Gut–liver axis, cirrhosis and portal hypertension: the chicken and the egg

Juan P. Arab[1,2], **Rosa M. Martin-Mateos**[1], **Vijay H. Shah**[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First ST SW, Rochester, MN, USA

[2]Departamento de Gastroenterologia, Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile

Abstract

The term gut–liver axis is used to highlight the close anatomical and functional relationship between the intestine and the liver. The intestine has a highly specialized epithelial membrane which regulates transport across the mucosa. Due to dysbiosis, impairment of the intestinal barrier and altered immunity status, bacterial products can reach the liver through the portal vein, where they are recognized by specific receptors, activate the immune system and lead to a proinflammatory response. Gut microbiota and bacterial translocation play an important role in the pathogenesis of chronic liver diseases, including alcoholic and non-alcoholic fatty liver disease, cirrhosis, and its complications, such as portal hypertension, spontaneous bacterial peritonitis and hepatic encephalopaty. The gut microbiota also plays a critical role as a modulator of bile acid metabolism which can also influence intestinal permeability and portal hypertension through the farnesoid-X receptor. On the other hand, cirrhosis and portal hypertension affect the microbiota and increase translocation, leading to a "chicken and egg" situation, where translocation increases portal pressure, and vice versa. A myriad of therapies targeting gut microbiota have been evaluated specifically in patients with chronic liver disease. Further studies targeting intestinal microbiota and its possible hemodynamic and metabolic effects are needed. This review summarizes the current knowledge about the role of gut microbiota in the pathogenesis of chronic liver diseases and portal hypertension.

Keywords

Introduction

The gut microbiota comprises a wide spectrum of microorganism (mainly bacteria) that contributes to digestion, synthesis of vitamins, and resistance to colonization. The

microbiota may also stimulate the immune system in the gastrointestinal tract and decrease pathogens by competing for nutrients and space [1]. Intestinal bacteria can be critically influenced by environmental factors, such as dietary modifications, alcohol consumption, or certain drugs (proton pump inhibitors or probiotics among others) [2, 3]. Various liver disorders such as alcoholic liver disease, non-alcoholic fatty liver disease and primary sclerosing cholangitis have been associated with qualitative and quantitative (overgrowth) changes in gut microbiota [4–6]. Dysbiosis, defined as the imbalance between protective and harmful bacteria, and the alteration of intestinal barrier may also influence the degree of hepatic steatosis, inflammation and fibrosis through multiple interactions with the host's immune system and other cell types [7].

The term gut–liver axis has been coined to highlight the close anatomical and functional relationship between both organs. The liver is strategically placed in the proximity of the gut receiving 75% of its blood supply through the portal vein. The portal vein flow carries nutrients, but also translocated microbial products and bacteria which provide the liver with a broad spectrum of antigens. Most of them are harmless dietary and commensal products, but pathogens or bacterial-derived factors from the gastrointestinal tract can also reach the liver via the enterohepatic circulation [8]. Although a highly specialized epithelial barrier regulates transport across the intestinal mucosa, a wide variety of gut-derived antigens may reach the liver through the portal vein. The hepatic immune system must remain tolerant to harmless stimuli while, at the same time, must be activated against bacterial pathogens and prevent them from reaching the systemic circulation [8, 9]. The recognition of these bacteria-derived antigens by specific receptors and the subsequent proinflammatory response has been linked to the development and progression of chronic liver disease [10]. Therefore, the intestinal barrier, the microbiota, the liver and the immune system must establish complex interactions to maintain homeostasis. Disturbance of this balance can lead to increased intestinal permeability and result in disease.

This review intends to integrate and summarize the current knowledge about the role that the gut microbiota plays in the pathogenesis of chronic liver diseases and portal hypertension, and provides a glimpse of its clinical and therapeutics perspectives.

