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REVIEW

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# Recent updates on the role of the gut-liver axis in the pathogenesis of NAFLD/NASH, HCC, and beyond

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**Abstract**

The gut and the liver are anatomically and physiologically connected, and this connection is called the "gut-liver axis," which exerts various influences on liver physiology and pathology. The gut microbiota has been recognized to trigger innate immunity and modulate the liver immune microenvironment. Gut microbiota influences the physiological processes in the host, such as metabolism, by acting on various signaling receptors and transcription factors through their metabolites and related molecules. The gut microbiota has also been increasingly recognized to modulate the efficacy of immune checkpoint inhibitors. In this review, we discuss recent updates on gut microbiota-associated mechanisms in the pathogenesis of chronic liver diseases such as NAFLD and NASH, as well as liver cancer, in light of the gut-liver axis. We particularly focus on gut microbial metabolites and components that are associated with these liver diseases. We also discuss the role of gut microbiota in modulating the response to immunotherapy in liver diseases.

## INTRODUCTION

Approximately 500 species of microbes exist in symbiotic relationships with their host in the human gastrointestinal tract. The gut microbiota is useful for the host owing to the fermentation ability of nondigestible substrates, such as dietary fibers. This fermentation ability also contributes to the maintenance of microbiota that produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, in the gut.[1] In addition, the gut microbiota produces various metabolites, such as secondary bile acids (BA) and indols.[2] Moreover, gut microbiota can chemically modify or degrade intestinal substances.[3] Gut microbiota also affects the innate immune system by binding to innate immune receptors, such as Toll-like receptors (TLRs),[4] as well as the adaptive immune system by being recognized by intestinal IgA, thereby contributing to homeostasis of the gut microbiota.[5,6]

Recent findings indicate that the influence of the gut microbiota extends beyond the gut itself, affecting distant organs as microbial metabolites and bacterial components circulate throughout the body through

**Abbreviations**: α-SMA, α-smooth muscle actin; AhR, Aryl hydrocarbon receptor; BA, bile acid; COX-2, cyclooxygenase 2; DBMA, 7,12-dimethylbenzathracene; DCA, deoxycholic acid; FMT, fecal microbiota transplantation; GPCR, G protein-coupled receptor; HFD, high-fat diet; ICI, immune checkpoint inhibitors; LPS, lipopolysaccharide; LSECs, liver sinusoidal endothelial cells; LTA, lipoteichoic acid; MAMPs, microbe-associated molecular patterns; NO, nitric oxide; PAMP, pathogen-associated molecular patterns; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; $PGE_2$, prostaglandin E2; SASP, senescence-associated secretory phenotype; SCFA, short-chain fatty acid; TLR, toll-like receptor; TMA, Trimethylamine; TMAO, Trimethylamine N-oxide.

the blood. Most of these substances are absorbed from the gut, transported to the liver through the portal vein, and influence liver function. This axis is called the "gut-liver axis" and is increasingly being recognized as an important pathway for the onset and progression of liver diseases.[7] Because the liver is continuously exposed to these gut-derived factors, enteric dysbiosis could be directly associated with liver diseases. Absorbed substances from the gut first reach the hepatic sinusoids from the portal vein. In the sinusoidal area, liver sinusoidal endothelial cells (LSECs), specialized vascular endothelial cells, are lining the sinusoids where portal blood flows. HSCs, which become myofibroblasts when activated, reside in the space of Disse between hepatocytes and LSECs. In addition, tissue-resident macrophages, called KCs, as well as various types of immune cells, are present in the hepatic sinusoids and maintain liver homeostasis.[8,9]

In this review, we discuss recent advances in our understanding of the pathogenesis and mechanisms in the development of liver diseases, including NAFLD, NASH, and NAFLD/NASH-associated HCC, in light of the gut-liver axis. We particularly focus on gut microbial metabolites and components that are associated with these liver diseases (Figure 1). In addition, the association between gut microbiota and immune cells affecting the efficacy of antitumor immunity is also discussed.

## BARRIERS TO THE LIVER

### Gut barrier

Dysfunction of the gut barrier is thought to be caused by intestinal epithelial cell damage due to tissue-damaging diets, such as alcohol and a long-term high-fat diet. The intestinal epithelial barrier consists of tight junction proteins, including claudin-1, occludin, and ZO-1,[10,11] and barrier dysfunction is correlated with the down-regulation of tight junction proteins. Gut barrier dysfunction is known to lead to not only the hepatic accumulation of gut microbiota-derived substances through the portal vein but also systemic increase after passing through the liver.[12]

