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Gut microbiota in non-alcoholic fatty liver disease and alcohol-related liver disease: current concepts and perspectives

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Abstract

The term gut-liver axis is used to highlight the close anatomical and functional relationship between the intestine and the liver. It has been increasingly recognized that the gut-liver axis plays an essential role in the development and progression of liver disease. In particular, in non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD), the two most common causes of chronic liver disease, a dysbiotic gut microbiota can influence intestinal permeability allowing some pathogens or bacteria-derived factors from the gut reaching the liver via the enterohepatic circulation contributing to liver injury, steatohepatitis and fibrosis progression. Pathways involved are multiple, including changes in bile acid metabolism, intestinal ethanol production, generation of short-chain fatty acids, and other by-products. Bile acids act through dedicated bile acid receptors farnesoid X receptor and TGR5 in both the ileum and the liver, influencing lipid metabolism, inflammation, and fibrogenesis. Currently, both NAFLD and ALD lack of effective therapies and therapeutic targeting of gut microbiota and bile acids enterohepatic circulation hold promise. In this review, we summarize current knowledge about the role of gut microbiota in the pathogenesis of NAFLD and ALD, as well as the relevance of microbiota or bile acid-based approaches in the management of those liver diseases.

Keywords

gut-liver axis; cirrhosis; NAFLD; ALD; alcohol; fatty liver; steatosis; microbiota; translocation; bile acids

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INTRODUCTION

The term gut-liver axis highlights the increasingly recognized crosstalk between both organs that are strictly anatomically and functionally related (1-3). The gut and the liver communicate through the biliary tract, the portal vein, and systemic circulation exchanging a myriad of signaling compounds. On the one hand, the liver secretes bile acids and other bioactive mediators and releases them into the biliary tract reaching the intestine, and on the other hand, the intestine signals back to the liver secreting enterokines from the terminal ileum. In addition, in the distal gut, microbiota, which is mainly composed of bacteria and other microbial components such as fungi, have many functional roles in health and disease (such as digestion, vitamins production, resistance to colonization by pathogenic bacteria, and stimulation of the immune system) (4). Gut microbiota composition is modified by diet, alcohol consumption, and medications (antibiotics, probiotics, proton pump inhibitors, etc.) (5, 6). Also, microbiota metabolizes bile acids and amino acids, which are transported to the splanchnic blood vessels to reach the liver. The liver receives 75% of its blood supply through the portal vein, which it comes from the gut carrying both nutrients and microbial products exposing the liver to a multiple types of antigens. Despite the highly specialized intestinal epithelial barrier, some bacteria-derived molecules will enter the enterohepatic circulation reaching the liver and acting on both parenchymal and non-parenchymal cells (7).

It has been increasingly recognized that the gut-liver axis plays critical roles in the pathogenesis and progression of the most common causes of liver disease worldwide, non-alcoholic fatty liver disease (NAFLD), and alcohol-related liver disease (ALD). Gut-liver axis-related events facilitating development and progression of liver disease in both NAFLD and ALD include mainly the occurrence of intestinal dysbiosis, defined as the imbalance between microbial communities leading to disruption of the symbiotic relationship between gut resident microbes and the host, and increased intestinal permeability leading to a pro-inflammatory state (3). The molecular underpinnings of how these phenomena modulate liver disease are still incompletely understood, but significant advances have been made in recent years (8, 9). Dysbiosis and the alteration of the intestinal barrier have been described to act as a disease-drivers in NAFLD and ALD by influencing liver injury (i.e. promoting steatosis, inflammation, and fibrosis) through the modulation of the immune system by multiple mechanisms (10).

The hepatic immune system must balance its responses differentiating between harmless stimuli and dangerous bacterial pathogens, preventing them from reaching the systemic circulation (7, 11). If the latter fails, the subsequent proinflammatory response from pathogen-derived substances may promote the development and progression of chronic liver disease (12). Hence, in order to maintain the homeostasis, a complex interaction must be established between the gut epithelia, the microbiota, the immune system, and the liver. When an imbalance occurs, microbial products translocation drives disease progression. The present review aims to summarize the current knowledge about the role that gut microbiota plays in liver disease, especially in NAFLD and ALD.

