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

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### 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.

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**Core tip:** The integrity of the gut-liver axis is crucial for the maintenance of the homeostasis of the organism. The disruption of the intestinal barrier and consequent increased intestinal permeability has been recently associated with the development of liver damage. This review summarizes present evidence on the relevance of the derangement of the gut-liver axis in the pathogenesis of liver damage and non-alcoholic fatty liver disease, the development of the complications of liver cirrhosis and its modifications after liver transplantation.

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## 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<sup>[1]</sup>. 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<sup>[2,3]</sup>.

The gut and the liver are anatomically connected by portal circulation, and their functional unit realizes the gut-liver axis<sup>[4]</sup>. Thus, any type of substance that goes beyond the gut barrier can reach the liver where 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<sup>[5]</sup>. 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<sup>[5]</sup>.

## 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<sup>[1,6]</sup>. 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<sup>[7]</sup>.

Several factors, such as birth mode, age, diet and lifestyle, influence the human gut microbiota. In physiological conditions, its compositional and functional harmony 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

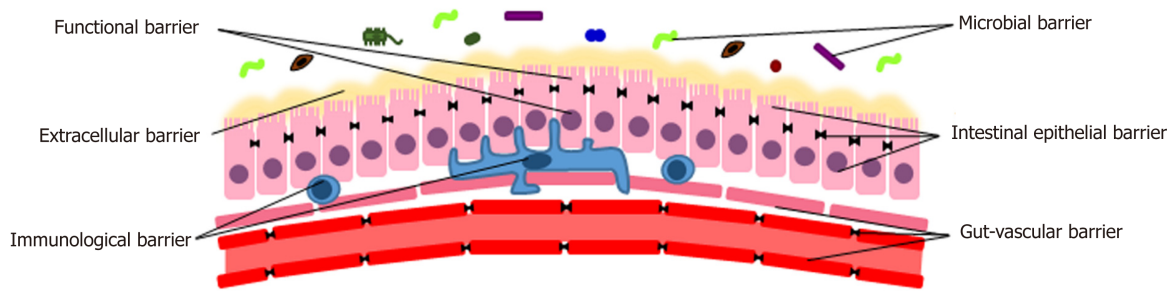


Figure 1 Physiological gut barrier.

and endogenous substances<sup>[8]</sup>. Microorganisms host in the lumen interact with the intestinal mucosa, shaping the mucus<sup>[9]</sup>, exerting a trophic and protective function towards enterocytes. Moreover, it plays a pivotal role in the development, maturation and maintenance of the immune system<sup>[10-15]</sup> and induces local production of antimicrobial peptides and immunoglobulins<sup>[8,12]</sup>.

### Extracellular barrier

Intestinal mucus is a gel formed by glycosylated proteins secreted by intestinal goblet cells called mucins<sup>[16]</sup>. It covers the whole gut and its thickness depends on the location, being almost absent in the stomach and maximum in the colon<sup>[17]</sup>. Mucus prevents harmful substances and bacteria from directly contacting cell surface, causing inflammation<sup>[18-20]</sup>. 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<sup>[20]</sup>. Indeed, quantitative or qualitative alterations of the mucus layer has been documented in several diseases, such as cystic fibrosis<sup>[21]</sup> and inflammatory bowel disease (IBD)<sup>[22]</sup>. 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<sup>[23]</sup>. An increased mucus thickness has been related to alcohol intake and cirrhosis<sup>[24]</sup>. Conversely, an incorrect assembly of MUC2 inside the epithelial cells leads to the development of an inflammatory disease resembling ulcerative colitis in mice<sup>[23,25]</sup>. This process may be responsible of the depletion of goblet cells documented in IBD<sup>[16]</sup>.

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<sup>[18]</sup> 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<sup>[26]</sup>.

### 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<sup>[1,27]</sup>. 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<sup>[28]</sup>. Bile acids, the main constituents of bile, have direct antimicrobial properties interfering with membrane and protein production and integrity<sup>[29-32]</sup>. 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<sup>[28,33]</sup>.