### LSEC barrier

LSECs are located in the sinusoidal area of the liver, composing an important barrier in the liver. Unlike other capillary vessels, LSECs lack an organized basement membrane and have cytoplasm that is penetrated by open fenestrae, which enables direct communication between HSCs as well as hepatocytes in the space of Disse to access oxygen and nutrients from the blood.[13,14] Moreover, LSECs are also known to act as antigen-presenting cells, regulating immune homeostasis by the release of cytokines to modulate immune cell activity.[15,16] In this context, LSECs play a role as efficient scavenger cells,[17] participating in the clearance of Ags reaching the liver sinusoid from the gut and contributing to the liver homeostasis collaborating with KCs.[18,19] Recently, we reported that LSECs form an intracellular gap that is caused by the destruction of fenestrae under pathological conditions. The intracellular gap formation has been found to contribute to liver metastasis of cancer cells.[20] It is one of the barrier dysfunctions in the liver and could be formed in various liver pathologies.

## MICROBIAL-ASSOCIATED MOLECULAR PATTERNS (MAMPs) AND PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs): INNATE IMMUNE RESPONSES IN LIVER DISEASES

Gut microbiota provides MAMPs and PAMPs, which are small molecular motifs in microbes that are not present in the host. They are recognized by innate immune receptors, such as TLRs and other pattern recognition receptors in the host, which trigger innate immune responses.[4] The hepatic transfer of microbiota-derived MAMPs and PAMPs contributes to the alteration of the liver immune microenvironment, leading to the development of chronic inflammation and sometimes eventually, HCC. Gut microbial alterations, particularly small intestinal bacterial overgrowth syndrome, are often observed in chronic liver diseases.[21] In patients with NAFLD and NASH, *Escherichia coli*-derived lipopolysaccharides (LPS) have been reported to be abundant in the gut.[22]

### Lipopolysaccharides

LPS are the main components of the outer membrane of gram-negative bacteria and have been well studied as MAMPs and PAMPs in the gut microbiota. LPS consists of lipid A attached to a core oligosaccharide and an O-Ag saccharide. Structural differences in lipid A alter the severity of LPS-mediated inflammation.[23,24] LPS is recognized by TLR4, which activates NF$\kappa\beta$-mediated proinflammatory signals. We describe below LPS-mediated liver diseases.

#### Effects of LPS on alcohol-associated liver disease

Alcohol-associated liver disease (ALD) is a liver damage-associated liver disease caused by excessive alcohol consumption. It reveals to develop liver steatosis,

