acids. SCFAs, which are produced by bacterial fermentation of dietary fibers, have been recently implicated in HCC. SCFAs, including butyrate, propionate and acetate, are generally associated with metabolic health [52]. For instance, in a randomized controlled trial that administered the fermentable fiber inulin coupled to a propionate ester to overweight adults reported decreased abdominal adiposity, lipid accumulation in the liver and body weight gain compared to controls receiving inulin alone [53].

This effect could be mediated by enhanced fat acid oxidation and energy metabolism, as shown in a second trial in which a mixture of SCFAs was infused in the colon of overweight or obese men [54]. Butyrate and propionate production are also altered in ALD. The reduction of butyrate is associated with a weakness of intestinal permeability, while the administration of butyrate in the form of tributyrin reduced intestinal permeability and subsequent liver injury in ethanol-fed mice [55]. However, this notion has been recently challenged by the group of Vijay-Kumar, who showed that large amounts of SCFA, particularly butyrate in a context of dysbiosis, may instead create a tumor-promoting environment. They reported that, while inulin protected mice from obesity, a longer period of inulin feeding, i.e., over 6 months, promoted cholestatic HCC in 40% of TLR5-deficient mice with a pre-existing dysbiotic microbiota [56]. Soluble-fiber-induced HCC was shown to be microbiota-dependent and transmissible to wild-type (WT) mice in cohousing or cross-fostering experiments. More importantly, interventions that deplete butyrate-producing bacteria, e.g., with metronidazole, inhibit gut fermentation, e.g., via supplementation of plant-derived -acids, exclude soluble fiber from the diet, or prevent enterohepatic recycling of BAs with cholestyramine reverted inulin-induced HCC in these mice [56].

Choline. Another host-microbiota-controlled metabolite is the macronutrient choline. Choline processing into phosphatidylcholine by the host prevents steatosis. Indeed, feeding mice a choline-deficient diet is a classical model of NASH. Alternatively, choline can be converted into trimethylamine (TMA) by intestinal bacteria, and it is then further metabolized in the liver into trimethylamine-N-oxide (TMAO). In contrast to phosphatidylcholine, TMAO is at the origin of hepatic steatosis by promoting triglyceride accumulation (**Figure 2**). Increased systemic circulation of TMAO is associated with a reduced level of phosphatidylcholine, and this imbalance is characteristic of patients with NAFLD [57] and NASH [58][59].

Ethanol. Ethanol metabolism greatly impacts HCC development through different mechanisms. The commensal microorganisms express genes that can ferment dietary sugars into ethanol that is absorbed by the gastrointestinal tract by simple diffusion. Moreover, liver cells, enterocytes and gut microbiota components express alcohol dehydrogenase, which co-metabolizes ethanol into toxic acetaldehyde that is then converted by CYP2E1—if this pathway is not saturated—to acetate. Acetaldehyde has been involved in weakening tight junctions of the intestinal epithelial barrier ^[23], eliciting gut barrier permeability and enabling translocation of microbial products, as shown in ethanol-fed mice ^[60]. In addition, ethanol exacerbates oxidative stress and hepatic inflammation and is a known carcinogen ^[61].

6. Conclusion

While much progress has been made in this field, for instance, in cataloguing enriched or depleted microorganisms in health versus disease, we now need to move to next-generation studies of the functional microbiome in order to be able to design microbial strategies to counter liver diseases and HCC.

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