### 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 (transcellular pathway)<sup>[1]</sup>. 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<sup>[34,35]</sup>. Both tight and adherens junctions are connected to the cytoskeleton<sup>[36]</sup>. TJ are important elements for both active and passive transport through the gut barrier<sup>[37]</sup>. They regulate the passive flow of the solutes and water through the paracellular pathway, operating both as a size- and charge-selective filter<sup>[38]</sup>. 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<sup>[1,38-40]</sup>.

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<sup>[41]</sup>. Moreover, the complex system of TJ is finely regulated by the influence of cytokines, particularly tumor necrosis factor- $\alpha$  (TNF $\alpha$ )<sup>[42]</sup> and interferon gamma (IFN $\gamma$ )<sup>[42]</sup>, and by signaling kinases and cytoskeleton, like myosin light chain kinases (MLCK)<sup>[43,44]</sup>. Both qualitative and quantitative alterations of TJ have been described in the context of liver disease<sup>[45,46]</sup>. 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<sup>[47]</sup>.

### **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<sup>[5]</sup>. These elements are secreted into the gut lumen and are host in the inner face of the mucin layer hosts<sup>[48]</sup>. 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<sup>[49-51]</sup>. 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<sup>[52]</sup>. Observing functional similarities between blood-brain barrier and intestinal barrier, Spadoni *et al.*<sup>[52,53]</sup> 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<sup>[53,54]</sup>. Glial cells play an important role in the homeostasis of the gut and in the regulation of IP<sup>[52,53]</sup>. In fact, in murine models, it has been demonstrated that either genetical or autoimmune targeting of glial cells determines the development of fulminant enteritis with increased translocation of microbes and evidence of bacteremia<sup>[55,56]</sup>. 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<sup>[52,53]</sup>. 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 plasmalemma 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<sup>[52]</sup>. 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

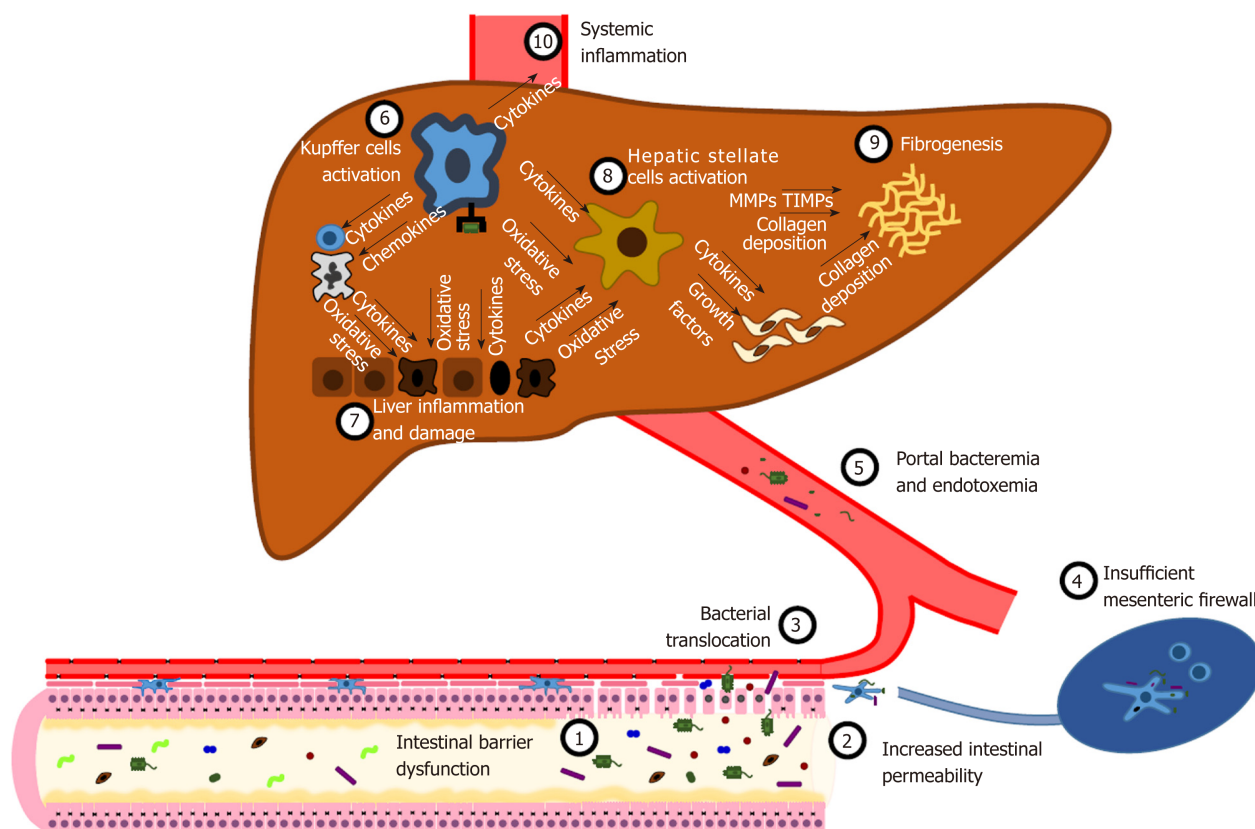
In liver diseases, increased IP is the consequence of multiple disorders that affect the homeostasis of the barrier. Several studies in animal models and in human pathology correlated liver damage and dysfunction to alterations of the gut microbiota composition<sup>[57]</sup>, mucus quality and quantity<sup>[24]</sup>, gastrointestinal motility<sup>[33]</sup>, intestinal epithelial barrier and TJ<sup>[45]</sup>, and the immune system<sup>[58]</sup>.