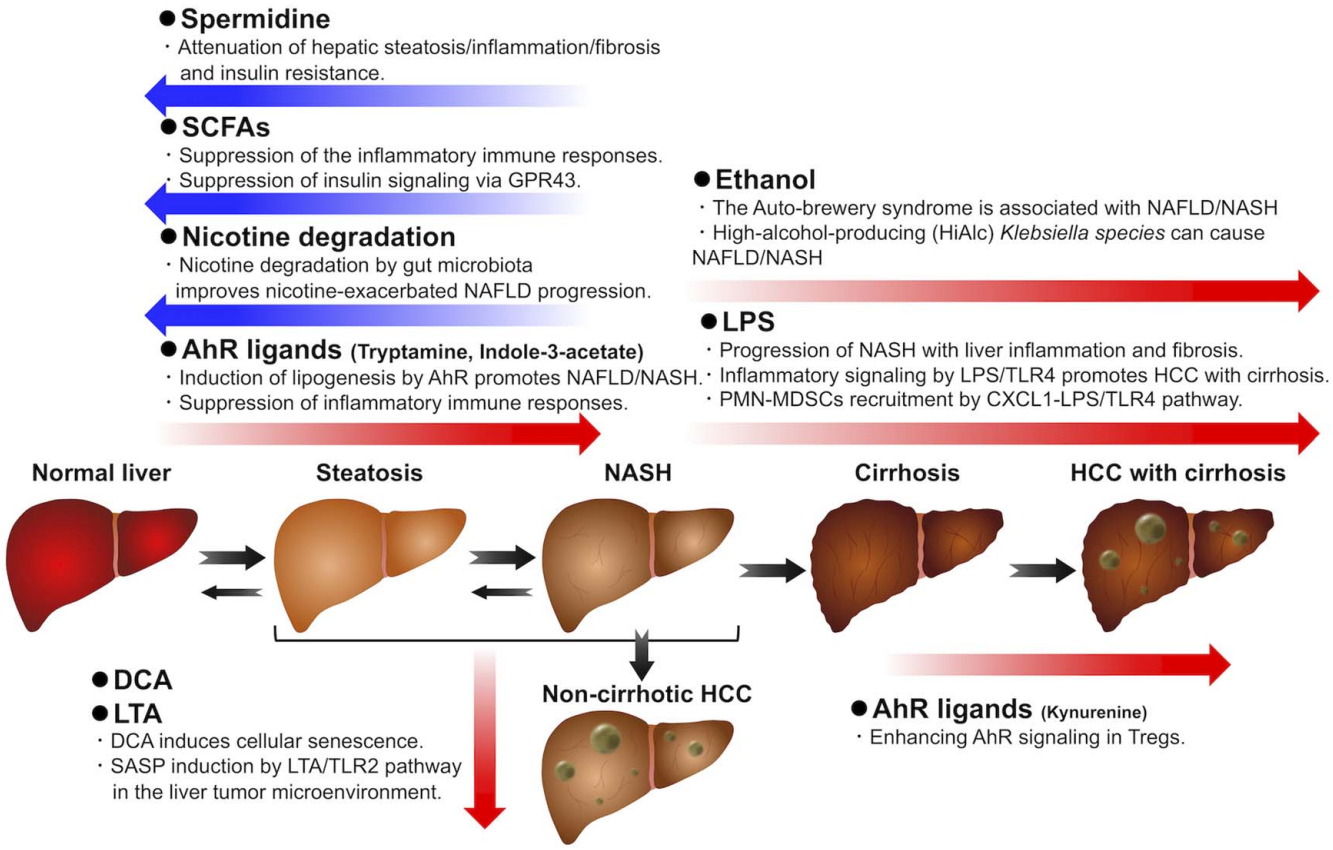


**FIGURE 1** Gut microbial metabolites and components that could drive the progression of NAFLD/NASH and HCC. Red arrows indicate the progression of diseases. Blue arrows indicate the alleviation of diseases, as shown. Abbreviations: AhR, Aryl hydrocarbon receptor; DCA, deoxycholic acid; LPS, lipopolysaccharide; LTA, lipoteichoic acid; SCFA, short-chain fatty acid.

steatohepatitis, cirrhosis, and HCC.[25] In addition to direct liver damage caused by the increase of acetaldehyde, alchol-associated metabolite by aldehyde dehydrogenase, alcohol intake strongly damages intestinal epithelial cells to create leaky gut, where gut microbial components, such as LPS, can easily translocate to the liver. This serum endotoxin (mainly LPS) and bacterial translocation contributed to systemic inflammation, hepatocyte injury, hepatocyte death, and, subsequently, acute liver injury through the gut-liver axis.

## Effects of LPS on NAFLD/NASH

Many reports have suggested that LPS is associated with NAFLD/NASH progression. Small intestinal bacterial overgrowth is frequently observed in patients with NAFLD/NASH and is often associated with increased serum LPS levels due to the increased growth of *E. coli*, which serve as a source of LPS.[26] Moreover, continuous low-dose exposure to LPS in the liver upregulates CD14 expression in KCs and increases sensitivity to LPS in a high-fat diet-induced fatty liver model.[27] LPS-mediated inflammatory signaling has been shown to accelerate the progression of NASH with liver inflammation and fibrosis.[28]

KCs residing in the sinusoid play a protective role against NAFLD and NASH by the clearance of gut-derived components such as LPS. Consistent with such a role, KCs are predominantly found in the peri-portal regions of the liver, where the intestinal blood enters the liver. The reduction or loss of the resident KC population has been observed in a series of liver diseases, including NAFLD and NASH, partly because of the increased lipotoxicity.[29] Moreover, KCs have been recently suggested to be protective in NASH pathogenesis through the clearance of gut-derived microbial DNA containing extracellular vesicles from the blood by inhibiting cGAS/STING-mediated inflammatory responses, an innate immune sensor that recognizes aberrant cytoplasmic DNA fragments (derived from pathogens such as bacteria and viruses, and damage-associated micronuclei and mitochondria), in a mouse model.[30]

An interesting study also recently described the relationship between LPS and NAFLD in humans.[22,31] LPS is partially metabolized by hepatocytes and is usually detected in the blood at concentrations between 10 and 200 pg/mL.[32] Systemic LPS levels are higher in patients with liver disease than in healthy individuals,[33] indicating that LPS is also cleared in hepatocytes, and this ability is reduced in patients with liver disease.

Interestingly, patients with NASH have higher serum LPS levels and hepatocyte-localized LPS than healthy individuals. Serum LPS levels correlate with serum zonulin levels, whose increase reflects decreased gut barrier function. Zonulin is an important tight junction regulator of intestinal epithelial cells, which is thought to play a key role in maintaining gut barrier integrity.[34] Liver biopsies of patients with NASH also show a higher percentage of TLR4-positive platelets. This suggests that *E. coli*-derived LPS accelerates liver injury by inducing platelet activation through TLR4.[22] Platelet accumulation in the liver has also been shown to exacerbate NASH and promote NASH-associated HCC.[35,36] The activation of TLR4-positive platelets and their function in response to LPS is scientifically interesting but remains to be further investigated.