Intestinal permeability and microbiota

The highly specialized intestinal epithelial barrier allows the transport of nutrients, but, at the same time, protects against microbial-derived products and pathogens (13). This barrier is composed of a mucus layer that capture bacteria and large molecules avoiding them to reach the epithelium (14); a monolayer of epithelial cells that actively limit the transit of hydrophilic molecules; and finally, the intercellular tight junctions (claudins, occludins, and zonula occludens) that maintain closed the space between cells controlling the passage across the intestinal mucosa. It is known that alcohol, in particular acetaldehyde (a byproduct of the intestinal metabolism of alcohol), can disrupt the intestinal barrier by impairing the integrity and expression of the intercellular tight junctions leading to translocation and endotoxemia (15-18). Alcohol also induces changes in the expression of zonula occludens-1 and claudin-1, impairing the epithelial barrier function (19, 20), similar to the effect produced by pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and interferon-gamma (21, 22).

Dysbiosis and bacterial translocation due to disruption of the intestinal epithelial barrier in patients with advanced chronic liver disease is detrimental in natural history and can lead to serious infections (23). This chronic activation of the immune system by bacterial products perpetuates liver injury and inflammation (24). The immune system identifies bacterial products through recognition of specific pathogen-associated molecular patterns (PAMPs), which are a limited and defined set of conserved molecular patterns carried by all microorganisms of a given class (25), such as lipopolysaccharide (LPS) from gram-negative bacteria. Intraperitoneal LPS administration has shown to increase portal pressure (26-28) and influence intestinal permeability (29, 30). The liver has anti-inflammatory mechanisms to maintain homeostasis and immunotolerance, such as the hepatic antigen-presenting cells that drives the tolerogenic adaptative response (11).

When microbial products reach the liver through the portal vein, activation of membrane-bound Toll-like receptors (TLRs) and the cytoplasmic nucleotide-binding oligomerization domain-like receptors (NLRs) present in both parenchymal and non-parenchymal cells occur. TLRs recognize PAMPs and DAMPs (damage-associated molecular patterns) and trigger the innate immune system activation (i.e. macrophages and dendritic cells) (31, 32), but also activation of hepatic stellate cells and endothelial cells that will amplify the inflammatory and fibrotic response (24, 33). Downstream TLRs activate NF-κB (34), which is constitutively expressed in all cell types and has a pivotal role in the regulation of the inflammatory response in the liver (inducing the release of pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β) and it is known to drive the pathogenetic process in many liver diseases (35-37). Activation of TLRs leads to sterile inflammation and plays a role in the pathogenesis of the non-alcoholic and alcoholic liver disease (31, 38-42).

In patients with cirrhosis, impaired intestinal barrier function leads to microbial products to reach the liver triggering a pro-inflammatory response (43, 44). This has been particularly described in the pathogenesis of alcohol-related liver disease (45, 46), end-stage liver disease, and acute-on-chronic liver failure (ACLF) (47). In advanced cirrhosis, with worsening portal hypertension, there is a dysfunction of the intestinal tight junctions, as well as, intestinal bacterial overgrowth, and changes in microbiota, favoring bacterial

translocation (48). Small intestine bacterial overgrowth (SIBO) also occurs in cirrhotic patients (49) by multiple mechanisms including decreased bile acid secretion and impaired intestinal motility (autonomic neuropathy, inflammatory mediators, dysbiosis, and neuropeptides) (50, 51). Of note, SIBO is commonly seen in patients with cirrhosis with or without intestinal motility dysfunction (52). Cirrhotic patients have a decrease in the beneficial normal microbiota (Lactobacillus, Bifidobacterium, and Bacteroides species), which it can exacerbate liver disease (53). Additionally, there is an increase in Proteobacteria (particularly Enterobacteriaceae), Fusobacterium spp., Veillonellaceae, and Streptococcaceae, which are potentially pathogenic agents, responsible of most cases of spontaneous bacterial peritonitis (54-57).

