Intestinal permeability in the pathogenesis of liver damage: From non-alcoholic fatty liver disease to liver transplantation

Alberto Nicoletti, Francesca Romana Ponziani, Marco Biolato, Venanzio Valenza, Giuseppe Marrone, Gabriele Sganga, Antonio Gasbarrini, Luca Miele, Antonio Grieco

Abstract

The intimate connection and the strict mutual cooperation between the gut and the liver realizes a functional entity called gut-liver axis. The integrity of intestinal barrier is crucial for the maintenance of liver homeostasis. In this mutual relationship, the liver acts as a second firewall towards potentially harmful substances translocated from the gut, and is, in turn, implicated in the regulation of the barrier. Increasing evidence has highlighted the relevance of increased intestinal permeability and consequent bacterial translocation in the development of liver damage. In particular, in patients with non-alcoholic fatty liver disease recent hypotheses are considering intestinal permeability impairment, diet and gut dysbiosis as the primary pathogenic trigger. In advanced liver disease, intestinal permeability is enhanced by portal hypertension. The clinical consequence is an increased bacterial translocation that further worsens liver damage. Furthermore, this pathogenic mechanism is implicated in most of liver cirrhosis complications, such as spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis, hepatic encephalopathy, and hepatocellular carcinoma. After liver transplantation, the decrease in portal pressure should determine beneficial effects on the gut-liver axis, although are incompletely understood data on the modifications of the intestinal permeability and gut microbiota composition are still lacking. How the modulation of the intestinal permeability could prevent the initiation and progression of liver disease is still an uncovered area, which deserves further attention.
INTRODUCTION

The gut is one of the largest mucosal surfaces of the human body. Besides being involved in the absorption of nutrients and water introduced with ingested food, it acts as a barrier that guarantees protection against pathogenic microorganisms and potentially harmful substances, such as toxins and pollutants[1]. In addition, the interaction that occurs between the gut microbiota and immunological cells at this level is crucial for the development and maintenance of the immune system[2,3].

The gut and the liver are anatomically connected by portal circulation, and their functional unit realizes the gut-liver axis[4]. Thus, any type of substance that goes beyond the gut barrier can reach the liver where it is processed into metabolic pathways or interacts with the immune system cells or resident cells.

Liver disease affects gut homeostasis, altering intestinal permeability (IP) and the gut microbiota composition, proportionally to the degree of liver function impairment. Indeed, once portal hypertension (PHT) is established, the intestinal barrier functions are altered, causing the passage of substances that are normally kept in the intestinal lumen[5]. In particular, the translocation of bacterial fragments or products into the bloodstream activates the immune system, stimulating inflammation. This process not only could further worsen liver function, but it is implicated in a series of chain reactions involving the whole organism, realizing a systemic inflammatory condition typical of advanced liver cirrhosis[6].

PHYSIOLOGICAL GUT BARRIER

Normally, the gut constitutes a complex physical, chemical, functional and immunological barrier. In order to perform its tasks, different components are necessary[6,9]. Proceeding from the lumen inwards, they can be classified into the following levels: The microbiota, the extracellular elements, the epithelial cells, the immune system, the vascular structure (Figure 1).

The microbial barrier

The human gut microbiota harbors one hundred trillions of microorganisms, about ten times the number of eukaryotic cells. It has about ten times the genes of the human genome and has a mass of about 1-2 kg[7].

Several factors, such as birth mode, age, diet and lifestyle, influence the human gut microbiota. In physiological conditions, its compositional and functional armory is quite stable over time. However, the onset of disease and/or the use of certain drugs (e.g., antibiotics) can break this balance, resulting in dysbiosis with significant consequences on human homeostasis. Indeed, the gut microbiota integrates the metabolism of the organism providing crucial pathways to process nutrients, vitamins
and endogenous substances. Microorganisms host in the lumen interact with the intestinal mucosa, shaping the mucus, exerting a trophic and protective function towards enterocytes. Moreover, it plays a pivotal role in the development, maturation and maintenance of the immune system and induces local production of antimicrobial peptides and immunoglobulins.

**Extracellular barrier**

Intestinal mucus is a gel formed by glycosylated proteins secreted by intestinal goblet cells called mucins. It covers the whole gut and its thickness depends on the location, being almost absent in the stomach and maximum in the colon. Mucus prevents harmful substances and bacteria from directly contacting cell surface, causing inflammation. Thus, a proper structure of mucins is crucial for the maintenance of the gut barrier, and alterations could facilitate the absorption of harmful substances, leading to inflammation. Indeed, quantitative or qualitative alterations of the mucus layer has been documented in several diseases, such as cystic fibrosis and inflammatory bowel disease (IBD). In addition, it has been demonstrated in mice models that a high MUC2 mucin production increases the susceptibility of goblet cells to apoptosis and endoplasmic reticulum stress. An increased mucus thickness has been related to alcohol intake and cirrhosis. Conversely, an incorrect assembly of MUC2 inside the epithelial cells leads to the development of an inflammatory disease resembling ulcerative colitis in mice. This process may be responsible of the depletion of goblet cells documented in IBD.

The inner side of the intestinal mucus is made of a fluid, which is not reached by the mixing forces of the luminal flow and peristalsis, called unstirred layer. The inner face of the mucin layer is devoid of bacteria and directly contacts the intestinal epithelial cells, modulating the absorption of water and nutrients due to its static nature. A thicker unstirred layer has been observed in patients with coeliac disease and has been related to malabsorption.

**Functional barrier**

To make the picture more complex, it has to be considered that this system is dynamic and subject to regulation by gastrointestinal motility and secretions. The outer part of the mucus layer is continuously moved forward by peristalsis. The luminal flow prevents the proliferations of microorganism and a prompt clearance of detrimental elements. This is crucial in the protection against pathogens. Gastric acid decreases microbial colonization of the small intestine. Only acid resistant microorganism, such as Helicobacter pylori and Lactobacilli are able to survive at low pH. Bile acids, the main constituents of bile, have direct antimicrobial properties interfering with membrane and protein production and integrity. Thus, alterations of the bile and gastric fluid and impairment of the peristalsis cause both qualitative and quantitative modifications of the gut microbiota composition up to the derangement of intestinal homeostasis and the development of pathology.

**Intestinal epithelial barrier**

Underneath the intestinal mucus, there is a continuous monocellular layer of enterocytes. Goblet cells, responsible for the production of the mucus, and Paneth cells, which produce antimicrobial peptides, provide additional functions and support to the homeostasis of the gut barrier. Enterocytes plasma membrane represents the main mechanical element of the mucosal barrier. Because of its lipidic structure, it is impermeable to most solutes that need a specific transporter to cross the barrier. In order to limit the gut permeability, intercellular spaces are sealed by the presence of a specific apical junctional complex, which is composed by a tight junction (TJ) and an adherens junction. Overall, over 40 proteins form a TJ,
being claudins, peripheral membrane proteins, such as zonula occludens (ZO) 1 and 2, and occludin the main components. Both tight and adherens junctions are connected to the cytoskeleton. TJ are important elements for both active and passive transport through the gut barrier. They regulate the passive flow of the solutes and water through the paracellular pathway, operating both as a size- and charge-selective filter. The passive movement of substances across TJ occurs through two different routes: The leak pathway, that allows the transport of larger substances (e.g., proteins, bacterial components), and a second pathway mediated by claudin proteins, that is charge selective and limits the flow to molecules smaller than 4 Å.

As for active transport, an intact intestinal epithelial barrier, formed by TJ and the plasma membrane of intestinal cell, realizes a gradient between the lumen and the inner interstice. This condition prevents an uncontrolled translocation of substances, and allows an active transcellular transport through the enterocytes. Moreover, the complex system of TJ is finely regulated by the influence of cytokines, particularly tumor necrosis factor-alpha (TNFα) and interferon gamma (IFNγ), and by signaling kinases and cytoskeleton, like myosin light chain kinases (MLCK). Both qualitative and quantitative alterations of TJ have been described in the context of liver disease. Finally, intestinal cells own another defensive element. In fact, apical brush border microvilli are negatively charged, owing to the presence of polar carbohydrates and charged transmembrane proteins, and cause an electrostatic repulsive force towards bacterial cell wall, that is negatively charged as well.

**Immunological barrier**

In response to the exposure to bacteria and to their components, Paneth cells produce antimicrobial peptides, such as defensins, cathelicidines, resistin-like molecules, bactericidal-permeability-inducing proteins and lectins, and immunoglobulins, particularly secretory IgA. These elements are secreted into the gut lumen and are host in the inner face of the mucin layer hosts. Whenever microbial and pathogen-associated molecular patterns cross the intestinal barrier, they are identified through the interaction between pattern-recognition receptors, such as Toll-like receptors (TLRs) and nucleotide binding oligomerization domain-like receptors on the intestinal epithelial cells. Then, recruited dendritic cells are responsible for the transport of the captured antigens to the mesenteric lymph nodes (MLNs) for antigen presentation. This mechanism allows the priming and maturation of B and T lymphocytes, that become part of the adaptive immune response in the gut associated lymphoid tissue. Hence, immune response is compartmentalized in mucosal lymphatics in healthy individuals.

**Gut-vascular barrier**

Since 2015, the knowledge about barrier mechanisms for the modulation of IP stopped to the basocellular membrane of the enterocytes. Recent studies have successively revealed that the intestinal defense mechanisms actually go further, and also include a gut-vascular barrier. Observing functional similarities between blood-brain barrier and intestinal barrier, Spadoni et al. hypothesized that a parallel structure in the gut could be responsible for the prevention of the translocation of bacteria and/or microbial components passed through the extracellular and the intestinal epithelial barrier.