### Effects of LPS on liver cancer

The hepatic translocation of LPS due to gut barrier dysfunction results in persistent low-level inflammation in the liver. Dapito et al. reported that persistent inflammatory signaling by LPS/TLR4 promotes HCC in a diethylnitrosamine plus carbon tetrachloride-induced mouse liver cancer model.[37] Recently, it was reported that cholangiocarcinoma progression associated with primary sclerosing cholangitis is also accelerated by LPS, indicating that LPS could be involved in the suppression of antitumor immunity in both cases.[38] Gut barrier dysfunction is frequently observed in patients with primary sclerosing cholangitis. Enterobacteria such as *Klebsiella pneumoniae*, which are often observed in patients with primary sclerosing cholangitis, have been shown to have a strong ability to damage the intestinal epithelium, which may lead to gut barrier dysfunction and an increase in LPS in the liver.[39] Increased LPS induces CXCL1 expression in hepatocytes in a TLR4-dependent manner, which recruits suppressive immune cells, polymorphonuclear (PMN)-myeloid-derived suppressor cells (MDSCs), a subset of MDSC, to the liver. Polymorphonuclear-MDSCs suppress antitumor immunity in the cholangiocarcinoma microenvironment, thereby promoting cancer progression. Treatment with antibiotic neomycin has been shown to suppress CXCL1 levels, polymorphonuclear-MDSC accumulation, and tumor growth.[38]

## Lipoteichoic acid (LTA)

LTA is a major component of the cell walls of gram-positive bacteria. Gram-positive bacteria have an inner membrane and a thick outer peptidoglycan layer, and LTA extends from the inner membrane to the outer peptidoglycan wall. LTA is recognized by the innate immune receptor TLR2, which forms heterodimers with TLR1 or TLR6,[40,41] thereby triggering inflammatory responses. LTA has also been reported to be associated with chronic liver inflammation and cancer.[42,43] LTA could also be involved in ALD and NASH-associated hepatitis through its translocation to the liver.

### Induction of senescence-associated secretory phenotype (SASP) by the LTA/TLR2 pathway in the liver tumor microenvironment

The LTA/TLR2 innate immune pathway is associated with inflammation.[40,41] Here, we introduce our study the tumor-promoting role of the SASP in HSCs in the tumor microenvironment through TLR2-mediated signaling. In a high-fat diet (HFD)-induced hepatocarcinogenesis mouse model with histology similar to that of human NASH-associated HCC (in particular, steatohepatitc HCC showing high accumulation of lipids in the tumor) characterized by increased LTA accumulation in the liver, antibiotic treatment reduced hepatic LTA accumulation, indicating that LTA is derived from the gram-positive gut microbiota increased by the HFD.[44] In addition, the increased number of gram-positive gut bacteria due to long-term HFD produced high levels of deoxycholic acid (DCA), a secondary BA. Increases in DCA and LTA synergistically upregulated the expression of cyclooxygenase 2 (COX-2), the rate-limiting enzyme for prostaglandin production in HSCs in the tumor, and the production of SASP factors in DCA-induced senescent HSCs. This was consistent with the increased expression of TLR2, the receptor for LTA in the HSCs, suggesting that the accumulation of DCA and LTA in the liver activates a positive feedback loop that further promotes the TLR2 signaling pathway. The production of prostaglandin $E_2$ ($PGE_2$) by COX-2 in HSCs suppresses antitumor immunity, thereby promoting HCC progression.[42] The results that the treatment of the antagonist EP4 (one of the $PGE_2$ receptors that express predominantly in immune cells) was effective to prevent HCC development, which further supports the immunosuppression by $PGE_2$. Overexpression of COX-2 and overproduction of $PGE_2$ have been observed in the HSCs in human NASH-associated HCC, particularly in steatohepatitic HCC (Figure 2). Coinciding with these findings, the expression of (NAD(+))-dependent 15-hydroxyprostaglandin dehydrogenase, a $PGE_2$ degrading enzyme, was reported to be reduced in mouse HCC models, suggesting that $PGE_2$ produced by COX-2 may remain to promote liver cancer.[45] Moreover, COX-2 expression is reported to be epigenetically regulated in HCC, and its potential as a prognostic marker has been suggested.[46] On the other hand, other studies reported that transgenic mice expressing COX-2 in hepatocytes revealed a minor contribution to other HCC mouse models, such as chemical diethylnitrosamine (DEN) and other genetic mouse models.[47,48] Therefore, the role of COX-2 in HCC