In order to target gut microbiota in liver disease, non-absorbable disaccharides, such as lactulose and lactitol have been used. However, despite its widespread use, no studies have clearly shown that lactulose leads to significant changes to microbiota composition or function (58). The proposed mechanisms of action of lactulose are: laxative, prebiotic, acidifying and modifying the colonic flora (59, 60). A recent trial assessed the effects of single-dose lactulose ingestion on the growth of intrinsic Escherichia coli. The authors concluded that the ingestion of a single dose of 50 g lactulose does not significantly alter E. coli density in stool samples of healthy volunteers, however, this dose seems unlikely to be sufficient to alter alter gut microbiota (61). Gut microbiota changes after the use of rifaximin has been also evaluated (62, 63). An elegant study by Bajaj *et al.* (64) showed that cirrhotic patients under rifaximin treatment despite having a slight change in microbiota composition, have less endotoxemia and an improvement in cognition. In the same study, rifaximin changed bile acid composition. Recently, a randomized, double-blind, placebo-controlled trial in 54 patients with cirrhosis and ascites showed no effect on hemodynamics (hepatic venous pressure gradient or systemic hemodynamics) (65).

Bile acids and enterohepatic circulation

Bile acids (BAs) are amphipathic steroid molecules synthesized in the liver from cholesterol and excreted into bile as one of its main components. BAs (amino-acyl-conjugates of the primary BAs, cholic acid [CA] and chenodeoxycholic acid [CDCA], and their secondary metabolites) are actively secreted by the hepatocyte into the canaliculus where they serve as the main driving force for bile production by specific transporters (i.e., bile salt export pump, BSEP)(66). Once in the small intestine, BAs function aiding in the emulsification and absorption of dietary fat, cholesterol, and fat-soluble vitamins. After reaching the terminal ileum, BAs are efficiently absorbed (95% recapture) by an active uptake mechanism mediated by the apical sodium bile acid transporter (Asbt). BAs loss in feces are approximately 0.2-0.6 g/day, which is balanced by the daily hepatic synthesis of BAs. In the gut, the primary BAs, CA and CDCA, undergo deconjugation and dehydroxylation by microbiota, resulting in the formation of secondary BAs (i.e., deoxycholic acid [DCA] and lithocholic acid [LCA]) (67). These secondary BAs can be reabsorbed passively and constitute a portion of the total BA pool that cycles in the enterohepatic circulation, a system of exchange between the gut and the liver. (68). As a result of their efficient hepatic extraction, the concentration of BAs in the systemic circulation and peripheral tissues is extremely low, with only small incremental rises in postprandial periods (69). For decades

BA were considered just detergents helping digestion of ingested food, but in last decades BA have emerged as relevant signaling molecules that may act at both hepatic and extrahepatic tissues to regulate both lipid and carbohydrate metabolism as well as energy homeostasis (67, 70). These actions are exercised through activation or modulation of BA receptors, such as the farnesoid X receptor (FXR; also known as NR1H4) and G protein-coupled bile acid receptor 1 (GPBAR1; also known as TGR5), and may be influenced by changes in abundance or activity of BA transporters, such as the Asbt, the sodium-dependent taurocholate polypeptide (NTCP) or the export pump BSEP (66, 67, 71). Bile acids activate FXR in the ileum and liver, leading to the production of fibroblast growth factor 19 (FGF19; FGF15 in mouse). FGF19 is an endocrine, gastrointestinal hormone that suppresses the hepatocyte expression of CYP7A1, a rate-limiting enzyme in the synthesis of BAs, thereby creating a negative feedback loop. Activation of FXR and TGR5 may affect both steatotic and inflammatory responses and therefore influence NAFLD and ALD pathogenesis at multiple levels (72, 73). FGF19 has shown to regulate glucose homeostasis, body weight and alcohol consumption at central nervous system level (74, 75). Of note, dysregulated BA levels have also been found in patients with severe AH (76). Additionally, BAs bind to TGR5 on the plasma membrane and act on tissues beyond enterohepatic circulation. This binding mediates host energy expenditure (77, 78), glucose homeostasis (79), and anti-inflammatory immune responses (80, 81).