Intestinal barrier: the forefront of the defense

Only a small part of the intestinal luminal content reaches the portal circulation, since a highly specialized barrier limits direct interaction between this content, the underlying lamina propria and the immune system. This barrier promotes nutrient and water transport while also protecting against gut-derived pathogens [11]. The intestinal epithelial barrier is composed of a mucus lining, an epithelial monolayer of specialized cells, and the intercellular junctions that seal the space between them and control trafficking across the intestinal mucosa. The luminal mucus layer prevents large particles and intact bacteria from coming into contact with the epithelium [12]. The major components of the mucus are mucins, which are large glycoproteins secreted by intestinal globet cells [13]. Below this layer, the apical surface of the epithelium forms a single and continuous border that restricts the passage of most hydrophilic solutes. The apical junctional proteins (claudins, occludins,

and zonula occludens), known as tight junctions and adherens junctions, regulate paracellular transport and seal the space between the epithelial cells.

Some hepatotoxic compounds, such as alcohol, can directly affect the intestinal epithelial tight junctions impairing the intestinal barrier and inducing translocation and endotoxemia [14–16]. Acetaldehyde, an oxidative metabolite that is generated by intestinal metabolism of alcohol, increases intestinal permeability by disrupting integrity and expression of epithelial tight junction molecules. Dunagan et al. showed that acetaldehyde mediates protein phosphatase 2A (PP2A) translocation to tight junctions and dephosphorylation of occludin on threonine residues [17]. Furthermore, alcohol may induce a change in the expression of zonula occludens-1 (ZO-1) and claudin-1, increasing intestinal epithelial barrier permeability [18]. Ethanol-induced miR-212 over-expression has been also linked to decreased ZO-1 protein levels [19]. Finally, tight junction-mediated permeability may be regulated by the local expression of pro- and anti-inflammatory interleukins, such as interferon gamma (IFN-γ), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [20, 21].

Intestinal microbiota: the key regulator

Alteration of gut microbiota has been linked with liver disease development and progression, especially related to non-alcoholic liver disease (NAFLD) and alcoholic liver disease (ALD), although the exact mechanisms at play remain unknown [22–25].

As cirrhosis progresses, portal hypertension leads to an increase in intestinal permeability due to the loosening of the tight junctions, higher transcytosis, and a decrease of mediators that limit contact between bacteria and intestinal microvilli [26]. In addition, intestinal bacterial overgrowth and changes in the composition of intestinal bacterial flora can promote bacterial translocation, defined as the migration of bacteria or bacterial products from the gut to the extra-intestinal space [27] (Fig. 1).

Several studies have shown a decrease in beneficial autochthonous bacteria in cirrhotic patients, such as *Lactobacillus, Bifidobacterium*, and *Bacteroides* species. Decreased abundance of these species, in particular *Bifidobacterium*, can exacerbate hepatic injury and impede regeneration [28]. Furthermore, there is an increase in potentially pathogenic families such as Proteobacteria (particularly Enterobacteriaceae which is responsible of most of the spontaneous bacterial peritonitis episodes), *Fusobacterium* spp., Veillonellaceae, and Streptococcaceae [29–32] (Table 1). An interesting, and not yet addressed, question in liver diseases relates to the impact of metabolites produced by gut microbiota in the host immune response. There is some evidence about how microbiota-derived metabolites modulate the activation of the inflammasome (NLRP6 inflammasome signaling) to influence microbial community stability [33], but further studies are needed in patients with liver diseases.

Small intestine bacterial overgrowth (SIBO) in cirrhotic patients has been demonstrated by quantitative analyses of bacterial cultures from jejunal aspirates [34]. This fact is linked to a decrease in bile acid secretion and the impairment of intestinal motility, mainly characterized by prolonged transit time [35, 36]. Decreased intestinal motility contributes to

SIBO, but may be observed in patients without bacterial overgrowth [37]. The pathogenesis of this dysmotility is multifactorial, including autonomic neuropathy, inflammatory mediators, dysbiosis and neuropeptides.