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<sup>[5]</sup>. At this site, microbial killing occurs without systemic inflammatory response<sup>[59,60]</sup>. This process is crucial for the modulation of the immune system and the development of immune tolerance<sup>[2,3]</sup>. Despite the fact that the liver is usually devoid of bacteria<sup>[61]</sup>, in healthy individuals it is physiologically exposed to trace amounts of bacterial mRNAs and lipopolysaccharide (LPS)<sup>[4,62,63]</sup>, mainly acting as a firewall detoxifying bacterial components<sup>[61,64]</sup>. 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<sup>[4,61,64]</sup>. 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<sup>[4,61,65-67]</sup>. Several experiments have demonstrated the importance of liver resident macrophages in the clearance of microorganisms and microbial- and pathogen- associated molecular patterns (MAMPs and PAMPs). In fact, <sup>3</sup>H- and <sup>14</sup>C-labelled endotoxin purified from *E. coli* is actively processed by Kupffer cells<sup>[68]</sup>. 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 glucocorticoids 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)<sup>[69,70]</sup>. CD14, either expressed on myeloid cells (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<sup>[71-73]</sup>. Moreover, an elegant imaging-based study by Lee *et al*<sup>[65]</sup> documented the ability of Kupffer cells to perform filtration of blood, phagocytosis and killing of green fluorescent protein expressing *B. burgdorferii* 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<sup>[61]</sup>.