There is a close, and the bidirectional interplay between BA metabolism and the gut microbiota and cholestasis may alter intestinal bacterial populations (3, 82). Changes in BA pool composition have been found in ALD patients suggesting that FXR activation may be decreased (83). The role of gut microbiota in controlling BA pool composition has also been recognized as BAs, and gut microbiota have a reciprocal relationship (84-86). Indeed, on the one hand, BAs shape the intestinal microbiome through direct antimicrobial effects and FXR-induced production of antimicrobial peptides and in the other hand gut microbiota modify the BA pool composition through defined enzymatic activities (such as deconjugation, dihydroxylation, oxidation, and epimerization, among others) (87, 88). Additionally, FXR modulates the gut-vascular barrier by regulating the entry sites for bacterial translocation (89). In the setting of NAFLD and ALD, both altered BA metabolism and changes in microbiota composition have been found, which potentially promotes disease development (83, 90-94). Recent studies have explored the effects of ursodeoxycholic acid (UDCA) on gut microbiome composition in healthy subjects and also in individuals with liver dysfunction (95, 96). Interestingly, UDCA influenced bacterial populations inducing a marked decrease in abundance of Bifidobacterium, Lactobacillus, and Lactobacillaceae (95). If these effects have any relevance for the therapeutic action of UDCA, remain to be determined. One interesting recent study showed that the absence of the intestinal microbiota results in exacerbation of liver injury in a murine model of primary sclerosing cholangitis (PSC), the *mdr2*−/− mice (97). This genetically engineered mouse is deficient in the canalicular transporter of phospholipid and has very low levels of biliary phosphatidylcholine, which results in biliary injury. The biliary alterations of this experimental model are similar to those observed in PSC (98). In the study by Tabibian et al. (97), germ-free *mdr2*−/− mice exhibited significantly worse liver chemistry and histological lesions than conventionally housed mice underscoring the importance of commensal

microbiota in protecting against biliary damage. Furthermore, few studies have analyzed the gut microbiome in cholestatic diseases (99, 100). Of note, a significant reduction of within-individual microbial diversity has been found in primary biliary cholangitis (PBC) (101), which is partially relieved by UDCA administration. Similarly, reduced diversity and significant shifts in the microbiome composition have been found in stool samples from PSC patients (102) but is unclear the relationship to the bile secretory failure present in cholestatic diseases. Furthermore, oral microbiota correlates with gut microbiota, and oral dysbiosis influences liver disease (103-108). Collectively, these findings suggest that an imbalance in BAs and gut microbiota elicits a cascade of host immune responses relevant to the progression of liver diseases.

Microbiota and ALD

Gut microbiota modulates ALD, however, the exact mechanisms are not fully understood (67, 109-111). Ethanol is absorbed in the stomach (20%) and small intestine (70%) by simple diffusion (112, 113). The largest portion of ethanol in the intestine comes from the systemic circulation, although microbial fermentation also contributes to luminal ethanol concentration (114).

ALD is characterized by increased levels (both luminal and circulating) of ethanol and its metabolites (115, 116). These high levels promote leaky gut with translocation of bacterial products, triggering inflammatory and adaptative host immune responses. Gut microbiota and enterocytes metabolize alcohol through enzymes such as alcohol dehydrogenase into byproducts like acetaldehyde (117, 118). Once alcohol reaches the liver is also metabolized, and the liver can upregulate its metabolic pathways to adapt to higher concentrations (118, 119).