Disruption of intestinal barrier, translocation and liver immunology: the last stand

Dysbiosis, increased intestinal permeability induced by disruption of the intestinal barrier, and overwhelming of the defense mechanisms leads to bacterial translocation [10, 38]. Bacterial translocation occurs when bacteria adhere to the epithelium, pass through the intestinal wall and reach the mesenteric lymph nodes. The capacity of the lymph nodes to eliminate intestinal bacteria can be overcome in certain situations, favoring their access to other territories and increasing the risk of infections. In cirrhosis, this phenomenon is the consequence of a "leaky" intestinal barrier, and its occurrence is considered detrimental in the natural history of a patient with chronic liver disease [39]. This fact also contributes to the chronic activation of the immune system and inflammation in the liver [38].

Bacterial products are identified by the immune system through recognition of pathogen-associated molecular patterns (PAMPs), which are a limited and defined set of conserved molecular patterns carried by all microorganisms of a given class [40]. The most studied gut-derived PAMP is the bacterial endotoxin known as lipopolysaccharide (LPS), which is found in the outer membrane of Gram-negative bacteria. The administration of intraperitoneal LPS has been shown to increase portal pressure [41], which at the same time increases intestinal permeability [42, 43]. Furthermore, bacterial translocation, endotoxemia and proinflammatory cytokines impair the contractility of mesenteric vessels in patients with cirrhosis, increasing portal pressure [44, 45]. In a portal-vein ligation model, mice colonized with intestinal microbiota presented with significantly higher portal pressure as compared to germ-free mice [46]. On the other hand, Tabibian et al. [47] have recently shown that the absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis, and that this also increases cholangiocyte senescence.

Although LPS and other bacterial products can activate different signaling pathways promoting a proinflammatory cascade, anti-inflammatory and antifibrogenic mechanisms are present concurrently to balance these processes and maintain liver homeostasis and immunotolerance. Hepatic antigen-presenting cells (APC) are central to the tolerogenic nature of the liver due to their capacity to preferentially suppress adaptive immunity by killing or inactivating T cells or by inducing maturation of naïve T cells into T-regulatory cells that suppress CD4^{+} and CD8^{+} T cell responses [9].

Once bacterial products reach the liver, they can activate immune cells through pattern recognition receptors (PRRs) such as the membrane-bound toll-like receptors (TLRs) and the cytoplasmic nucleotide-binding oligomerization domain like receptors (NLRs). TLRs are transmembrane proteins that play a key role in the innate immune system, usually expressed in sentinel cells such as macrophages and dendritic cells; however, TLRs have been identified in response to LPS of hepatic non-immune cells, including hepatic stellate cells and endothelial cells [38, 48]. TLRs recognize structurally conserved PAMPs and activate an

inflammatory response [49, 50]. There are 10 subtypes of TLRs [51], including TLR4 which activates the innate immune in response to LPS through the co-receptors CD14 or MD-2 [49, 52]. Downstream TLR4 signaling may be either MyD88-dependent or -independent [53]. The MyD88-dependent pathway involves nuclear translocation of NF-κB [54], which is a heterodimeric transcription factor constitutively expressed in all cell types. NF-κB has a central role in regulating the immune response to infection as well as in the pathogenesis of a wide variety of conditions affecting the liver, including viral hepatitis, steatohepatitis, cirrhosis and hepatocellular carcinoma [55]. NF-κB activation induces the release of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1β [56]. On the other hand, the MyD88-independent pathway implies the phosphorylation of the interleukin regulatory factor 3, which leads to induction of type-I interferon [57, 58]. TLRs can also be activated by damage-associated molecular patterns (DAMPs) released from injured cells or tissues [59]. This may lead to sterile inflammation and plays a role in the pathogenesis of non-alcoholic and alcoholic liver disease [49, 60]. DAMPS may also activate NLRs which regulate inflammatory and apoptotic responses along with TLRs [61, 62]. Activation of NLRs results in the up-regulation of cytokines and chemokines, such as IL-1β and IL-18, which are then released to recruit and activate additional inflammatory cells [63, 64].