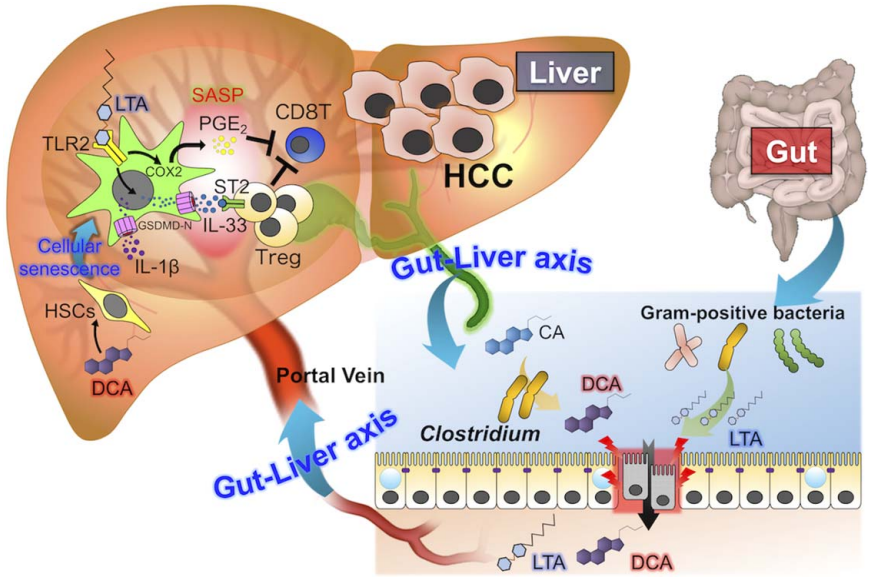


**FIGURE 2** Gut-microbially produced deoxycholic acid and lipoteichoic acid are translocated to the liver and provoke cellular senescence of HSCs and senescence-associated secretory phenotype (SASP). Senescent HSCs produce SASP factors, such as $PGE_2$, IL-33, and IL-1β. $PGE_2$ directly suppresses CD8T cells, and IL-33 activates ST2-positive Treg cells to suppress ant-tumor immunity. Abbreviations: COX-2, cyclooxygenase 2; DCA, deoxycholic acid; LTA, lipoteichoic acid; $PGE_2$, prostaglandin $E_2$; SASP, senescence-associated secretory phenotype; TLR2, Toll-like receptors2.

may be more complex and context-dependent. Additional research will be necessary to fully elucidate the role of COX-2 in HCC and to develop effective therapeutic strategies targeting this pathway.

In our recent study, moreover, we showed that LTA accumulated in the liver triggered the release of SASP factors, including IL-33 and IL-1β, through the gasdermin D N-terminus pore, which was cleaved by LTA-induced caspase-11. Gasdermin D is a pore-forming protein and is well-known as an executor of pyroptotic cell death activated and processed by caspase-1 or caspase-11.[49,50] We showed that senescent HSCs are quite resistant to pyroptotic cell death even under the LTA-induced caspase-11 induction and that IL-33 release from HSCs promoted HCC development through the activation of ST2 (IL-33 receptor)-positive Treg cells in the liver tumor microenvironment. Accumulation of the Gasdermin D N-terminus has also been detected in HSCs from human NASH-associated HCC patients, suggesting that a similar mechanism could be involved in a NASH-associated HCC (Figure 2).[43]

## GUT MICROBIAL METABOLITES AND LIVER DISEASES

### BAs: a general overview

BAs are steroidal skeletal molecules synthesized from cholesterol in the host liver.[51] BAs contribute to nutritional lipid absorption by means of micelle formation. Some BAs are known to be ligands for nuclear receptors, such as farnesoid X receptor (FXR), pregnane X receptor (PXR), constitutive androstane receptor (CAR) and vitamin D receptor (VDR), and vitamin D receptors, which function as transcription factors after the ligation of BAs. BAs also bind to Takeda-G-protein-receptor-5 (TGR5) (also known as GPBAR1 or M-BAR), a G protein-coupled receptor (GPCR). In contrast to nuclear receptors, GPCRs are localized on the plasma membrane and function as signaling molecules that regulate metabolism.[52] Signaling by the BA-activated transcription factor, farnesoid X receptor, is important for liver homeostasis, including gene expression regulation related to BA synthesis.[53,54] Farnesoid X receptor upregulates SHP to suppress CYP7A1 and reduces bile synthesis.[53,54]

Normal levels of DCA found in healthy individuals play a role in the elimination of pathogenic microorganisms.[55] The gut microbiota synthesizes secondary BAs by modifying primary BAs synthesized in the liver, including dehydroxylation, oxidation, and desulfurization, and more than 50 chemically distinct secondary BAs are currently known to be produced by gut microbiota.[56] BAs produced in the liver are excreted into the duodenum but are then reabsorbed from the ileum and returned to the liver, forming the enterohepatic circulation. This enterohepatic circulation results in sustained exposure of BAs to the liver, and BAs contribute to the homeostasis of both the liver and gut.