The fundamental structure of this entity is the gut-vascular unit. It is composed by the intestinal endothelium, which is anatomically and functionally associated with pericytes and enteric glial cells that surround it. The barrier is completed by TJ and adherens junctions, which are permeable to most of the small nutrients. Endothelial plasma membrane provides isolation and is equipped with active and passive transporters. Glial cells play an important role in the homeostasis of the gut and in the regulation of IP. In fact, in murine models, it has been demonstrated that either genetic or autoimmune targeting of glial cells determines the development of fulminant enteritis with increased translocation of microbes and evidence of bacteremia. When the endothelium is intact, it allows the free diffusion of 4 kD dextran, whereas 70 kD dextran is blocked. Infection with Salmonella enterica serovar Typhimurium disrupts the gut-vascular barrier, allowing the translocation of larger substances, and this happens independently of the increase in the blood flow provoked by inflammation. Furthermore, 70 kD dextran was only found in the liver and not in the spleen, demonstrating that dissemination occurs through the portal circulation rather than the lymphatic vessels. The increase in plasmalemna vesicle-associated protein-1 (PV1), a marker of endothelial permeability, during Salmonella infection confirms this evidence. Finally, the authors demonstrated that bacteria with the ability to cross the intestinal epithelial barrier do not disseminate to liver and spleen, blocked by a second barrier. These experiments definitively prove the existence of a gut-vascular barrier.
ALTERED GUT BARRIER, INTESTINAL PERMEABILITY AND BACTERIAL TRANSLOCATION IN THE PATHOGENESIS OF LIVER DAMAGE

In liver diseases, increased IP is the consequence of multiple disorders that affect the homeostasis of the barrier. Several studies in animal models and in human pathologies correlated liver damage and dysfunction to alterations of the gut microbiota composition\(^4\), mucus quality and quantity\(^5\), gastrointestinal motility\(^6\), intestinal epithelial barrier and TJ\(^7\), and the immune system\(^8\).

Nevertheless, bacterial translocation (BT) is a physiological process that consists in the passage of small amounts of microorganisms and their constituents from the intestinal lumen to the MLNs\(^9\). At this site, microbial killing occurs without systemic inflammatory response\(^10,11\). This process is crucial for the modulation of the immune system and the development of immune tolerance\(^12,13\). Despite the fact that the liver is usually devoid of bacteria\(^14\), in healthy individuals it is physiologically exposed to trace amounts of bacterial mRNAs and lipopolysaccharide (LPS)\(^15,16\), mainly acting as a firewall detoxifying bacterial components\(^17\). In healthy mice, it has been demonstrated that the liver can act as a second firewall for microorganisms penetrated after mucosal damage and escaped from MLNs surveillance activity\(^18,19\).

This function is supposed to be mainly exerted by the hepatic sinusoids, where Kupffer cells - representing over the 80% of all tissue macrophages - are able to phagocytize and kill microbes derived from the bloodstream\(^20,21,22\). Several experiments have demonstrated the importance of liver resident macrophages in the clearance of microorganisms and bacterial- and pathogen- associated molecular patterns (MAMPs and PAMPs). In fact, \(^3\)H- and \(^14\)C-labelled endotoxin purified from \(E.\ coli\) is actively processed by Kupffer cells\(^23\). Similarly, lipopolysaccharide binding protein (LBP), an acute-phase protein synthesized in the liver and secreted after interleukin-1 (IL-1), interleukin-6 (IL-6), and glucocorticoid stimulation, after binding with LPS mediates the activation of liver mononuclear cells in a way that is dependent on the presence of functional Toll-like receptor 4 (TLR4)\(^24\). CD14, either expressed on myeloid cells (mCD14) or the isoform secreted into the bloodstream by monocytes\(^25\), either expressed on functional Toll-like receptors (mCD14) or the isoform secreted into the bloodstream by monocytes and hepatocytes (sCD14), acts as a co-receptor of TLR4 binding the LPS-LBP complex and allowing its uptake by liver resident myeloid cells\(^26\). Moreover, an elegant imaging-based study by Lee et al\(^27\) documented the ability of Kupffer cells to perform filtration of blood, phagocytosis and killing of green fluorescent protein expressing \(B.\ burgdorferi\) and antigen presentation to natural killer (NK) cells. Finally, in Kupffer cells depleted mice, the clearance of \(E.\ coli\) K-12 during bacteremia is delayed\(^28\).

Yet, the “liver buffer” is exhaustible too. The disruption of the intestinal barrier at any level leads to an increase inIP (Figure 2). Thus, harmful substances, such as MAMPs and PAMPs (LPS, microbial DNA, peptidoglycans and lipopolysaccharides), metabolic products, and whole bacteria massively reach local MLNs, that are unable to provide an adequate clearance\(^29,30,31\). Hence, a variable amount of detrimental products is delivered to the liver through the mesenteric and portal circulation\(^32\). The maintenance of a damaging insult triggers a systemic inflammatory response, developing from the liver\(^33,34\). Kupffer cells play a pivotal role in orchestrating this mechanism\(^35,36,37\). Indeed, the interaction between pathogen-associated molecular patterns and TLRs activate intracellular molecular pathways, either MyD88-dependent or MyD88-independent, resulting in the activation of NF-κB and the expression of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, IL-18), chemokines (CXC1, CXC2, CCL2, CCL5, CCL3, CCL4), vasoactive factors [nitric oxide (NO)] and reactive oxygen species (ROS)\(^38\). This local inflammatory storm leads to the recruitment of systemic leukocytes, such as neutrophils, CD4+ T cells and monocytes, that perpetuate liver inflammation\(^39,40\). Net result of this process is the induction of hepaticocyte apoptosis and necrosis\(^41\). Both inflammatory cytokines and cell death cause the activation and proliferation of hepatic stellate cells (HSC) and the development of fibrosis under the stimulation of transforming growth factor-β (TGFβ)\(^42,43\).

As a consequence of inflammatory cytokines, HSCs and several other liver cells upregulate the expression of matrix metalloproteinases (MMPs). The overexpression and hyperactivation of MMPs result in the destruction of the hepatic tissue\(^44,45\). Tissue inhibitors of matrix metalloproteinases (TIMPs) are the main modulators of the activity of MMPs. While a decrease in the levels of TIMPs have been associated with liver damage in acute liver injury, an increase in their expression in chronic liver diseases favor the accumulation of collagen and liver fibrogenesis, by inhibiting degradation of collagen\(^46,47\). Furthermore, as proof of the relevance of these enzymes in the pathogenesis of liver damage, TIMP-1 has been identified as a predictive marker for the presence of non-alcoholic steatohepatitis (NASH)\(^48\).
Figure 2  Intestinal permeability in the pathogenesis of liver damage. Several disorders, such as gut dysbiosis and primary and secondary intestinal diseases, can cause increased intestinal permeability. Consequently, viable bacteria and microbial-associated molecular patterns cross the intestinal epithelial barrier, a process known as bacterial translocation. An efficient immunological barrier limits this process, promoting a local immune response in activated mesenteric lymph nodes. When this primary firewall fails, microbes and microbial compounds reach the liver, where they activate Kupffer cells by binding Toll-like receptors. Kupffer cells orchestrate several processes, such as the release of inflammatory cytokines and reactive oxygen species, the recruitment of innate immune cells, the activation of hepatic stellate cells. The uncontrolled perpetuation of this pathogenic mechanism results in liver inflammation and damage, fibrogenesis and systemic inflammation. See text for further details.

Oxidative stress plays a critical role in the development of liver damage. The production of reactive oxygen species is a physiological consequence of aerobic life. Hence, organisms have developed antioxidant mechanisms in order to face the harmful effects of these agents. The detrimental effect of these species depends on the balance with antioxidant elements.

When this equilibrium is deranged, ROS can negatively affect both sides of the gut-liver axis. On the one hand, oxidative stress is responsible for intestinal barrier damage. Indeed, diet, alcohol, infectious and primary inflammatory diseases, and drugs are able to cause an imbalance in the redox state in the gut, resulting in increased IP. Furthermore, in advanced liver diseases PHT causes hypoperfusion of the intestinal mucosa. Subsequent hypoxia enhances the activity of xanthine oxidase, resulting in increased ROS release and oxidative damage. On the other hand, the liver is an important scavenger of free radicals, since it plays a crucial role in the restoration of endogenous antioxidants and metabolism of exogenous ones. A significant increase in the level of oxidative stress has been observed in all chronic liver diseases, irrespective of the etiology of the liver disorder. Moreover, all the liver cells are sensitive to oxidative stress-related molecules. The activation of TLR causes the generation of ROS by Kupffer cells. ROS signaling causes the activation and proliferation of HSC. Conversely, as a consequence to the exposure to ROS, Kupffer cells produce cytokines and chemokines, which further stimulate HSCs.

Nevertheless, there are some protective mechanisms. IL-10 mediates remarkable protective effects towards the intestinal mucosa and liver. At the intestinal level, the release of IL-10 by macrophages modulates innate immune activation, preventing an excessive response and consequent tissue damage. Hence, adequate IL-10 levels improve the integrity of the gut barrier, resulting in a decrease in endotoxin absorption. In the liver, IL-10 reduces liver inflammations and fibrosis, inhibiting several Kupffer cells functions.

Similarly, NK cells regulate fibrogenetic mechanisms in the liver. Indeed, NK cells...
perform immunosurveillance activity by killing early activated and senescent HSCs, thus limiting fibrogenesis[11,12]. Interestingly, TIMP-1-expressing HSCs are resistant to NK cells activity[12].