When there is chronic and high alcohol consumption, ALD can develop. ALD is a consequence of multiple environmental (diet, viral hepatitis, etc.), genetic/epigenetic, immune, and microbiome factors interaction (120-122). Similar to what occurs in NAFLD, the early stage of ALD is characterized by the accumulation of fat within the liver (steatosis), and it can progress to more advanced forms of liver disease with inflammation and liver injury (alcoholic steatohepatitis [ASH]).

During recent years, many studies at the preclinical and experimental level have shed light on the relationship between ALD and gut microbiota. Dysbiosis and SIBO have been demonstrated as relevant disease factors in both human (123, 124) and mouse models (122, 125). Microbiota in subjects with ALD is characterized by marked enrichment of Enterobacteriaceae and reduction of Bacteroidetes and Lactobacillus (56, 125, 126). This phenomenon of dysbiosis is only partially reversible by alcohol withdrawal or probiotic therapy (56, 127). The presence of SIBO has been shown to significantly correlate with a higher prevalence of spontaneous bacterial peritonitis and with the severity of alcohol-related cirrhosis (128). These changes in the gut microbiota of ALD patients seem to be accompanied by changes in colonic pH and liver steatosis (129). It also correlates with a higher level of serum endotoxin and increased intestinal TNF-α levels, as well as increased levels of nitric oxide, IL-6, and IL-8 (2). Another recent discovery is that patients with ALD not only have bacterial dysbiosis but also display reduced fungal diversity as well as

Candida overgrowth (130-133). Indeed, using antifungal agents in mouse models have shown to decrease β-glucan translocation and ameliorate alcohol-induced liver injury produced via the C--type lectin domain family 7 member A receptor on hepatic Kupffer cells (130). In the same line, since microbiota has been shown to be a relevant disease driver in ALD, fecal microbiota transplantation (FMT) has been explored as a therapeutic option for ALD (122, 134). Philips et al. demonstrated an improvement in 1-year survival rate in FMT-treated patients compared to historical controls (87.5% vs. 33.3%). The FMT was given daily for 7 consecutive days in 8 patients (134). However, larger and carefully designed trials are needed before FMT can be considered safe in routine clinical practice for managing ALD. Careful donor selection is recommended considering the risk of transmission of drug-resistant bacteria (135).

Preclinical studies using animal models of ALD have advanced our knowledge regarding the role of microbiota in the pathogenesis and progression of the disease. Using TLR4 chimeric mice, it has been shown that endotoxin--induced release of TGFβ is mediated by an MYD88–NF-κB-dependent pathway, providing an explanatory mechanism for endotoxin-induced liver inflammation (136). Other studies have used Reg3b/g KO or Muc2-deficient mice to show that REG3 lectins protect against alcohol-induced liver injury by reducing mucosa-associated microbiota, thereby preventing translocation of viable bacteria (137, 138). Moreover, IgA KO mice led to increased levels of IgM and overall protection against alcohol-induced liver injury (139). Recently, Duan Y *et al.* described that the presence of cytolysin-positive E. faecalis correlated with the severity of liver disease and with mortality in patients with AH. Furthermore, using humanized mice that were colonized with bacteria obtained from feces of patients with AH, they investigated the therapeutic effects of bacteriophages that target cytolytic E. faecalis. The authors found that bacteriophages decreased cytolysin in the liver and abolish ethanol-induced liver disease in humanized mice. These findings link cytolytic E. faecalis with more severe clinical outcomes and increased mortality in patients with AH, and it can specifically be targeted by bacteriophage againts cytolytic E. faecalis (140).