#### Novel function of bacterially modified secondary BAs

As mentioned in section 1.2.1 on LTA, we reported that DCA induces cellular senescence and the SASP in

HSCs to form an HCC-promoting microenvironment through persistent secretomes. In humans, DCA and lithocholic acid are produced from the primary BAs, cholic acid, and chenodeoxycholic acid, respectively, through 7α-dehydroxylation by gut microbiota.[51]

Secondary BAs have been known to have detergent activity and are cytotoxic and carcinogenic. Recently, various modified forms of lithocholic acid have been found to exert anti-inflammatory effects[57,58] and are associated with longevity.[59] 3-oxo-lithocholic acid has been shown to strongly suppress Th17 activity,[57,58] and iso-allo-lithocholic acid increases Treg activity.[57,58] These modified forms of lithocholic acid suppress colitis in a colitis mouse model.[57,58] Interestingly, Sato et al showed that iso-allo-lithocholic acid is abundant in the intestines of centenarians compared with younger individuals, suggesting that iso-allo-lithocholic acid-producing bacteria are associated with healthy longevity.[59] This modified form of lithocholic acid is produced by a pathway distinct from the 7α-dehydroxylation of primary BAs.[59]

## Bacterially produced fatty acids

It is well-known that gut microbiota produces SCFAs, including acetate, propionate, and butyrate, in the gut through the anaerobic fermentation of dietary fibers.[60] SCFAs have been suggested to prevent inflammation and obesity. The anti-obesity and anti-inflammatory effects of SCFAs are also associated with the prevention of NAFLD and NASH progression. Recently moreover, it was reported that gut microbiota produces an anti-obesity long-chain fatty acid called 10-hydroxy-cis-12-octadecenoic acid, which is bacterially produced from linoleic acid.[61]

### Short-chain fatty acids (SCFAs)

SCFAs are the end products of the anaerobic bacterial fermentation of dietary fiber in the gut and can prevent obesity by increasing energy expenditure. They are converted to acetyl-CoA during β-oxidation, which is then metabolized for energy production. SCFA treatment results in the inhibition of AMPK by AMP depletion and the activation of mTOR, which, in turn, increases the glycolytic activity of cells.[62,63] Moreover, SCFAs exert anti-inflammatory effects and can act as histone deacetylases inhibitors, thereby facilitating Treg cell activation.[64] In addition, butyrate inhibits the expression of proinflammatory cytokines such as TNF-α, IL-6, and IL-12 produced by neutrophils and monocytes.[65] Moreover, SCFAs directly exert anti-inflammatory effects by stimulating peroxisome proliferator-activated receptor-γ[66] and activating GPCR (eg, GPR41, GPR43, and GPR109a). SCFAs-GPCR interaction also contributes to the prevention of obesity. GPR41 is expressed in the sympathetic ganglia of mice and humans, and propionate promotes sympathetic outflow through GPR41.[67] Moreover, the SCFA receptor, GPR43, in adipocytes, is activated by SCFA to suppress insulin signaling, thereby inhibiting fat accumulation in adipose tissues.[68] These actions of SCFA seem to be effective in alleviating NAFLD and NASH in mice and humans.[69–71]

### Bacterially modified long-chain fatty acids

Gut microbiota has been reported to contribute to resistance to HFD-induced obesity by modifying dietary long-chain fatty acid metabolism. 10-hydroxy-cis-12-octadecenoic acid is a linoleic acid-derived gut microbial metabolite that attenuates HFD-induced obesity in mice by improving metabolic conditions. Several Lactobacillus species, such as *Lactobacillus plantarum, Lactobacillus salivarius,* and *Lactobacillus gasseri,* can reportedly produce 10-hydroxy-cis-12-octadecenoic acid.[61]

## Trimethylamine (TMA) and Trimethylamine N-oxide (TMAO)

The gut microbiota metabolizes methylamine-containing nutrients such as choline, lecithin, and L-carnitine to generate TMA, which is processed into trimethylamine N-oxide (TMAO) by flavin monooxygenases in the liver. Circulating TMAO levels are correlated with the risk of cardiovascular diseases[72] and NASH in type 2 diabetes patients.[73] TMAO and choline levels were significantly associated with NAFLD histological features and NASH risk, particularly in type 2 diabetes patients.