Coeliac disease is the hallmark of the pathogenic mechanism linking increased IP and liver inflammation[6]. Liver damage is a common disorder associated with coeliac disease[11-119]. In a recent meta-analysis, the prevalence of cryptogenic hypertransaminasemia in newly diagnosed coeliac disease is 27%[120]. In coeliac patients, increased permeability has been proved as well[121]. Although the pathogenesis is poorly understood, the theory that liver involvement could be secondary to increased IP and BT is widely accepted[101,108,110]. Bardella et al[110] reported a normalization of transaminases levels in about 90% of patients with increased levels at the time of coeliac disease diagnosis after six months of gluten free diet (GFD). In the remaining 10% other possible causes of liver damage were proven by liver biopsy. Another study demonstrated a significant correlation between serum transaminases levels and IP, assessed with lactulose/mannitol test. The authors found similar response to GFD (64/72 patients, 88.9%) and reported that IP index significantly decreased in conjunction with the normalization of serum transaminases levels within one year of diet. Conversely, in patients who were not compliant with GFD, liver injury persisted and permeability tests remained altered[122]. Furthermore, histological alterations in the liver of patients with newly diagnosed coeliac disease and transaminases elevation suggest that increased IP could be responsible for liver damage in this setting. As reported by Jacobsen et al[119], among 37 liver biopsies performed in coeliac patients, 25 showed non-specific patterns, 7 were diagnostic for other diseases, 5 were classified as normal. Liver histological features of the 25 non-specific specimens documented an increased number of Kupffer cells (52.0%), expanded portal tracts (48.0%) and parenchymal or portal mononuclear infiltration (36% and 20% respectively). Interestingly, some of these alterations are comparable to those observed in other experiments reproducing liver damage in context of increased IP[122]. Thus, these results are consistent with the hypothesis that IP per se could trigger the development of liver damage.

Also in the setting of primary liver disease, increasing evidence is linking IP to liver damage. Occludin deficient (Ocln−/−) mice do not show intestinal TJ alteration[123], but ethanol feeding induces a decrease in E-cadherin and β-catenin distribution, which are other proteins involved in the maintenance of TJ integrity, causing gut barrier dysfunction[124]. Although both ethanol fed Ocln−/− and wild type mice had increased plasma transaminase levels, liver damage was worse in occludin deficient mice, and histopathological examination of the liver confirmed the presence of inflammatory lesion only in Ocln−/− mice[125,126]. As for human studies, Cariello et al[126] demonstrated that plasma levels of inflammatory cytokines (TNF-α and IL-6) are higher in patients with both liver disease and increased IP compared to those with normal IP. A positive correlation between altered IP and liver inflammation and fibrosis was observed in a population of children with non-alcoholic fatty liver disease (NAFLD)[127]. Finally, a recent meta-analysis showed that patients with NAFLD, particularly those with increased liver injury markers, more frequently exhibit altered IP[128]. Altogether, these data suggest a pathogenic mechanism that determines liver damage through the alteration of the gut barrier.

GUT-LIVER AXIS: ROLE IN THE PATHOGENESIS OF NAFLD

The pathogenesis of liver damage in patients with NAFLD is still incompletely understood. However, a growing body of experimental and clinical data suggests a primary role of the gut-liver axis dysfunction. Traditionally, a “double-hit” pathogenetic model has been hypothesized for NAFLD development. Lipid accumulation into the liver (steatosis) represents the first step. Then, a second insult is needed to cause liver injury and inflammation[107,108]. The discovery of a linkage between small intestinal bacterial overgrowth (SIBO) and NAFLD[111-113] and the observation that endotoxin triggers liver inflammation in mice with steatosis[124] brought to the formulation of this hypothesis[125]. Several experiments in animal and human models confirmed the influence of increased IP both in the development of liver steatosis and in the pathogenesis of liver inflammation and fibrosis.

Brun et al[125] reported gut barrier dysfunction, tested as higher epithelial permeability to horseradish peroxidase in obese mice, both genetically deficient in leptin (C57BL/6Job/db) and functionally deficient for the long-form leptin receptor (C57BL/6Jdb/db). Immunochemistry and Western blot confirmed important alterations of TJ proteins (ZO-1 and Occludin) distribution in obese mice. Hence, endotoxin in portal circulation and levels of circulating proinflammatory cytokines...
FIAF is an inhibitor of lipoprotein lipase (LPL), which determines, when suppressed, fasting-induced adipocyte factor (FIAF) by the intestinal L cells and the enterocytes.

Glucagon-like peptide-1, which enhances glucose-dependent insulin release, favors energy absorption. Another important consequence is the release of peptide YY (PYY), a hormone able to slow gastric emptying and intestinal transit and interacting with G-protein coupled receptors GPR41 and gluconeogenesis.

Following the intestinal absorption, SCFAs reach the liver through the portal microbiota in physiological conditions as a result of carbohydrates fermentation. Ethanol production in the pathogenesis of NASH.

These evidences have confirmed the relevance of endogenous oxidative stress; indeed, a significant correlation between ethanol-producing bacteria (SCFAs) and trimethylamine) or by products of their metabolism (e.g., LPS) or by products of their metabolism (e.g., ethanol, short-chain fatty acids (SCFAs) and trimethylamine).

Proteobacteria, particularly Enterobacteriaceae, can ferment carbohydrates to ethanol. In the presence of adequate conditions, the amount produced can be remarkable; indeed, a significant correlation between ethanol-producing bacteria abundance, blood ethanol concentration and liver inflammation has been demonstrated. Besides causing direct toxic effects to the liver, this overproduction determine the activation of hepatic ethanol metabolic pathways and increases liver oxidative stress. These evidences have confirmed the relevance of endogenous ethanol production in the pathogenesis of NASH.

Acetic, propionic and butyric acid are the main SCFAs produced by the gut microbiota in physiological conditions as a result of carbohydrates fermentation. Following the intestinal absorption, SCFAs reach the liver through the portal circulation, where they serve as energy source and exert a relevant role in lipogenesis and gluconeogenesis. Interacting with G-protein coupled receptors GPR41 and GPR43 of intestinal enteroendocrine L cells, SCFAs stimulate the release of the peptide YY (PYY), a hormone able to slow gastric emptying and intestinal transit and favor energy absorption. Another important consequence is the release of glucagon-like peptide-1, which enhances glucose-dependent insulin release. Altogether, these effects may favor the development of NAFLD and NASH.

Furthermore, the intestinal microbiota inhibits the production and secretion of fasting-induced adipocyte factor (FIAF) by the intestinal L cells and the enterocytes. FIAF is an inhibitor of lipoprotein lipase (LPL), which determines, when suppressed,
the activation of LPL and the increase in triglyceride accumulation in the liver and the adipocytes\cite{124}. Hence, increased hepatic lipid storage activates the carbohydrate-responsive element-binding protein and the sterol regulatory element-binding protein 1, perpetuating fat accumulation\cite{159}.

Finally, choline is implicated in the synthesis of very-low density lipoprotein (VLDL). Hence, choline deficiency cause a decrease in the production and release of VLDL and triglyceride accumulation in the liver\cite{170}. Bacteria of the taxa \textit{Erysipelotrichia} are able to metabolize choline to methylamines, toxic compounds that have been correlated to liver damage\cite{157,158}. In NAFLD patients, augmented intestinal metabolism of choline, choline deficiency and abundance of \textit{Erysipelotrichia} taxa have been observed\cite{160}.

Recent studies reported qualitative alterations of the gut microbiota composition in patients with NAFLD. Particularly, \textit{Bacteroides} genus is correlated with NASH and a parallel decrease in \textit{Prevotella} abundance was found\cite{159,160}. In fact, diet enriched in fat, proteins of animal origin and simple sugars, like Western one, promotes \textit{Bacteroides} abundance, whilst an increase in \textit{Prevotella} abundance is favored by a diet rich in fibers and vegetal carbohydrates\cite{159,157}. \textit{Ruminococcus} genus has been positively associated with significant liver fibrosis (≥ F2) in humans\cite{156}, and a correlation between the abundance of this genus and the development of metabolic impairment has been observed in animal models\cite{158}. Alcohol production, due to the ability of \textit{Ruminococcus} to ferment complex carbohydrates, may be responsible for further liver damage\cite{171}. An increase in \textit{Proteobacteria}/\textit{Enterobacteriaceae}/\textit{Escherichia} abundance has been described in NASH and correlates with serum levels of alcohol\cite{156}.

Furthermore, NAFLD-related liver cirrhosis patients showed a low gut microbiota diversity compared to healthy controls. At the genus level, an abundance in \textit{Lactobacillus}, \textit{Bacteroides}, \textit{Ruminococcus}, \textit{Klebsiella}, \textit{Prevotella}, \textit{Enterococcus}, \textit{Haemophilus}, \textit{Pseudomonas}, \textit{Parabacteroides}, \textit{Phascolarctobacterium}, \textit{Veillonella}, \textit{Streptococcus}, \textit{Atopobium}, \textit{Dialister}, \textit{Christensenella}, and decrease in \textit{Methanobrevibacter} and \textit{Akkrmansia} was observed\cite{160}.

It is well known that diet also is a key regulator of IP\cite{154}. In animal models of NAFLD, adaptation of a high-fat diet or high-fructose intake has been associated with increased gut permeability\cite{159,160,157}. Elevated concentrations of saturated fat or fructose favors pro-inflammatory microbiota; on one hand, suppressing production of SCFAs that are essential for intestinal barrier function, on the other hand recruiting macrophages and leading to the release of TNF-α and other cytokines causing mucosal inflammation\cite{159,160,157}. The consequence is a decreased expression of TJ proteins and a higher permeability of the gut barrier\cite{159,154}. Diet-induced increases in blood LPS levels are known as metabolic endotoxaemia and play an important role in the activation of TLR-mediated low-grade liver inflammation, which are associated with NAFLD and NASH\cite{171}. Current evidence from animal studies suggests that a high-fat diet or a high-fructose diet can induce metabolic endotoxaemia by altering the intestinal TJ proteins, mainly ZO-1 and occluding\cite{159,157}. In NAFLD adolescents, postprandial endotoxin levels were increased compared to healthy subjects in response to fructose, but not glucose, beverages (consumed with meals) in a 24-h feeding challenge\cite{172}.