Besides bacterial product translocation and immunological responses, it has been recognized the role of bile acids as signaling compounds. Alcohol leads to an increase in bile acid biosynthesis in both humans and mice (141, 142). Of note, clinically, as in other chronic liver diseases, mild cholestasis is common in patients with ALD (143). Bile acids activate FXR in the ileum; impaired FXR activation has been associated with more alcohol-induced liver injury (144). Currently, multiple FXR agonists are being tested, and initial results have shown a protective effect against alcoholic steatohepatitis (145). A recent preclinical study showed that obeticholic acid (OCA), INT-767, or INT-777 (BA derivatives with selective agonist properties for FXR, TGR5, or both, respectively) administration are effective in reducing acute and chronic ethanol-induced steatosis and inflammation in mice, with varying degrees of efficacy depending on the duration of ethanol administration, indicating that both FXR and TGR5 activation can protect from liver injury in ALD models (146). Additionally, it has been shown that the modulation of the intestinal BA/FXR/FGF15 axis improves ALD in mice by modulation of hepatic Cyp7a1 and lipid metabolism (92). Concordantly, *Lactobacillus rhamnosus GG* showed to prevent liver fibrosis through inhibiting hepatic bile acid synthesis and enhancing bile acid excretion in mice (92).

Lactobacillus rhamnosus GG supplementation decreased hepatic BA by increasing intestinal FXR/FGF15 signaling pathway-mediated suppression of BA de novo synthesis and enhanced BA excretion, which prevents excessive BA-induced liver injury and fibrosis in mice (92).

Microbiota and NAFLD

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term used to describe a clinicopathological entity defined by the presence of a spectrum of hepatic histological changes that range from simple steatosis, steatohepatitis to cirrhosis (147). The hepatic histological findings in NAFLD are similar to those observed in heavy-drinkers but detected in patients that deny significant alcohol consumption and in whom other known causes of chronic liver disease (i.e., viral hepatitis, autoimmune liver disease or exposure to hepatotoxic drugs) are excluded (148). The histological hallmark of NAFLD is steatosis, which refers to the pathological accumulation of fat in the liver predominantly in the form of triglycerides, although several additional lipid species accumulate inside hepatocytes in this setting. Hepatic steatosis may or may not be accompanied by the presence of necro-inflammatory changes (i.e., cellular ballooning) and various degrees of hepatic fibrosis. When the latter features are present, the term non-alcoholic steatohepatitis (NASH) is used (149). NAFLD is commonly associated with overweight or obesity as well as impaired glucose tolerance, type 2 diabetes mellitus, arterial hypertension, and hypertriglyceridemia (148). For this reason, NAFLD is widely considered as the hepatic manifestation of the metabolic syndrome and is thought to be mainly driven by the occurrence of insulin resistance (148, 150).

In recent years, it has become evident that NAFLD pathophysiology is complex and involves diverse immunological and metabolic pathways. Importantly, these pathways can influence disease phenotype in diverse fashion, thus determining disease heterogeneity (151, 152). Several studies have highlighted the role of the gut microbiota in NAFLD (153-155). Pre-clinical studies have shown that germ-free mice are protected against obesity and hepatic steatosis (156). Despite the large number of preclinical data investigating and demonstrating a relationship between microbiota and NAFLD, only a limited number of human studies, mostly cross-sectional, are available with variable results. NAFLD patients have a higher prevalence of dysbiosis with increased Bacteroides, Escherichia, and Ruminococcus and decreased Prevotella bacteria (115, 157) in those with advanced forms of the disease indicating an association between Gram-negative bacteria and progression of liver fibrosis (108). Additionally, fecal-microbiome-derived signatures associated with fibrotic NASH and NAFLD-related cirrhosis has been described (158, 159). Also, a significant association between NAFLD and SIBO has been established (111, 160, 161), Studies using mouse models have shown that impairment of intestinal permeability, achieved by using junctional adhesion molecule A protein (Jam1)-knockout mice or mice deficient in Muc2, leads to increased liver inflammation when the high-fat diet is administrated (138, 162). The role of translocated bacterial products has also been assessed by using inflammasome-deficient mouse models (Nlrp3 KO or Nlrp6 KO). NLRP3 inflammasome pathway is important in the modulation of microbiota in the intestine. Defective NLRP3 inflammasome pathway results

in dysbiosis with an increased translocation of endotoxins, accumulation of PAMPs in the portal circulation, and, thereby, promoting liver inflammation and NASH progression (10).