## Bacterially produced Ethanol

Ethanol is produced in the gut through the fermentation of glucose by microbes, including yeasts and several microbial species, such as *Candida species, Saccharomyces cerevisiae*, *K. pneumoniae, E. coli*, and so on.[74] In the liver, ethanol is primarily metabolized to acetaldehyde by alcohol dehydrogenase and subsequently to acetate by aldehyde dehydrogenase. Serum alcohol concentration is reportedly higher in adult patients with NAFLD and NASH than in healthy controls,[75,76] suggesting that endogenous ethanol production is associated with NASH pathology. Some individuals with severe NASH were found to be auto-brewery syndrome (or gut fermentation syndrome).[77] Some strains of *K. pneumoniae* were isolated and identified from the patient and were shown to have various alcohol-producing activities, suggesting a strong association between NASH and endogenous alcohol production.[77] More recently, a cohort study

focusing on high-alcohol-producing *K. pneumoniae* has been performed,[78] and the same group suggested the effectiveness of bacteriophage therapy targeting the high-alcohol-producing *K. pneumoniae* in mouse models.[79] Therefore, the results of these studies suggested that NASH, and NAFLD in general, may be induced by endogenous alcohol production by intestinal bacteria. However, further investigation regarding the effects of endogenous ethanol production by gut bacteria on the progression of NAFLD and NASH, as well as NASH-associated HCC, may be required.

## Aryl hydrocarbon receptor (AhR) and the gut-liver axis-mediated liver diseases

AhR is a ligand-activated transcription factor that regulates a variety of biological processes, including suppression of immune cell activities and cancer progression. A variety of AhR ligands, including dioxins, kynurenine, and indole-3-carbinol, have been identified; the gut microbiome is a major source of endogenous AhR ligands.[80] Certain commensal bacteria, for example, *Lactobacillus reuteri*, produce tryptophan-derived AhR ligands that suppress inflammatory immune responses in the gut.[81] Gut microbial dysbiosis could be associated with the pathogenesis of NAFLD/NASH, and it has been reported that the levels of the AhR ligands tryptamine and indole-3-acetate are decreased in HFD-fed mice. These AhR ligands suppress the production of inflammatory cytokines, such as TNF-α and IL-1β. Moreover, indole-3-acetate suppresses the expression of AhR-regulated lipogenic enzymes, fatty acid synthase, and the cholesterol metabolism regulator sterol regulatory element-binding protein-1c in hepatocytes,[82] contributing to the prevention of NAFLD/NASH.

In contrast, kynurenines, constitutively produced within the liver by the hepatocyte-specific enzyme tryptophan-2,3-dioxygenase (TDO), are thought to be tumor-promoting AhR ligands.[83] Kynurenine-mediated AhR activation induces immunosuppression of both T cells and Ag-presenting cells.[84] Likewise, the induction of kynurenine-producing indoleamine-2,3-dioxygenase-1 (IDO-1) in HSCs leads to enhanced AhR signaling in Tregs, which suppresses antitumor immunity.[85] These endogenous AhR ligands appear to strongly contribute to tumor immune escape. Increased AhR expression, together with increased kynurenine production, can result in sustained AhR activation and perpetuation of a protumorigenic immunosuppressive microenvironment.[86] IDO-1 knockout mice show significantly lower tumor burden than wild-type mice, which overexpress IDO-1 and L-kynurenine in HCC. Interestingly, the immune checkpoint molecule programmed death-ligand 1 (PD-L1) is an AhR target gene.[87] In line with these findings, the expression of AhR, together with IDO-1, kynurenine, and PD-L1, has been shown to correlate with poor prognosis in patients with HCC.[87]

## Nicotine-degrading gut microbiota alleviate NASH

Smoking is positively correlated with NAFLD/NASH.[88] Recently, beneficial nicotine-degrading gut microbiota has been reported to alleviate NASH.[3,89] This report suggests that nicotine accumulates in the gut during smoking and activates intestinal AMPKα. *Bacteroides xylanisolvens* effectively degrades nicotine, thereby improving nicotine-exacerbated NAFLD progression. AMPKα promotes the phosphorylation of sphingomyelin phosphodiesterase 3, by stabilizing and increasing intestinal ceramide levels, which contribute to the NAFLD to NASH progression. These findings suggest that the use of *B. xylanisolvens* may reduce smoking-induced NAFLD progression.