There are currently no data concerning diet modulation of IP in patients with NAFLD, and it is plausible that a healthy diet can reduce IP in patients with NAFLD by restoring the integrity of tight junctions. The Mediterranean diet contains a high intake of mono- and polyunsaturated fatty acids, fibers, polyphenols, antioxidants and phytochemicals; many of these components promote short-chain fatty acid-producing gut bacteria and have significant prebiotic effects\cite{171}. As such, Mediterranean diet was an attractive tool for reducing impaired IP in patients with NAFLD. In a cross-over pilot study\cite{174}, twenty patients with NAFLD underwent 16 weeks of a Mediterranean diet and 16 weeks of a low-fat diet; although the majority of patients presented at baseline, as expected, high IP evaluated according to 51Cr-EDTA, none of the two diets were sufficient to modulate it. Diet-modulation of IP in humans is much more difficult to obtain than in animal models and further research is needed.

**GUT-LIVER AXIS: ROLE IN THE PATHOGENESIS OF CIRRHOSIS**

Increased IP and BT are hallmarks of liver cirrhosis\cite{157,159}. As previously described, the contribution of BT to liver damage could be crucial for the progression to liver cirrhosis. On the other hand, the once liver cirrhosis is establishment it further enhances IP. The magnitude of BT is proportional to the stage of the disease\cite{158} and...
correlates with prognosis\(^\text{(78)}\).

PHT can reasonably be considered the primary determinant of the onset of altered IP in the setting of advanced liver disease. Indeed, increased splanchnic vasodilation induces a decrease in the blood flow and venous congestion at the intestinal mucosal level, leading to ischemia and edema, up to the disruption of the TJ and epithelial barrier dysfunction\(^\text{(197,198)}\). Consequently, BT is enhanced and in most cases it becomes clinically relevant, due to the large extent of the mucosa involved in the pathogenic mechanism\(^\text{(191-193)}\). To confirm of the importance of PHT in the pathogenesis of increased IP, the reduction of hepatic venous pressure gradient by non-selective beta-blocker therapy decreases IP\(^\text{(106)}\).

Endotoxia further worsens the hemodynamics of cirrhotic patients. In fact, the systemic inflammatory response activated by bacteria and their products/fragments leads to the release of cytokines and the consequent synthesis of (NO) by inducible nitric oxide synthase (iNOS)\(^\text{(194-196)}\). The result is a decrease in systemic vascular resistance and the secondary development of hyperdynamic circulation\(^\text{(153,154)}\) that further worsen IP and BT\(^\text{(106)}\). In fact, there is evidence that intestinal decontamination improves the hyperdynamic state in liver cirrhosis\(^\text{(196,197)}\).

Furthermore, increased IP and consequent BT are fundamental pathogenic steps in the development of complications of chronic liver disease\(^\text{(198)}\). In cirrhotic patients, impaired hemodynamics in advanced phases may negatively affect renal function, causing the hepatorenal syndrome (HRS). LPS per se leads to renal vasoconstriction, but it can worsen renal function. In cirrhotic patients, the development of complications of chronic liver disease\(^\text{(74)}\) improves the hyperdynamic state in liver cirrhosis\(^\text{(196)}\).

In liver cirrhosis, the liver capacity to detoxify ammonia, neurotoxic substances and false neurotransmitters, produced by the gut microbiota from the catabolism of dietary proteins, is insufficient\(^\text{(199,201)}\). On the other hand, the formation of portosystemic shunts further decrease the part of blood depurated\(^\text{(211)}\). Thus, entering the bloodstream, these substances are delivered to the brain, where they have detrimental effects, causing edema and altering neurotransmission, causing hepatic encephalopathy (HE)\(^\text{(202,204)}\).

A perturbation in the gut microbiota composition has been linked to the development of HE. In particular, *Alcaligenaceae*, *Porphyromonadaceae*, *Enterobacteriaceae* abundance has been correlated with cognitive impairment and neuroinflammation in cirrhotic patients\(^\text{(212)}\). Moreover, the systemic inflammatory state resulting from the perpetuation of BT independently affects brain functions and worsens cognitive performance\(^\text{(205,206)}\), and finally, inflammation secondarily extends to the brain, where a self-maintaining process is then established\(^\text{(212,213)}\). Hence, the modulation of the gut microbiota and its metabolism represents the basis for the treatment and prevention of overt HE\(^\text{(214,215)}\).

The pathogenesis of portal vein thrombosis (PVT) is incompletely understood. However, besides reduced portal vein flow velocity and prothrombotic state, BT into portal vein could favor the activation of the coagulative cascade\(^\text{(224,225)}\). Indeed, it is known that endotoxin is able to increase thrombin generation via the increased production of tissue factor (TF)\(^\text{(226)}\). Similarly, LPS stimulates the release of factor VIII and von Willebrand factor release, in a way that could be mediated by TLR4 activation\(^\text{(227)}\). Since the liver acts as a firewall towards BT\(^\text{(1)}\), there is a gradient between the concentration of LPS in the portal vein and in the systemic circulation\(^\text{(228)}\). Hence, this could be a significant pathogenic mechanism for the development of PVT in cirrhotic patients\(^\text{(224,225)}\). Interestingly, endotoxin-induced prothrombotic state in the portal system can cause microembolism to hepatic sinusoids, contributing to liver
damage and inflammation\(^{229}\).

Increasing evidence supports the involvement of the gut-liver axis in hepatocarcinogenesis. As aforementioned, intestinal hyperpermeability and consequent BT activate TLRs through the binding with LPS\(^{230}\). The subsequent activation of NF-κB signaling initiates the inflammatory cascade that favors carcinogenesis\(^{230,231}\). Indeed, in animal models, it has been demonstrated that the infusion of LPS stimulates the development as well as the growth of liver tumors\(^{229,230}\). Conversely, the lack of IKK-b, a kinase that frees NF-κB from inhibitory proteins, decreases hepatocarcinogenesis\(^{230}\). An inflammatory environment is crucial for the development of hepatocellular carcinoma (HCC). Cytokines modify the microenvironment by recruiting innate immune cells and altering the extracellular matrix\(^{230,231}\). Moreover, the production of ROS cause direct DNA damage\(^{229}\) and inflammation stimulate cell turnover and proliferation, favoring the accumulation of DNA mutations\(^{230,231}\).

Other MAMPs and PAMPs and microbial metabolites have also been proposed as potential carcinogens\(^{229,230}\). Hence, recent studies have analyzed the gut microbiota of patients with HCC in order to find a microbial fingerprint of the disease. Ponziani et al\(^{246}\) described the gut microbiota of NAFLD cirrhotic patients with HCC. At the genus level, a significant increased abundance of the *Phascolarctobacterium*, *Enterococcus*, *Streptococcus*, *Gemella*, *Bilophila* genera was observed. In another recent study, the abundance of the *Haemophilus*, *Eggerthella*, *Bifidobacterium*, *Butyricimonas*, *Christensella*, *Odoribacter* genera, an unknown genus from Tenericutes phylum and an unknown genus from Firmicutes phylum was significantly increased by 2-3 fold in the HCC group. Interestingly, the authors found a correlation between changes in the gut microbiota and liver inflammation\(^{246}\).

Finally, as regards the gut microbiome in liver cirrhosis, a decreased bacterial diversity has been observed compared to healthy controls. At the phylum level, the abundance of *Bacteroidetes* is reduced, whilst *Proteobacteria* and *Fusobacteria* are increased. The increase in the abundance of potentially pathogenic bacteria, such as *Streptococcus*, *Veillonella*, and *Enterobacteriaceae*, may explain the frequent involvement of these bacteria in the pathogenesis of infectious complications in these patients\(^{230,231}\). A relocation in the distribution of microorganisms along the gastrointestinal tract has been correlated with the onset of the complications of liver cirrhosis, as well\(^{246}\). In particular, a higher abundance of *Streptococcus salivarius* has been correlated with the minimal HE\(^{246}\). In parallel, a decrease in the abundance of potentially beneficial *Lachnospiraceae* and *Clostridium* cluster XIVa has been reported\(^{246,230}\).

---

**GUT-LIVER AXIS AFTER LIVER TRANSPLANTATION**

PHT, which is responsible for increased IP in the setting of liver cirrhosis, is reverted by liver transplantation (LT)\(^{232,234}\). Accordingly, IP should decrease after LT. In a study analyzing IP 2 to 3 years after LT in patients on immunosuppressant drugs (tacrolimus and cyclosporine), Parrilli et al\(^{249}\) reported an increase in lactulose/rhamnose ratio (LacL/L-Rh ratio) that was only due to a decrease in L-Rh excretion. The authors concluded that IP was restored, in spite of the effects of antirejection drugs on intestinal barrier function. Moreover, serum endotoxin levels were similar between LT patients and controls. Another study soon after LT in patients receiving tacrolimus therapy showed that IP, assessed with L/R ratio, was elevated compared to healthy controls. Furthermore, about 50% of the patients had increased serum levels of endotoxin\(^{249}\). Therefore, IP could still be impaired soon after LT and improve later. However, further studies are needed to analyze the modification of IP in patients with cirrhosis after LT.

Few studies analyzed the alterations of the gut microbiota after LT. In particular, a decrease in *Eubacteria*, *Bifidobacterium* spp, *Fecalibacterium prausnitzii* and *Lactobacillus* spp abundance and a decrease in *Enterobacteriaceae* and *Enterococcus* spp has been observed\(^{164}\). Interestingly, in a recent study microbial diversity did not show significant modification during the first week after LT. Instead, during postoperative days 8 to 14 the influence of surgical operation, antibiotics and antirejection therapy reduced microbial diversity\(^{246,249}\). Afterwards diversity was progressively restored\(^{246,249}\). No association was been found between intestinal dysbiosis and acute cellular rejection, post-transplant bloodstream infections and/or the recurrence of liver disease\(^{246,249}\).
CONCLUSION

Increased IP, BT and alterations of the gut microbiota composition are important pathogenic elements responsible for the development of liver damage, the initiation of fibrosis changes up to the development of liver cirrhosis and its complications. At present, there are very few evidences of the efficacy of the role of the gut microbiota modulation in the modification of the natural course of liver disease. Further studies are needed to investigate the efficacy of these strategies.