A growing number of studies confirm the association between NAFLD and microbiota at both the observational and mechanistic levels. Microbiota from adult subjects with NAFLD exhibits differences in carbon and amino acid metabolism (157). Also, they have increased serum TMAO and hepatic bile acid synthesis (123) and decreased the production of phosphatidylcholine (163). Interestingly, a recent elegant paper by Yuan J. et al. showed that high-alcohol-producing Klebsiella pneumoniae was associated with up to 60% of individuals with NAFLD in a Chinese cohort. (164). These results suggest that, at least in some cases of NAFLD, an alteration in the gut microbiome drives the condition due to excess endogenous alcohol production, highlighting the link between NAFLD and ALD, and the pivotal role of microbiota (133, 165). Gut microbiota is also altered in subjects with hepatocellular carcinoma-associated NASH. Clostridium, Escherichia, and Helicobacter species have been found to be enriched in mouse models of NASH-related hepatocellular carcinoma as well as in humans with this neoplasia (166-171).

The role various bacterial metabolites and microbiota-generated secondary BA in NAFLD pathophysiology has been unveiled in recent years (165). These substances may affect a myriad of signaling pathways that may directly influence metabolic dysfunction and contribute to NAFLD development and progression. Importantly, gut microbiota can modulate BA metabolism contributing to diversification of host BA, thus regulating BA-dependent pathways mediated by dedicated BA receptors such as FXR and TGR5 (67, 172). In addition, similar to ALD, early in the disease, subjects with NAFLD may exhibit impaired BA secretion resulting in increased intracellular BA concentrations (173). Thus, BA retention and changes in BA metabolism might have a role as mediators of liver injury and triggers of inflammation, promoting disease progression (67, 174) including HCC development (90). On these grounds, therapeutic approaches based in the activation or modulation of FXR and TGR5, as well as of specific BA transporters, such as the ileal apical sodium-dependent bile acid transporter, has been explored in NAFLD/NASH and hold promise (67). Also, modulation of gut microbiota using probiotics, prebiotics, symbiotics of FMT could have impact on NAFLD/NASH through their effects in BA metabolism among other mechanisms (175). Given the shared histological features of AH and NASH, BA dependent targets investigated in NASH could be tested in AH (176), for example, the already available NGM282 (a non-tumorigenic variant of FGF19 analogue) and tropifexor (non-steroidal FXR agonist). Currently, an FXR agonist is already available and under study as a therapeutic agent for severe AH (TREAT, NCT02039219 on ClinicalTrials.gov). Further preclinical and clinical studies are needed to advance our knowledge about the relationship between gut microbiota and NAFLD.

Conclusions

It has been increasingly recognized that the gut-liver axis plays an important role in the development and progression of liver disease, where bacterial products and bile acids reach the liver through the portal circulation and modulate liver injury (Figure 1). NAFLD and ALD are the two most common causes of liver disease, and in both effective therapies are

urgently needed. Gut-liver axis signaling pathways such as BA-related pathways and microbiota-related mechanisms (i.e., dysbiosis and endogenous ethanol production are attractive candidates for new targeted therapies.

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Abbreviations used in this paper:

ACLF	acute-on-chronic liver failure
ALD	alcohol-related liver disease
Asbt	apical sodium bile acid transporter
ASH	alcoholic steatohepatitis
BAs	bile acids
BSEP	bile salt export pump
CA	cholic acid
CDCA	chenodeoxycholic acid
DAMPs	damage-associated molecular patterns
DCA	deoxycholic acid
FGF19	fibroblast growth factor 19
FMT	fecal microbiota transplantation
FXR	farnesoid X receptor
NAFLD	non-alcoholic liver disease
NASH	non-alcoholic steatohepatitis
NLR	nucleotide-binding oligomerization domain-like receptors
NTCP	sodium-dependent taurocholate polypeptide
LCA	lithocholic acid
LPS	lipopolysaccharide
OCA	obeticholic acid
PAMPs	pathogen-associated molecular patterns