In normal conditions, the intestinal barrier prevents translocation of most of the bacteria, so only small amounts of microbial products can reach the liver. Once there, they are cleared by immune cells, particularly Kupffer cells [48]. In cirrhotic patients, due to a disrupted intestinal barrier, a greater influx of bacterial products to the liver occurs, leading to activation of liver immune cells and release of pro-inflammatory cytokines [65, 66]. This mechanism is especially relevant in alcoholic liver disease [67, 68], where studies in animal models have shown that the use of antibiotics or Kupffer cells elimination can alleviate alcohol-induced liver injury [69, 70]. Translocation of bacteria and their products from a leaky lumen has also been recognized as a major contributor to systemic inflammation in advanced cirrhosis and acute-on-chronic liver failure (ACLF) [71].

Role of bile acids in portal hypertension: the old-new players

The gut microbiota also plays a critical role as modulator of bile acids (BAs) pool size and composition, through defined enzymatic activities (dihydroxylation, oxidation and epimerization among others), and significantly modifying the signaling properties of BAs and their actions on BA receptors [22, 72, 73].

BAs mediate the absorption of dietary lipids but also play a pivotal role contributing to select intestinal microbiome [74] by means of their direct antimicrobial effects through the farnesoid-X receptor (FXR)-induced production of antimicrobial peptides such as angogenin1 and RNase family member 4 [75, 76]. These prevent bacterial overgrowth and promote epithelial cell integrity [77]. Bile acids therefore inhibit bacterial proliferation directly and indirectly by modulating host cell expression of antimicrobial genes. Consequently, decreased intraluminal concentration of bile acids on end-stage-chronic liver diseases may promote bacterial overgrowth [78]. Several studies on germ-free and FXR-deficient mice have shown that the gut microbiota also modulates BA profiles and influences FXR signaling [22, 79]. On the other hand, it has been described that FXR activation

markedly inhibits inflammation and preserves the intestinal barrier function reducing bacterial translocation in inflammatory bowel disease [80] and in a rat model of cholestatic liver injury [81] (Fig. 2).

Modulation of the BAs nuclear receptor with obeticholic acid (OCA), a potent selective FXR agonist, has been shown to improve portal hypertension by two distinct pathways in a rat model of intoxication with thioacetamide and in the bile-duct-ligation (BDL) model of liver injury. In both models, treatment with OCA reactivated the FXR downstream signaling pathway and decreased portal pressure by lowering total intrahepatic vascular resistance without deleterious systemic hypotension [82]. Additionally, OCA has been shown to reduce bacterial translocation and reduce intestinal inflammation in ascitic cirrhotic rats [83]. Thus, modulation of BAs signaling could be a novel target for modulation of portal hypertension, in part through effects on the microbiome.

Clinical and therapeutic perspectives

As previously described, the gut microbiota plays a pivotal role in liver disease natural history, both in the progression of the disease and in the development of its complications such as spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE) [84], but, at the same time, cirrhosis and portal hypertension affect the microbiota and increase translocation, leading to a "chicken and egg" situation. The initial process of translocation of bacterial products ("chicken") from the gut to the bloodstream triggers a response in the liver increasing the portal pressure ("egg"), and the latter ("chicken") in turn leads to intestinal edema, disruption of epithelial integrity and more translocation ("egg") (Fig. 3).

Patients with liver disease from different etiologies (viral hepatitis, alcohol, NAFLD, primary biliary cholangitis, primary sclerosing cholangitis, etc.) have been shown to have elevated levels of LPS in plasma and endotoxemia [85–88]. For this reason, attempts to target gut microbiota (with probiotics, antibiotics or depletion of Kupffer cells) have been pursued with some success in alcoholic liver disease models [69, 70, 89]. The mutual interdependence between the pathogenesis of the cirrhotic process, intestinal bacterial translocation and portal pressure make the gut–liver axis an attractive target for specific therapeutic interventions. Non-selective beta-blockers (NSBB), broadly used in cirrhotic patients, have been shown to be beneficial by reducing bacterial translocation, while other therapies evaluated in patients with cirrhosis specifically aiming gut microbiota are antibiotics (rifaximin), prebiotic (lactulose), probiotics and proton-pump inhibitors (PPI), with different results. These drugs are discussed in more detail below.