REFERENCES

1. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 2009; 9: 799-809 [PMID: 19855405 DOI: 10.1038/nri2653]
2. Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. Nat Rev Immunol 2004; 4: 478-485 [PMID: 15137836 DOI: 10.1038/nri1377]
3. Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature 2012; 489: 231-241 [PMID: 22972296 DOI: 10.1038/nature11511]
4. Brandli K, Kumar V, Eickmann L. Gut-liver axis at the frontier of host-microbial interactions. Am J Physiol Gastrointest Liver Physiol 2017; 312: G413-G419 [PMID: 28232456 DOI: 10.1152/ajpgi.00361.2016]
5. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014; 60: 197-209 [PMID: 2390919 DOI: 10.1016/j.jhep.2013.07.044]
6. Okumura R, Takeda K. Maintenance of intestinal homeostasis by mucosal barriers. Inflamm Regen 2018; 38: 5 [PMID: 29619135 DOI: 10.1186/s12321-018-0063-z]
7. Lynch SV. The Human Intestinal Microbiome in Health and Disease. N Engl J Med 2016; 375: 2369-2379 [PMID: 27974040 DOI: 10.1056/NEJMoa1600266]
8. Jandhyala SM, Talukdar R, Subramanyam C, Vyavghar H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol 2015; 21: 8787-8803 [PMID: 26269608 DOI: 10.3748/wjg.v21.i29.8787]
9. Jakobsson HE, Rodriguez-Piñeiro AM, Schüttle A, Ermund A, Boysen P, Bemark M, Sonnem F, Bäckhed F, Hansson GC, Johansson ME. The composition of the gut microbiota shapes the colon mucus barrier. EMBO Rep 2015; 16: 164-177 [PMID: 25252071 DOI: 10.1525/embr.201439263]
10. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012; 336: 1266-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]
11. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016; 535: 65-74 [PMID: 27383981 DOI: 10.1038/nature18847]
12. Britanova I, Diefenbach A. Interplay of innate lymphoid cells and the microbiota. ImmunoL Rev 2017; 279: 36-51 [PMID: 28557040 DOI: 10.1111/imr.12580]
13. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]
14. Rescigno M. mucosal immunity and bacterial handling in the intestine. Best Pract Res Clin Gastroenterol 2013; 27: 17-24 [PMID: 23768549 DOI: 10.1016/j.bpcg.2013.03.004]
15. Rescigno M. Intestinal microbiota and its effects on the immune system. Cell Microbiol 2014; 16: 1004-1013 [PMID: 24720613 DOI: 10.1111/cmi.12301]
16. Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. Curr Gastroenterol Rep 2016; 12: 319-330 [PMID: 27038338 DOI: 10.1007/s11894-016-0131-2]
17. Felsaeedy T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GM, Schüttle A, van der Post S, Svensson F, Rodriguez-Piñeiro AM, Nyström EE, Wissing C, Johansson ME, Hansson GC. The mucins and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system. Immunol Rev 2014; 260: 8-20 [PMID: 24942678 DOI: 10.1111/imr.12182]
18. Johansson ME, Phillipson M, Petersson J, Velech V, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucous layers in colon is devoid of bacteria. Proc Natl Acad Sci U S A 2008; 105: 15604-15609 [PMID: 18806221 DOI: 10.1073/pnas.0803142105]
19. Hollingsworth MA, Swanson BJ. Mucins in cancer: protection and control of the cell surface. Nat Rev Cancer 2004; 4: 45-60 [PMID: 14681689 DOI: 10.1038/nrc1251]
20. Veecke LE, Beyaert R, van Loo G. Enterocyte death and intestinal barrier maintenance in homeostasis and disease. Trends Mol Med 2011; 17: 584-593 [PMID: 21741311 DOI: 10.1016/j.molmed.2011.05.011]
21. Gustafsson JK, Ermund A, Ambort D, Johansson ME, Nilsson HE, Thorell K, Hebert H, Sjövall H, Hansson GC. Bicarbonate and functional CFTR channel are required for proper mucin secretion and link cystic fibrosis with its mucus phenotype. J Exp Med 2012; 209: 1263-1272 [PMID: 22711878 DOI: 10.1084/jem.20120562]
22. Schultz C, Van Den Berg FM, Ten Kate FW, Tytgat GN, Dankert J. The intestinal mucus layer from patients with inflammatory bowel disease harbors high numbers of bacteria compared with controls. Gastroenterology 1999; 117: 1089-1097 [PMID: 10535871]
23. Tawiah A, Cornick S, Moreau F, Gorman H, Kumar M, Twari S, Chude K, High MUC2 Mucin Expression and Misfolding Induce Cellular Stress, Reactive Oxygen Production, and Apoptosis in Goblet Cells. Am J Pathol 2018; 188: 1354-1373 [PMID: 29545196 DOI: 10.1016/j.ajpath.2018.02.007]
24. Husemann M, Pernow B, Eickmann L, Brandi K, Kärkel P, Belzer C, Hellebrand C, Tsukamoto H, Ho SB, Schnabl B. Deficiency of intestinal mucin-2 ameliorates experimental alcoholic liver disease in mice. Hepatology 2015; 58: 108-119 [PMID: 25488308 DOI: 10.1002/hep.28232]
25. Heazlewood CK, Cook MC, Eri R, Price GR, Tauro SB, Taupin D, Thornton DJ, Peng CW, Crockford TL, Cornell RJ, Adams R, Kato M, Nelm KA, Hong NA, Florin TH, Goodnow CC, McGuckin MA. Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis. PLoS Med 2008; 5: e54 [PMID: 18318598 DOI: 10.1371/journal.pmed.0050054]
26. Strocali A, Corazza G, Fumia J, Fine C, Di Sario A, Gasharrini G, Levin MD. Measurements of the jejunal unstirred layer in normal subjects and patients with celiac disease. Am J Physiol 1996; 270: G487-
Nicoletti A et al. Intestinal permeability and liver diseases

G491 [PMID: 8638715 DOI: 10.1152/ajpgi.1996.270.3.4847]

Ponziani FR. Zocca MA, Cerritto L, Gasbarri A, Pompili M. Bacterial translocation in patients with liver cirrhosis: physiological, clinical consequences, and practical implications. Expert Rev Gastroenterol Hepatol 2018; 12: 641-656 [PMID: 29606847 DOI: 10.1080/17474124.2018.1461747]

Ponziani FR, Gerardi V, Gasbarri A. Diagnosis and treatment of small intestinal bacterial overgrowth. Expert Rev Gastroenterol Hepatol 2016; 10: 215-227 [PMID: 26636484 DOI: 10.1586/17474124.2016.1110017]

Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Am Rev Biochem 2003; 72: 137-174 [PMID: 12547708 DOI: 10.1146/annurev.biochem.72.1.161712]

Duparc T, Plovier H, Marraccioli VG, Van Hul M, Essaghir A, Slåttem L, Matamoros S, Geurts L, Pardo-Tendero MM, Druart C, Delzenne NM, Demoulin JB, van der Merwe SW, van Pelt J, Bäckhed F, Monleon D, Everard A, Cani PD. Hepatocyte MyD88 affects bile acids, gut microbiota and metabolism contributing to regulate glucose and lipid metabolism. Gut 2017; 66: 620-632 [PMID: 27196572 DOI: 10.1136/gutjnl-2015-310904]

Lorenzo-Zaúña V, Bartoli R, Planas R, Hofmann AF, Viñado B, Hayge LR, Hernández JM, Mafi J, Alvarez MA, Asuina V, Gasull MA. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. Hepatology 2003; 37: 551-557 [PMID: 12601352 DOI: 10.1053/jlhep.2003.50116]

Bertók L. Bile acids in physico-chemical host defence. Pathophysiology 2004; 11: 139-145 [PMID: 15561510 DOI: 10.1016/j.pathphys.2004.09.002]

Theocaris et al. E. Lithium, Pathophysiology of the tight junction. Pathophysiology 2014; 21: 1705-1720 [PMID: 24923100 DOI: 10.1111/j.1742-7156.2014.00377.x]

Eriksson J, Théron P, Macpherson AJ. Processing and transport of microbiota-derived signals influencing the host. Nature Rev Gastroenterol Hepatol 2014; 11: 411-421 [PMID: 24823015 DOI: 10.1038/nrgastro.2014.50]

Van Itallie CM. Physiology and function of the tight junction. Cold Spring Harb Perspect Biol 2009; 1: a002584 [PMID: 20660690 DOI: 10.1101/cshperspect.a002584]

Van Itallie CM, Holmes J, Bridges A, Gookin JL, Coccaro MR, Proctor W, Coleogio OR, Anderson JM. The density of small tight junction pores varies among cell types and is increased by expression of claudin-2. J Cell Sci 2008; 121: 298-305 [PMID: 18198187 DOI: 10.1242/jcs.021485]

Coleogio OR, Van Itallie C, Rahner C, Anderson JM. Claudin extracellular domains determine paracellular charge selectivity and resistance but not tight junction fibril architecture. Am J Physiol Cell Physiol 2004; 286: C1346-C1354 [PMID: 12700140 DOI: 10.1152/ajpcell.00655.2003]

Amashah S, Meini N, Gitter AH, Schönberg T, Mankertz J, Schulze JK, Fromm M. Claudin-2 expression induces cation-selective channels in tight junctions of epithelial cells. J Cell Sci 2002; 115: 4969-4976 [PMID: 12432083]