PBC	primary biliary cholangitis
PSC	primary sclerosing cholangitis
SIBO	small intestine bacterial overgrowth
TNF-α	tumor necrosis factor-α
TLRs	toll-like receptors
UDCA	ursodeoxycholic acid

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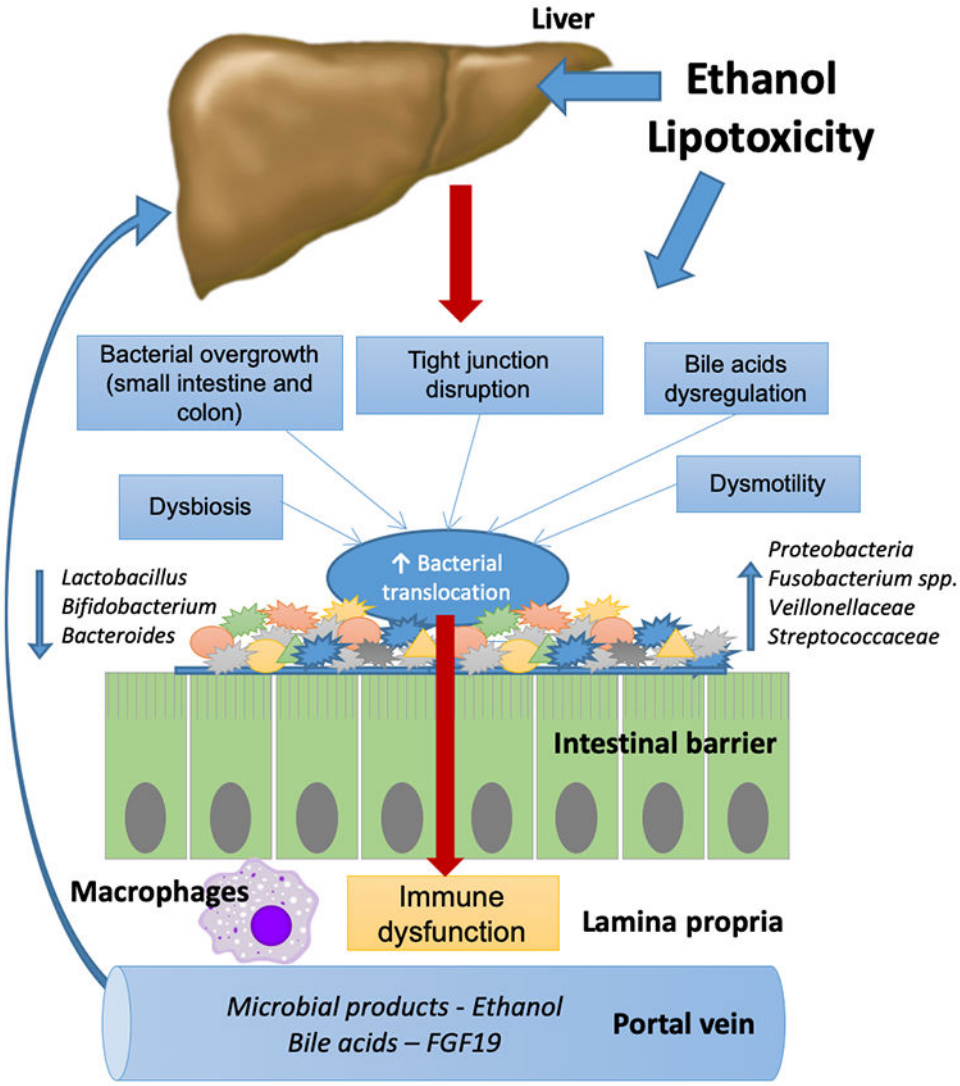

Figure 1:

Gut-liver axis in NAFLD and ALD: In response to ethanol or diet, bacterial overgrowth, dysbiosis, impaired intestinal permeability, bile acids dysregulation, and dysmotility promote bacterial translocation from the intestinal lumen to the portal vein. Microbial products and ethanol can reach the liver contributing to liver disease.