Non-selective beta-blockers (NSBB)

NSBB reduce sympathetic tonus, decrease portal pressure, and protect against variceal hemorrhage in cirrhosis, by lowering cardiac output through blockade of $\beta-1$ adrenoreceptors, and increase splanchnic vasoconstriction through blockade of $\beta-2$ adrenoreceptors [90]. A meta-analysis also confirmed that NSBB protect against SBP independently of their hemodynamic effects [91]. In cirrhotic patients, treatment with NSBB has been shown to increase intestinal transit, reduce intestinal bacterial overgrowth, decrease intestinal permeability, and reduce bacterial translocation [92, 93].

Antibiotics

Despite pre-clinical models having shown that rifaximin treatment improves microbiota composition and function, clinical trials have not shown significant differences in those endpoints, probably due to these studies have been carried out in patients with advanced cirrhosis, and, therefore, the microbiota reflects the cirrhotic status rather than the effect of rifaximin [94, 95]. Regarding clinical endpoints, an elegant study by Bajaj et al. [96] 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 treatment increased serum fatty acid metabolites, changed bile acid composition and promoted an anti-inflammatory status, changing the correlation networks between bacteria and metabolites. 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) [97]. Currently, large studies are being carried out to evaluate the effect of rifaximin on the complications of decompensated cirrhosis and portal pressure (ClinicalTrials.gov ID: and).

Prebiotics

Despite its widespread use, no studies have clearly shown that lactulose leads to significant changes in microbiota composition or function [98]. The proposed mechanisms of action of lactulose are as a laxative, increasing the volume of stools, and as a prebiotic, acidifying and modifying the colonic flora. This potential modification of the microbiota could lead to a displacement of urease-producing bacteria with non-urease-producing *Lactobacillus*, and, therefore, to a reduction in the formation of potentially toxic short-chain fatty acids (e.g., propionate, butyrate, and valerate) [99, 100]. Currently, a clinical trial is being carried out to elucidate the influence of lactulose intake on the gut microbiota composition ().

Probiotics

Probiotics, in particular lactose-fermenting Lactobacilli and Bifidobacteria, promote mucosal barrier function and modulate the gut microflora, suppressing pathogenic microbial growth [101–103]. Probiotics and synbiotics (a combination of probiotics and prebiotics in a form of synergism) have been used broadly in trials addressing HE. Among the different combinations *Lactobacillus GG* and VSL#3 have shown improvements in endotoxemia, endothelial dysfunction, and dysbiosis over placebo, along with modifications on bile acid pool composition [104–106]. VSL#3 has shown improvements in hepatic and systemic hemodynamics [107], but larger clinical trials with clinically significant outcomes are needed.

Fecal microbiota transplantation

The role of fecal microbiota transplantation is becoming increasingly recognized as an emergent treatment in gastrointestinal pathologies. Evidence regarding liver diseases includes potential benefits in primary sclerosing cholangitis, NAFLD, and, most recently, in preventing alcohol-induced liver injury in mice [108–110]. However, further studies are needed before proposing strong recommendations.

Proton-pump inhibitors (PPI)

Another widespread medication involves PPI, which have been reported to be used by half of cirrhotic patients on a regular basis [111]. PPI have been shown to change microbiota composition in cirrhotic and non-cirrhotic patients [112]. Omeprazole increases oral-origin Streptococcaceae in the stools, similar to the effect of the use of broad antibiotic therapy [112]. This could set the stage for SIBO or *Clostridium difficile* infection. In two recent studies, PPI were identified as a risk factor for HE and SBP in patients with cirrhosis with ascites, with the risk increasing with dose [111, 113].

Conclusions

The gut–liver axis plays an important role in the development and progression of cirrhosis and portal hypertension, interplaying a role of "chicken and egg", where bacterial translocation from the intestine reaches the liver and increases portal pressure, while, on the other hand, portal hypertension leads to intestinal edema, disruption of epithelial integrity and more translocation. This disruption of the intestinal barrier leads to bacterial translocation recognized by TLRs and NLRs, which induces a proinflammatory response. Additionally, BAs receptors play a role in the gut barrier function and portal pressure. While no studies have shown a definitive beneficial effect of rifaximin, lactulose or probiotics in large clinical trials of portal hypertension, further studies to delineate the impact of therapies on bacterial composition and function, as well as therapies aimed to regulate intestinal permeability and bacterial translocation, are urgently needed.