## Spermidine

The natural polyamine spermidine, a well-known autophagy inducer, has recently emerged as an important substance that maintains cellular and physical homeostasis. Spermidine can be administered orally and is also produced by commensal gut bacteria. The intestinal luminal concentration of spermidine critically depends on the gut microbiota.[90] The benefits of spermidine include lifespan extension, neuroprotection, and anti-tumorigenic effects. Spermidine is also used for posttranslational hypusination of the translation factor EIF5A.[91]

Recently, spermidine was reported to alleviate NASH. A study reported spermidine-mediated hypusination of the translation factor EIF5A as a mechanism for alleviating NASH.[92] The hypusination of EIF5A improves mitochondrial fatty acid oxidation and prevents NASH progression. The study showed that the mRNA expression of hepatic deoxyhypusine hydroxylase, which catalyzes the hypusination of the translation factor EIF5A, as well as the levels of hypusinated EIF5A are decreased in patients and mice with NASH. The decrease in hypusinated EIF5A correlated with decreased mitochondrial activity and fatty acid β-oxidation. Spermidine treatment restored hypusinated EIF5A levels, partially recovered protein synthesis and mitochondrial function in NASH, and prevented NASH progression in vivo.[92]

Another study showed that serum and fecal spermidine levels negatively correlate with NASH phenotypes in humans. Spermidine supplementation significantly attenuated hepatic steatosis/inflammation/fibrosis and insulin resistance in Western-diet-induced NASH model mice, suggesting that spermidine may be a potential therapeutic supplement for NASH. Mechanistically, spermidine ameliorates NASH through thyroid hormone-responsive protein signaling, which has recently been focused on in clinical trials as a promising signaling pathway for the treatment of NASH.[93]

## GUT MICROBIOTA AND ANTITUMOR IMMUNITY

Finally, we discuss the link between gut bacteria and antitumor immunity, which has gained attention recently owing to its emerging role in regulating antitumor immunity. Immune checkpoint inhibitors (ICIs) have increasingly been recognized to be useful in many types of cancers. However, ICIs are ineffective in NASH-associated HCC, suggesting impaired cancer immune surveillance.[94] This report showed that distinct $CD8^+$ T cells helped induce NASH-HCC by $CD8^+PD\text{-}1^+CXCR6^+$T cells in a mouse model.[94] A meta-analysis of 3 randomized phase III clinical trials that tested inhibitors of PD-L1 or PD-1 in more than 1600 patients with advanced HCC revealed that ICI immune therapy did not improve survival in patients with nonviral HCC.[94] Therefore, there is an urgent need for suitable therapeutics for NASH-associated HCC.

In recent years, several studies have shown that gut microbiota can modulate antitumor responses during ICI treatment.[95] Although the effect of the gut microbiota on ICI efficacy has been investigated well in malignant melanoma, this strategy is increasingly being attempted for other types of cancers, such as non-small cell lung cancer,[96] and attempts to treat many other cancers are strongly anticipated. Antibodies against the immunosuppressive molecule PD-1 and its ligand PD-L1, as well as CLTA4, have been used as ICIs to activate antitumor effects. Recently, some gut bacteria have been shown to enhance the efficacy of ICIs[97]

ICI responder melanoma patients reportedly have abundant *Ruminococcaceae* species in their gut,[98] and epithelial cell cancer patients, including colorectal and non-small cell lung cancer patients, reportedly have abundant *Akkermansia* species in their gut.[99] Germ-free mice subjected to fecal microbiota transplantation (FMT) from ICI responder melanoma patients showed remarkable antitumor effects.[98]

Recently, 2 clinical trials evaluated the safety and feasibility of ICI administration in patients with anti-PD-1 antibody-resistant malignant melanoma, in addition to FMT from ICI responders with malignant melanoma. In one trial, 3 of 10 patients,[100] and in another, 6 of 15 patients showed increased ICI efficacy.[101] Specifically, treatment with FMT resulted in antitumor changes, including increased $CD8^+$ T cell activation. These results suggest that ICI resistance can be overcome by altering the gut microbial profile.

These studies suggest that FMT affects the response to ICIs, perhaps because gut bacteria act as adjuvants that activate antitumor immunity. It has been suggested that certain *Enterococcus* muropeptides (a type of LTA) may enhance the effects of ICIs.[102] Recently, CBM588, a bifidogenic live bacterial product, has been reported to augment the ICI response in kidney cancer by modulating the gut microbiome.[103]

## FUTURE PERSPECTIVES

The gut microbiota has been shown to influence the pathogenesis of distant organs by circulating bacterial components and metabolites. This review focuses on the gut-liver axis-mediated effects of bacterial components and metabolites on the development of liver diseases and cancer (Figure 1). The evidence that gut microbial factors promote liver disease strongly suggests that gut barrier dysfunction is an important predisposing factor in the development and progression of liver cancer.

Recent developments in next-generation sequencing technology have led to significant advances in the computational analysis of data on liver diseases. However, the functions of many gut microbial metabolites remain unknown. In the future, clarification of the functions of gut microbial metabolites will promote our understanding of the onset and prevention of liver diseases.

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### CONFLICTS OF INTEREST

The authors have no conflicts to report.

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