Taylor CT, Daus AL, Colgan SP. Autocrine regulation of epithelial permeability by hypoxia: role for polarized release of tumor necrosis factor alpha. Gastroenterology 1998; 114: 657-668 [PMID: 9516386]

Madara JL. Staffod J. Interferon-gamma directly affects barrier function of cultured intestinal monolayers. J Clin Invest 1989; 83: 724-727 [PMID: 24923100 DOI: 10.1172/JCI113938]

Turner JR, Rill BK, Carlson SL, Barnes D, Kerner R, Mrsny RJ, Madara JL. Physiological regulation of epithelial tight junctions is associated with myosin light-chain phosphorylation. Am J Physiol 1997; 273: C1378-C1385 [PMID: 8357778 DOI: 10.1152/ajpcell.1997.273.C1378]

Hartmann P, Hainemier M, Mazogava M, Brenner DA, Schnabl B. Toll-like receptor 2-mediated intestinal injury and enteric tumor necrosis factor receptor II contribute to liver fibrosis in mice. Gastroenterology 2012; 143: 1330-1340.e1 [PMID: 22841787 DOI: 10.1053/j.gastro.2012.07.099]

Miele L, Valenza V, La Torre G, Montalto M, Cammarata G, Ricci R, Masciandò R, Forgione A, Gabrieli F, Balmer ML, Endt K, Geuking MB, Curtiss R, McCoy KD, Macpherson AJ. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. Science 2010; 328: 1705-1709 [PMID: 20576892 DOI: 10.1126/science.1188454]

Gautreaux MD, Deitch EA, Berg RD. T lymphocytes in host defense against bacterial translocation from the gastrointestinal tract. Infect Immun 1994; 62: 2874-2884 [PMID: 8017904 DOI: 10.1128/IAI.62.6.2874-2884.1994]

Gautreaux MD, Geller FB, Deitch EA, Berg RD. Adoptive transfer of T lymphocytes to T-cell-depleted mice inhibits Escherichia coli translocation from the gastrointestinal tract. Infect Immun 1995; 63: 3827-3834 [PMID: 7558287]

Hapfelmeier S, Lawson MA, Slack E, Kirndi JK, Stoel M, Heikenwalder M, Cahenzli J, Velaykoredko Y, Bäckhed F, Rea DR, Smith JC, Macpherson AJ. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. Science 2010; 328: 1705-1709 [PMID: 20576892 DOI: 10.1126/science.1188454]

Spadoni I, Zagoato E, Bertocchi A, Paolimelli R, Hot E, Di Sabatino A, Caprilli F, Boitigliari L, Oldani A, Viola G, Penna G, Dejana E, Rescigno M. A gut-vascular barrier regulates the systemic dissemination of bacteria. Science 2015; 350: 830-834 [PMID: 26564856 DOI: 10.1126/science.aac1035]

Spadoni I, Formasa G, Rescigno M. Organ-specific protection mediated by cooperation between vascular and epithelial barriers. Nat Rev Immunol 2017; 17: 761-773 [PMID: 28869253 DOI: 10.1038/nri.2017.100]

Spadoni I, Pietrelli A, Pesole G, Rescigno M. Gene expression profile of endothelial cells during perturbation of the gut vascular barrier. Gut Microbes 2016; 7: 540-548 [PMID: 27723418 DOI: 10.1080/19490976.2016.1211103]
Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin Invest 2015; 115: 497-509 [PMID: 25129800 DOI: 10.1122/jc20150319]

Macrophage CD14: The liver as a firewall--clearance of commensal bacteria that have escaped from the gut. Gastroenterol Hepatol 2015; 2: 185-188 [PMID: 25734591 DOI: 10.1016/j.gaster.2014.12.008]

Intravascular immune response to Borrelia burgdorferi involves Kupffer cells and iNKT cells. Nat Med 2014; 20: 1680-1687 [PMID: 24931816 DOI: 10.1038/nm.3652]

The liver: the liver as a firewall--clearance of commensal bacteria. Gut Microbes 2014; 5: 237ra66 [PMID: 24848256 DOI: 10.1002/gmi.16]

Liver: the liver as a firewall--clearance of commensal bacteria. Nat Commun 2014; 5: 4616 [PMID: 24853165 DOI: 10.1038/ncomms5616]

Intestinal permeability and liver diseases. Gut Microbes 2014; 5: 461-466 [PMID: 24682785 DOI: 10.1080/19490976.2013.791203]

Liver permeability and its role in nutrition. J Hepatol 2012; 56: 323-338 [PMID: 22467675 DOI: 10.1016/j.jhep.2011.09.021]

Liver inflammation and injury. Gut Liver 2011; 5: 16-27 [PMID: 21533657 DOI: 10.4049/gutliver.10-0091]

Liver as a firewall modulating bacterial translocation. World J Gastroenterol 2010; 16: 6387-6395 [PMID: 20847456 DOI: 10.3748/wjg.v16.i32.6387]

Liver inflammation. J Gastroenterol Hepatol 2006; 21 (Suppl 1): S96-S101 [PMID: 16931088 DOI: 10.1111/j.1440-1746.2006.04596.x]

Liver injury and repair. J Gastroenterol Hepatol 2006; 21 (Suppl 1): S102-S109 [PMID: 16931089 DOI: 10.1111/j.1440-1746.2006.04597.x]

Liver: the liver as a firewall. Gastroenterol Hepatol 2005; 1: 5-14 [PMID: 16169626 DOI: 10.1016/j.gl.2005.03.002]

Liver as a firewall. J Clin Gastroenterol 2005; 39: 299-301 [PMID: 15937418 DOI: 10.1097/01.mcg.0000161646.67847.e0]

Liver and nutrition. J Gastroenterol Hepatol 2005; 20 (Suppl 3): S287-S291 [PMID: 16059746 DOI: 10.1111/j.1440-1746.2005.03659.x]

Liver repair. J Gastroenterol Hepatol 2005; 20 (Suppl 3): S292-S295 [PMID: 16059747 DOI: 10.1111/j.1440-1746.2005.03658.x]
Seki E, De Minicis S, Österreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007; 13: 1324-1332 [PMID: 17952900 DOI: 10.1038/nm1663]

Seki E, Schnabl B. Role of innate immunity and the microbiota in liver fibrosis: crosstalk between the liver and gut. *J Physiol* 2012; 590: 447-458 [PMID: 22124143 DOI: 10.1113/jphysiol.2011.219691]

Wre A, Broderick L, Canbay A, Hoffman HM, Feldstein AE. From NAFLD to NASHI: cirrhosis-new insights into disease mechanisms. *Nat Rev Gastroenterol Hepatol* 2013; 10: 627-636 [PMID: 23958599 DOI: 10.1038/nrgastro.2013.149]

Tsichuda T, Friedmann SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017; 14: 397-411 [PMID: 28487545 DOI: 10.1038/nrgastro.2017.38]

Benyon RC. Arthur MJ. Extracellular matrix degradation and the role of hepatic stellate cells. *Semin Liver Dis* 2001; 21: 373-384 [PMID: 11586466 DOI: 10.1055/s-2001-17522]

Roderfeld M. Matrix metalloproteinase functions in hepatic injury and fibrosis. *Matrix Biol* 2018; 68-69: 452-462 [PMID: 29221811 DOI: 10.1016/j.matbio.2017.11.011]

Knittel T, Mehde M, Kobold D, Saile B, Dinter C, Ramadori G. Expression patterns of matrix metalloproteinases and their inhibitors in parenchymal and non-parenchymal cells of rat liver: regulation by TNF-alpha and TGF-beta1. *J Hepatol* 1999; 30: 48-60 [PMID: 9927150]

Schuppan D, Rühl M, Somasundaram R, Hahn EG. Matrix as a modulator of hepatic fibrogenesis. *Semin Liver Dis* 2001; 21: 351-372 [PMID: 11586465 DOI: 10.1056/semolbio.2001-17556]

Miele L, Fargione A, La Torre G, Vero V, Cefalo C, Racco S, Vellone VG, Vecchio FM, Gasbarini G, Rapaccini GL, Neuman MG, Gregico A. Serum levels of hyaluronic acid and tissue metalloproteinase inhibitor-1 combined with age predict the presence of nonalcoholic steatohepatitis in a pilot cohort of subjects with nonalcoholic fatty liver disease. *Transl Res* 2009; 154: 194-201 [PMID: 19766963 DOI: 10.1016/j.trsl.2009.06.007]

Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. *World J Gastroenterol* 2014; 20: 8082-8091 [PMID: 25099360 DOI: 10.3748/wjg.v20.i25.8082]

Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007; 39: 44-84 [PMID: 16979065 DOI: 10.1016/j.biocel.2006.07.001]

Gil-Carodoso K, Ginés I, Piment M, Arzévalo A, Tera X, Blay M. A cafeteria diet triggers intestinal inflammation and oxidative stress in obese rats. *Br J Nutr* 2011; 117: 218-229 [PMID: 21832633 DOI: 10.1017/S0007114511006609]

Keshavzarzian A, Farhadi A, Foronyh CB, Rangan J, Jakate S, Shaikh M, Banan A, Fields JZ. Evidence that chronic alcohol exposure promotes intestinal oxidative stress, intestinal hyperpermeability and endotoxemia prior to development of alcoholic steatohepatitis in rats. *J Hepatol* 2009; 50: 538-547 [PMID: 19155960 DOI: 10.1016/j.jhep.2008.10.028]

van Ampting MT, Schoneville AJ, Vink C, Brummer RJ, van der Meer R, Bovee-Oudenhoven IM. Intestinal barrier function in response to abundant or depleted mucosal glutathione in Salmonella-infected rats. *MBRC Physiol* 2009; 9: 6 [PMID: 19374741 DOI: 10.1472/1761-9793-9-6]