Acknowledgements

Abbreviations

ACLF	Acute-on-chronic liver failure
APC	Antigen-presenting cells
BAs	Bile acids
BDL	Bile-duct ligation
DAMPs	Damage-associated molecular patterns
DDAH-2	Dimethylarginine dimethylaminohydrolase 2
eNOS	Endothelial nitric oxide synthase
FXR	Farnesoid-X receptor
IFN-γ	Interferon gamma
IL-6	Interleukin-6

MLCK	Myosin-light chain kinase
NAFLD	Non-alcoholic liver disease
NLR	Nucleotide-binding oligomerization domain like receptors
NSBB	Non-selective beta-blockers
LPS	Lipopolysaccharide
OCA	Obeticholic acid
PAMPs	Pathogen-associated molecular patterns
PP2A	Protein phosphatase 2A
PPI	Proton-pump inhibitors
PRRs	Pattern recognition receptors
SIBO	Small intestine bacterial overgrowth
TNF-α	Tumor necrosis factor-α
TLRs	Toll-like receptors
ZO-1	Zonula occludens-1

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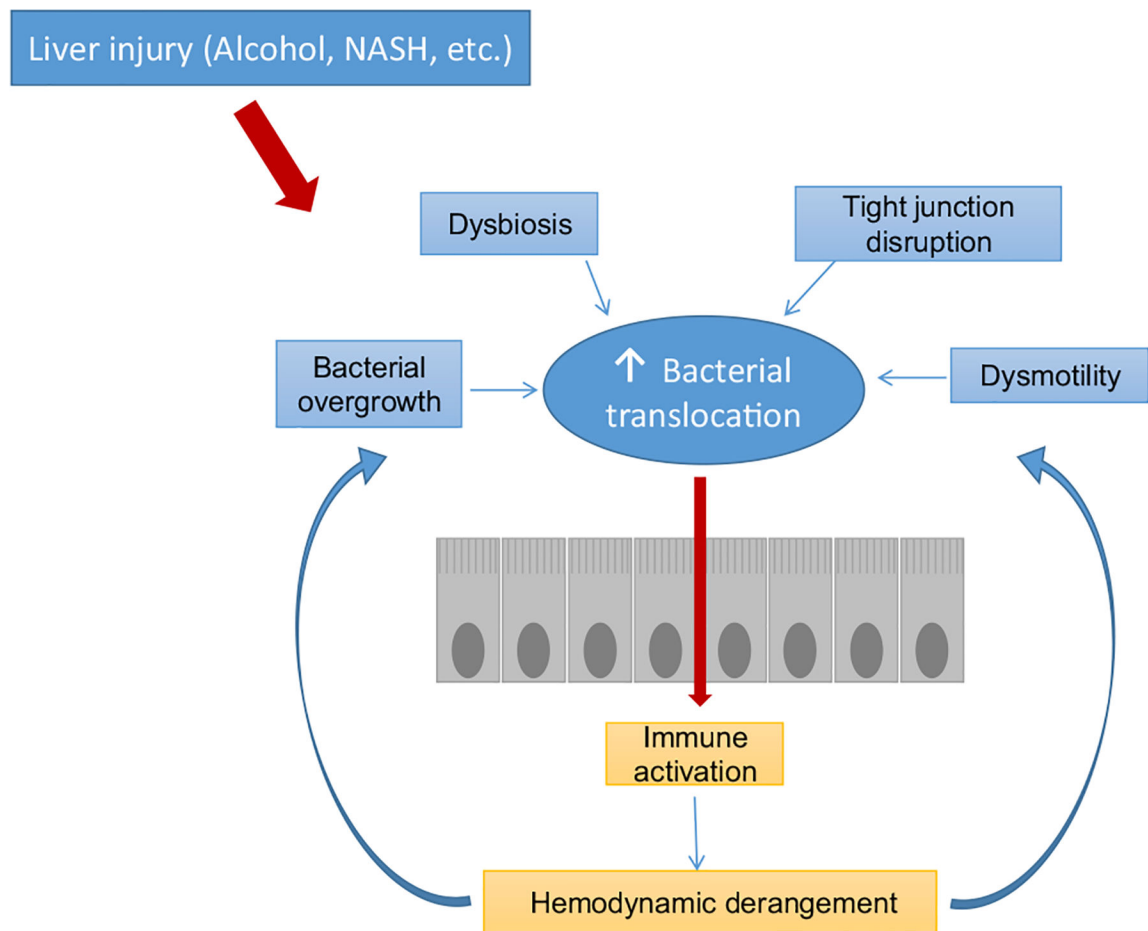
Fig. 1.
Mechanisms of bacterial translocation. Bacterial overgrowth, dysbiosis and altered intestinal permeability promote bacterial translocation from the intestinal lumen to the mesenteric lymph nodes and gut-associated lymphoid tissue. When the immune system capacity is