Novak EA, Mollen KP. Mitochondrial dysfunction in inflammatory bowel disease. *Front Cell Dev Biol* 2015; 3: 62 [PMID: 26484345 DOI: 10.3389/fcell.2015.00062]

Utteri E, Usai P. Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease. *World J Gastroenterol* 2017; 23: 3954-3963 [PMID: 28652650 DOI: 10.3748/wjg.v23.i22.3954]

Ramachandran A, Prabhu R, Thomas S, Reddy JB, Pulidwood A, Balasubramanian KA. Intestinal mucosal alterations in experimental cirrhosis in the rat: role of oxygen free radicals. *Hepatology* 2002; 35: 622-629 [PMID: 11870376 DOI: 10.1053/hepg.2002.51656]

Casas-Grajales S, Muriel P. Antioxidants in liver health. *World J Gastrointest Pharmacol Ther* 2015; 6: 59-72 [PMID: 26261734 DOI: 10.4292/wjgpt.v6.i3.59]

Maeloro E, Casini AF, Del Bello B, Comporti M. Lipid peroxidation and antioxidant systems in the liver injury produced by glutathione depleting agents. *Biochem Pharmacol* 1990; 39: 1513-1521 [PMID: 2373468]

Luangmonkong T, Suriguga S, Mutsaers HAM, Groothuis GMM, Olinga P, Boersema M. Targeting Oxidative Stress for the Treatment of Liver Fibrosis. *Rev Physiol Biochem Pharmacol* 2018; 217: 55-72 [PMID: 29786869 DOI: 10.1007/s00226-018-1012]

Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, Feng Y. The Role of Oxidative Stress and Antioxidants in Liver Diseases. *Int J Mol Sci* 2015; 16: 26087-26124 [PMID: 26540040 DOI: 10.3390/ijms161125942]

Liang S, Kisseleva T, Brenner DA. The Role of NADPH Oxidases (NOXs) in Liver Fibrosis and the Activation of Myofibroblasts. *Front Physiol* 2016; 7: 17 [PMID: 26869935 DOI: 10.3389/fphys.2016.00017]

Nieto N. Oxidative-stress and IL-6 mediate the fibrogenic effects of [corrected] Kupffer cells on stellate cells. *Hepatology* 2006; 44: 1487-1501 [PMID: 17133847 DOI: 10.1002/hep.21427]

Krause P, Morris V, Greenbaum JA, Park Y, Bjerheuden U, Mikulski Z, Muffley T, Shui JW, Kim G, Cheroutre H, Liu YC, Peters B, Kronenberg M, Muri M. IL-10-producing intestinal macrophages prevent excessive antibacterial innate immunity by limiting IL-23 synthesis. *Nat Commun* 2015; 6: 7055 [PMID: 25959063 DOI: 10.1038/ncomms8055]

Gómez-Hurtado I, Moratalla A, Moya-Pérez Á, Peiró G, Zapater P, González-Navaías JM, Giménez P, Such J, Sanz Y, Francés R. Role of interleukin 10 in norflaxcin prevention of luminal free endotoxin translocation in mice with cirrhosis. *J Hepatol* 2014; 61: 799-808 [PMID: 24882049 DOI: 10.1016/j.jhep.2014.05.031]

Thompson K, Malthy J, Fallowfield J, McAlayul M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. *Hepatology* 1998; 28: 1597-1606 [PMID: 9828224 DOI: 10.1002/hep.21427]

de Souza-Cruz S, Victoria MB, Tarragó AM, da Costa AG, Pimentel JP, Eres EF, Araújo L, Coelho-Reis RG, Gomes Mde S, Amaral LR, Teixeira-Carvalho A, Martins-Filho OA, Victoria Fda S, Malheiro A. Liver and blood cytokine microenvironment in HCV patients is associated to liver fibrosis score: a proinflammatory cytokine ensemble orchestrated by TNF and tuned by IL-10. *BMC Microbiol* 2016; 16: 3 [PMID: 26742960 DOI: 10.1186/s12866-015-0610-6]

Melhem A, Muhanna N, Bishara A, Alvarez CE, Ilan Y, Bishara T, Horani A, Nassar M, Friedmann SL, Safadi R. Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC.
Diet induced NAFLD mouse: Attention to the gut-vascular barrier dysfunction.

Tan J, Qian W, Zhang L, Hou X. Gut inflammation exacerbates hepatic injury in the high-fat diet induced NAFLD mouse: Attention to the gut-vascular barrier dysfunction. Life Sci 2018; 209: 157-166
Inflammation in Nonalcoholic Fatty Liver Disease.

Hepatology

Pompili M, Mazzaferro V. Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Paroni Sterbini F, Petito V, Reddel S, Calvani R, Camisaschi C, Picca A, Tuccitto A, Gasbarrini A, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, Sanguinetti M, Morelli D, Kendziorski C, Suen G. Unique aspects of fiber degradation by the ruminal ethanologen Ruminococcus, Dawson JA, Stevenson DM, Cunningham AC, Bramhacharya S, Weimer PJ, 2013;: 2833-2845 [PMID: 23651394 DOI: 10.1021/pr4001702]

Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking the human gastrointestinal microbiome and development of fatty liver with choline deficiency. Proc Natl Acad Sci USA 2011;108: 1285-1297 [PMID: 21745271 DOI: 10.1111/j.1478-3231.2011.02462.x]

Tung Z, Cliffler E, Bennett JJ, Koeth R, Levenson BS, Dugar B, Feldstein AE, Brit EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD, Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. Gut flora regulates adipokine expression and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. Liver Int 2011;31: 1285-1297 [PMID: 21745271 DOI: 10.1111/j.1478-3231.2011.02462.x]

Bäckhed F, Ley RE, Turnbaugh PJ, Beauty WS, Knight RD, Gordon JI. The gut microbiota shapes host metabolic responses. Nature 2006;444: 1066-1070 [PMID: 16548066 DOI: 10.1038/nature05394]

Bäckhed F, Ley RE, Turnbaugh PJ, Beauty WS, Knight RD, Gordon JI. The gut microbiota shapes host metabolic responses. Nature 2006;444: 1066-1070 [PMID: 16548066 DOI: 10.1038/nature05394]

Bäckhed F, Ley RE, Turnbaugh PJ, Beauty WS, Knight RD, Gordon JI. The gut microbiota shapes host metabolic responses. Nature 2006;444: 1066-1070 [PMID: 16548066 DOI: 10.1038/nature05394]
Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, Tilg H, Watson A, Wells JM. Intestinal permeability—a new target for disease prevention and therapy. *BMC Gastroenterol* 2014; 14: 189 [PMID: 25407211 DOI: 10.1186/s12876-014-0189-7]

Serino M, Luche E, Gres S, Baylac A, Bergé M, Cencar C, Waget A, Kopp P, Jaccovi J, Kopp C, Mariette J, Boucher O, Luch J, Ouarné F, Monsan P, Valet P, Roques C, Amar J, Bouloumnié A, Théodorou V, Burcelin R. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. *Gut* 2012; 61: 543-553 [PMID: 2210050 DOI: 10.1136/gutjnl-2011-301012]

Sprau A, Kanuri G, Wagnerberger S, Haub S, Bischoff SC, Berghiem I. Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatoasis in mice. *Hepatology* 2009; 50: 1094-1104 [PMID: 19637282 DOI: 10.1002/hep.23122]

Lambertz J, Weiskirchen S, Landert S, Weiskirchen R. Fructose: A Dietary Sugar in Crossstalk with Microbiota Contributing to the Development and Progression of Non-Alcoholic Liver Disease. *Front Immunol* 2017; 8: 1159 [PMID: 28970836 DOI: 10.3389/fimmu.2017.01150]

Ray K. NAFLD. Leaky guts: intestinal permeability and NASI. *Nat Rev Gastroenterol Hepatol* 2015; 12: 123 [PMID: 25645967 DOI: 10.1038/nrgastro.2015.15]

Miele L, Marrone G, Lauritano C, Cefalo C, Gasbarrini A, Day C, Grieco A. Gut-liver axis and microbiota in NAFLD: insight pathophysiology for novel therapeutic target. *Curr Pharm Des* 2013; 19: 5314-5324 [PMID: 23832692]

Kirpich IA, Marsano LS, McClain CJ. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. *Clin Biochem* 2015; 48: 923-930 [PMID: 26151226 DOI: 10.1016/j.clinbiochem.2015.06.023]

Canli PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; 57: 1470-1481 [PMID: 18305141 DOI: 10.23736/S0012-1878.07.01403-6]

Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magnes S, John C, Lund PK. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mice. *PLoS One* 2010; 5: e12191 [PMID: 20808947 DOI: 10.1371/journal.pone.012191]

Kavanagh K, Wylie AT, Tucker KL, Hamp TJ, Gharabeh RZ, Fodor AA, Cullen MJ. Dietary fructose induces endotoxemia and hepatic injury in calorically controlled primates. *Am J Clin Nutr* 2013; 98: 349-357 [PMID: 23783298 DOI: 10.3945/ajcn.112.057331]

Jin R, Willment A, Patel SS, Sun X, Song M, Mannery YO, Kosters A, McClain CJ, Bos MB. Fructose induced endotoxemia in pediatric nonalcoholic Fatty liver disease. *Int J Hepatol* 2014; 2014: 560620 [PMID: 25228713 DOI: 10.1155/2014/560620]

Bifulco M. Mediterranean diet: the missing link between gut microbiota and inflammatory diseases. *Eur J Clin Nutr* 2015; 69: 1078 [PMID: 26014263 DOI: 10.1038/ejcn.2015.81]

Biolato M, Manca F, Marrone G, Cefalo C, Racso S, Miggiano GA, Valenza V, Gasbarrini A, Miele L, Grieco A. Intestinal permeability after Mediterranean diet and low-fat diet in non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25: 509-520 [PMID: 30700946 DOI: 10.3748/wjg.v25.i4.509]

Zapater P, Françés R, González-Navajas JM, de la HO M, Moreu R, Pascual S, Monfort D, Montoliu S, Vila C, Escudero A, Torres X, Cirera I, Llanos L, Guarnier-Armente C, Palazón JM, Carneric F, Bellot P, Guarnier C, Planas R, Solà R, Serra MA, Muñoz C, Pérez-Mateo M, Such J. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. *Hepatology* 2008; 48: 1924-1931 [PMID: 19003911 DOI: 10.1002/hep.22564]

Iwao T, Toyonaga A, Ikekami M, Obo K, Sumino M, Harada H, Sakaki M, Shigemori H, Aoki T, Tanikawa K. Reduced gastric mucosal blood flow in patients with portal-hypertensive gastropathy. *Hepatology* 1993; 18: 36-40 [PMID: 8325619]

Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, Lammert F, Trauner M, Mariette J, Bouchez O, Torras X, Cirera I, Llanos L, Guarner-Argente C, Palazón JM, Carnicer F, Bellot P, Guarnier C, Planas R, Solà R, Serra MA, Muñoz C, Pérez-Mateo M, Such J. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. *Hepatology* 2008; 48: 1924-1931 [PMID: 19003911 DOI: 10.1002/hep.22564]

Théodorou V, Burcelin R. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota and hepatic injury in calorically controlled primates. *Am J Clin Nutr* 2013; 98: 349-357 [PMID: 23783298 DOI: 10.3945/ajcn.112.057331]

Francès R, Muñoz C, Zapater P, Uceda F, Gascoín I, Pascual S, Pérez-Mateo M, Such J. Bacterial DNA activates cell mediated immune response and nitric oxide overproduction in portaline macrophages from patients with cirrhosis and ascites. *Gut* 2004; 53: 860-864 [PMID: 15138214]

Albillos A, de la Hera A, González M, Moya JL, Calleja JL, Monserrat J, Ruiz-del-Arbol L, Alvarez-Mon M. Increased lipopolysaccharide binding protein in cirrhotic patients with marked and hemodynamic derangement. *Hepatology* 2003; 37: 208-217 [PMID: 12500206 DOI: 10.1002/hep.50038]

Mishima S, Xu D, Lu Q, Deitch EA. Bacterial translocation is inhibited in inducible nitric oxide synthase knockout mice after endotoxin challenge but not in a model of bacterial overgrowth. *Arch Surg* 1997; 132: 1190-1195 [PMID: 9367611]

McAvey NC, Semple S, Richards JM, Robson AJ, Patel D, Jardine AG, Leyland K, Cooper AS, Newby DE, Hayes PC. Differential visceral blood flow in the hyperdynamic circulation of patients with liver cirrhosis. *Aliment Pharmacol Ther* 2016; 43: 947-954 [PMID: 26947424 DOI: 10.1111/apt.13571]

Du Plessis J, Vanheel H, Janssen CE, Ross L, Slavik T, Shvartsik PI, Nieuwoudt M, van Wyk SG, Vieira W, Pretorius E, Beuke M, Fariol R, Tack J, Laleman W, Favery J, Nevens F, Roskams T, Van der Merwe SW. Activated intestinal macrophages in patients with cirrhosis related to IL-6 that may disrupt intestinal barrier function. *J Hepatol* 2013; 58: 1125-1132 [PMID: 23402745 DOI: 10.1016/j.jhep.2013.01.038]

Zhu Q, Zou L, Jagaveolu K, Simonetto DA, Huetbert RC, Jiang ZD, DuPont HL, Shah VH. Intestinal decontamination inhibits TLR4 dependent fibrinogen-mediated cross-talk between stellate cells and endothelial cells in liver fibrosis in mice. *J Hepatol* 2012; 56: 893-899 [PMID: 22173161 DOI: 10.1016/j.jhep.2011.07.026]
Mechanistic aspects.

5. J Clin Exp Hepatol 2015; 5: S21-S28 [PMID: 26041953 DOI: 10.1016/j.jceh.2015.10.008]

Nicoletti A et al. Intestinal permeability and liver diseases

WJG | https://www.wjgnet.com

September 7, 2019 | Volume 25 | Issue 33

4832
American Association for the Study of Liver Diseases. European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014; 61: 642-659 [PMID: 25012450 DOI: 10.1016/j.jhep.2014.05.042]

Ponziani FR, Gerardi V, Peccer S, D’Aversa F, Lopetuso L, Zocco MA, Pompili M, Gasbarrini A. Effect of rifaximin on gut microbiota composition in advanced liver disease and its complications. World J Gastroenterol 2015; 21: 12322-12333 [PMID: 26804640 DOI: 10.3748/wjg.v21.i43.12322]

Garcovich M, Zoce MA, Roccarina D, Ponziani FR, Gasbarrini A. Prevention and treatment of hepatic encephalopathy: focusing on gut microbiota. World J Gastroenterol 2012; 18: 6693-6700 [PMID: 23239905 DOI: 10.3748/wjg.v18.i46.6693]

Violi F, Ferro D, Basili S, Lionetti R, Rossi E, Merli M, Riggio O, Bezzi M, Capocaccia L. Ongoing prothrombotic state in the portal circulation of cirrhotic patients. Thromb Haemost 1997; 77: 44-47 [PMID: 9031447]

Violi F, Lip GY, Cancemi R. Endotoxemia as a trigger of thrombosis in cirrhosis. Haematologica 2016; 101: e162-e163 [PMID: 27033239 DOI: 10.3324/haematol.2015.139972]

Moore KL, Andreoli SP, Esmon CT, Bang NU. Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro. J Clin Invest 1987; 79: 124-130 [PMID: 3025256 DOI: 10.1172/JCI112772]

Carnevale R, Raparelli V, Nocella C, Bartimoccia S, Novo M, Severino A, De Falco E, Cammisotto V, Pasquale C, Crescioli C, Scavalli AS, Riggio B, Basili S, Violi F. Gut-derived endotoxin stimulates factor VIII secretion from endothelial cells. Implications for hypercoagulability in cirrhosis. J Hepatol 2017; 67: 950-956 [PMID: 28716745 DOI: 10.1016/j.jhep.2017.07.002]

Lumsden AB, Henderson JM, Kutter MH. Endotoxin levels measured by a chromogenic assay in portal, hepatic and peripheral venous blood in patients with cirrhosis. Hepatology 1988; 8: 232-236 [PMID: 3281884]

Shibayama Y. Sinusoidal circulatory disturbance by microthrombosis as a cause of endotoxin-induced hepatic injury. J Pathol 1987; 151: 315-321 [PMID: 3588589 DOI: 10.1002/path.1711510412]

Pikarsky E, Porta SM, Stein P, Abramovich R, Amler L, Kaser M, Gutkovich-Pyet E, Urieli-Shoval S, Galun E, Ben-Neriah Y. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature 2004; 431: 461-466 [PMID: 15329734 DOI: 10.1038/nature02924]

Bishaye A. The role of inflammation and liver cancer. Adv Exp Med Biol 2014; 816: 401-435 [PMID: 24318712 DOI: 10.1007/978-3-319-0387-8_16]

Dapito DH, Mencin A, Gwak GY, Pradera JP, Jang MK, Mederacke I, Caviglial JM, Khiabanian H, Ozychewski A, Bielat E, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cancer Cell 2019; 35: 977-990 [PMID: 31506736 DOI: 10.1016/j.ccell.2019.03.007]

Maeda S, Kamata H, Loo JL, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell 2005; 121: 977-990 [PMID: 15989949 DOI: 10.1016/j.cell.2005.04.014]

Nakagawa H, Maeda S. Inflammation- and stress-related signaling pathways in hepatocarcinogenesis. World J Gastroenterol 2012; 18: 4071-4081 [PMID: 22919237 DOI: 10.3748/wjg.v18.i31.4071]

Ma-Ou C, Sanpavat A, Sarnelli G, Corsaro MM, Coccoli P, Viglione L, Cuomo R, Budillon G. Effect of rifaximin on gut microbiota composition in advanced liver disease and its complications. World J Gastroenterol 2015; 21: 12322-12333 [PMID: 26804640 DOI: 10.3748/wjg.v21.i43.12322]

Thromb Haemost: 61: e162-e163 [PMID: 27033239 DOI: 10.3324/haematol.2015.139972]
chronic administration of tacrolimus and cyclosporine on human gastrointestinal permeability. Liver Transpl 2003; 9: 484-488 [PMID: 12740791 DOI: 10.1053/jlts.2003.50088]

246 Gabe SM, Bjarnason I, Tolou-Ghamari Z, Tredger JM, Johnson PG, Barclay GR, Williams R, Silk DB. The effect of tacrolimus (FK506) on intestinal barrier function and cellular energy production in humans. Gastroenterology 1998; 115: 67-74 [PMID: 9649460]

247 Wu ZW, Ling ZX, Lu HF, Zuo J, Sheng JF, Zheng SS, Li LJ. Changes of gut bacteria and immune parameters in liver transplant recipients. Hepatobiliary Pancreat Dis Int 2012; 11: 40-50 [PMID: 22251469]

248 Kato K, Nagao M, Miyamoto K, Oka K, Takahashi M, Yamamoto M, Matsumura Y, Kaido T, Uemoto S, Ichiyama S. Longitudinal Analysis of the Intestinal Microbiota in Liver Transplantation. Transplant Direct 2017; 3: e144 [PMID: 28405600 DOI: 10.1097/TXD.0000000000000661]

249 Doycheva I, Leise MD, Watt KD. The Intestinal Microbiome and the Liver Transplant Recipient: What We Know and What We Need to Know. Transplantation 2016; 100: 61-68 [PMID: 26647107 DOI: 10.1097/TP.0000000000001008]