overcome, bacteria may access the systemic circulation increasing the risk of infections and favoring hemodynamic derangement. This worsening in turn favors bacterial translocation, perpetuating the "chicken and egg" circle
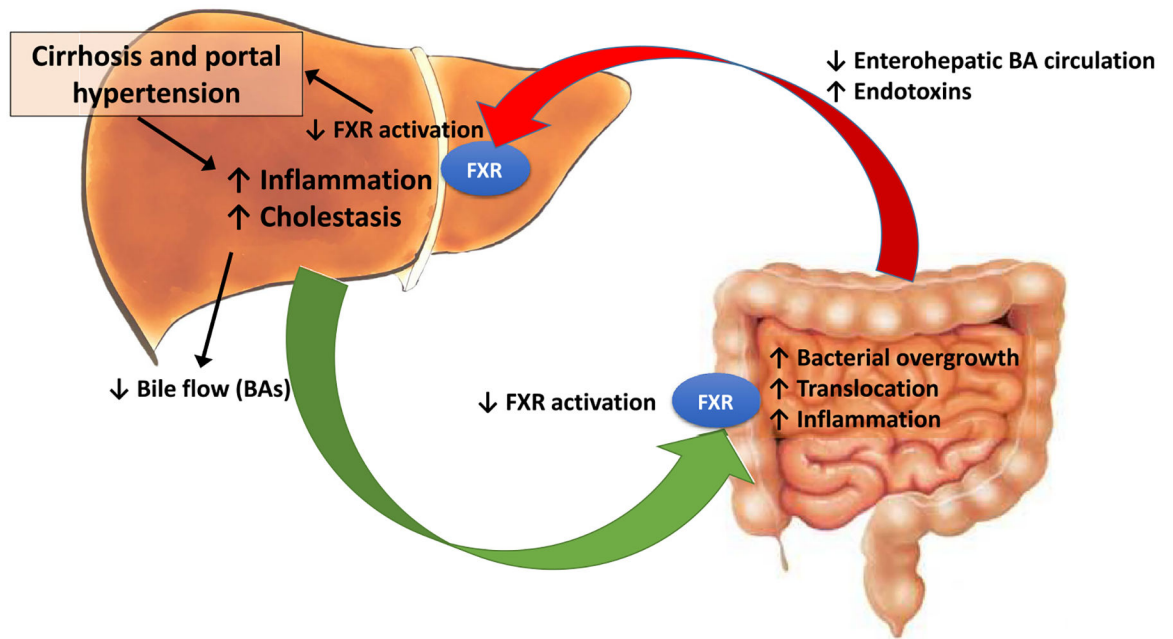
Fig. 2.
Schematic depicting the influence of cirrhosis and portal hypertension in bile acids and their circulation in relation to gut microbiota. *BAs* bile acids, *FXR* Farnesoid-X receptor
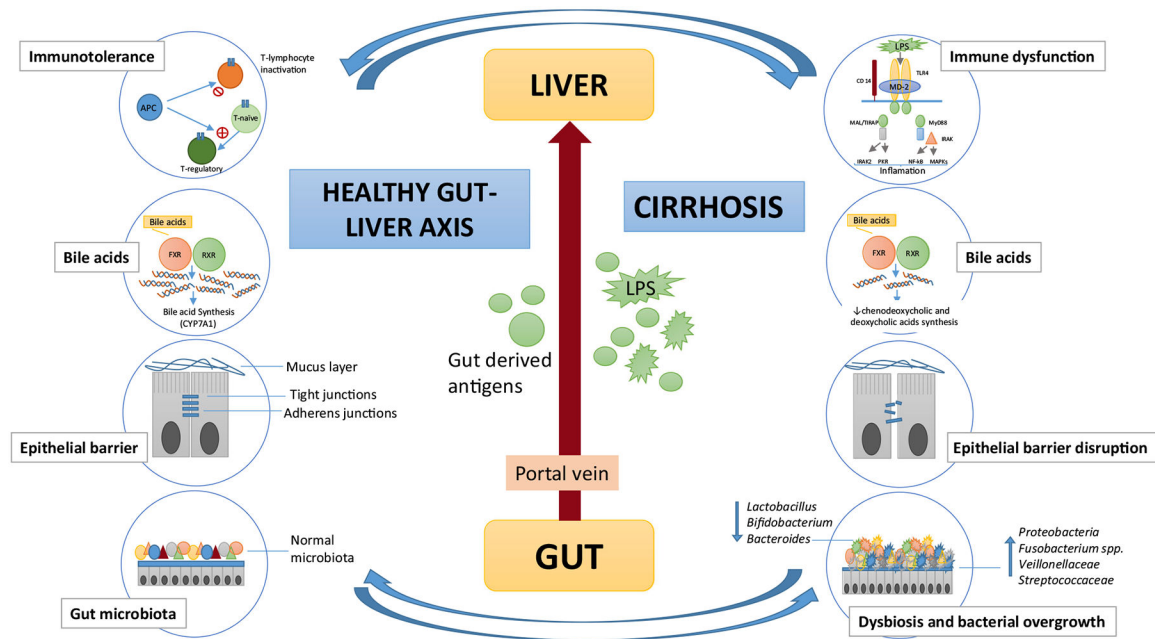
Fig. 3.
Gut liver axis in health and disease. In immune response, hepatic antigen-presenting cells (APC) are central to tolerogenic nature of the liver due to their capacity to suppress adaptive immunity by killing or inactivating T cells or by inducing maturation of naïve cells into regulatory cells that suppress CD4$^+$ and CD8$^+$ cell responses. In cirrhosis, TLR4 activation by LPS leads to a proinflammatory response. Persistent activation of the immune system leads to cirrhosis immune dysfunction. The bile acids are natural ligands of farnesoid-X receptor (FXR). FXR is a nuclear receptor highly expressed in the liver and intestine. When activated, FXR translocates to the nucleus and forms a heterodimer with RXR. In the liver, FXR negatively regulates bile acid production by repressing CYP7A1. Bile acid secretion is decrease in cirrhosis, which contributes to bacterial translocation and inflammation. The epithelial barrier regulates transport across the mucosa and prevents gut-derived pathogens reach the portal system. In cirrhosis, intestinal permeability increase due to disruption and altered expression of tight junction proteins. The gut microbiota are beneficial autochthonous bacteria (*Lactobacillus, Bifidobacterium*, and *Bacteroides* species) which decrease in cirrhotic patients, meanwhile potentially pathogenic families such as Proteobacteria, Fusobacterium, Veillonellaceae, and Streptococcaceae are increased, leading to dysbiosis and bacterial overgrowth

Table 1

Changes in microbiota composition in cirrhosis

Decreased bacterial species	Increased bacterial species
Lachnospiraceae [30]	Proteobacteria
Bifidobacterium [31]	(Enterobacteriaceae) [30]
Bacteroidetes (Bacteroidaceae) [31]	*Fusobacterium* spp. [32]
Blautia [31]	Veillonellaceae [32]
Ruminococcaceae [31]	Streptococcaceae [32, 114]