Yet, the "liver buffer" is exhaustible too. The disruption of the intestinal barrier at any level leads to an increase in IP (Figure 2). Thus, harmful substances, such as MAMPs and PAMPs (LPS, microbial DNA, peptidoglycans and lipopeptides), metabolic products, and whole bacteria massively reach local MLNs, that are unable to provide an adequate clearance<sup>[74-77]</sup>. Hence, a variable amount of detrimental products is delivered to the liver through the mesenteric and portal circulation<sup>[4]</sup>. The maintenance of a damaging insult triggers a systemic inflammatory response, developing from the liver<sup>[78-81]</sup>. Kupffer cells play a pivotal role in orchestrating this mechanism<sup>[67,80,82-84]</sup>. 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- $\kappa$ B and the expression of inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, IL-18), chemokines (CXCL1, CXCL2, CCL2, CCL5, CCL3, CCL4), vasoactive factors [nitric oxide (NO)] and reactive oxygen species (ROS)<sup>[85]</sup>. This local inflammatory storm leads to the recruitment of systemic leukocytes, such as neutrophils, CD4<sup>+</sup> T cells and monocytes, that perpetuate liver inflammation<sup>[80,82]</sup>. Net result of this process is the induction of hepatocyte apoptosis and necrosis<sup>[86]</sup>. 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- $\beta$  (TGF $\beta$ )<sup>[84,87]</sup>.

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<sup>[88,89]</sup>.

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<sup>[88-91]</sup>. 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)<sup>[92]</sup>



**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<sup>[93]</sup>. 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<sup>[94]</sup>.

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<sup>[95]</sup>, alcohol<sup>[96]</sup>, infectious<sup>[97]</sup> and primary inflammatory diseases<sup>[98]</sup>, and drugs<sup>[99]</sup> 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<sup>[100]</sup>. 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<sup>[101,102]</sup>. 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<sup>[93,103,104]</sup>. The activation of TLR causes the generation of ROS by Kupffer cells<sup>[105]</sup>. ROS signaling causes the activation and proliferation of HSC<sup>[106]</sup>. Conversely, as a consequence to the exposure to ROS, Kupffer cells produce cytokines and chemokines, which further stimulate HSCs<sup>[104]</sup>.

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<sup>[107]</sup>. Hence, adequate IL-10 levels improve the integrity of the gut barrier, resulting in a decrease in endotoxin absorption<sup>[108]</sup>. In the liver, IL-10 reduces liver inflammations and fibrosis, inhibiting several Kupffer cells functions<sup>[109,110]</sup>.

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<sup>[111,112]</sup>. Interestingly, TIMP-1-expressing HSCs are resistant to NK cells activity<sup>[113]</sup>.

Coeliac disease is the hallmark of the pathogenic mechanism linking increased IP and liver inflammation<sup>[45]</sup>. Liver damage is a common disorder associated with coeliac disease<sup>[114-119]</sup>. In a recent meta-analysis, the prevalence of cryptogenic hypertransaminasaemia in newly diagnosed coeliac disease is 27%<sup>[120]</sup>. In coeliac patients, increased permeability has been proved as well<sup>[121]</sup>. Although the pathogenesis is poorly understood, the theory that liver involvement could be secondary to increased IP and BT is widely accepted<sup>[114,115,118]</sup>. Bardella *et al*<sup>[115]</sup> 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<sup>[122]</sup>. 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*<sup>[119]</sup>, 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<sup>[123]</sup>. 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<sup>-/-</sup>) mice do not show intestinal TJ alteration<sup>[124]</sup>, but ethanol feeding induces a decrease in E-cadherin and  $\beta$ -catenin distribution, which are other proteins involved in the maintenance of TJ integrity, causing gut barrier dysfunction<sup>[125]</sup>. Although both ethanol fed Ocln<sup>-/-</sup> 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 lesions only in Ocln<sup>-/-</sup> mice<sup>[125]</sup>. As for human studies, Cariello *et al*<sup>[126]</sup> demonstrated that plasma levels of inflammatory cytokines (TNF- $\alpha$  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)<sup>[127]</sup>. Finally, a recent meta-analysis showed that patients with NAFLD, particularly those with increased liver injury markers, more frequently exhibit altered IP<sup>[128]</sup>. 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<sup>[129,130]</sup>. The discovery of a linkage between small intestinal bacterial overgrowth (SIBO) and NAFLD<sup>[131-133]</sup> and the observation that endotoxin triggers liver inflammation in mice with steatosis<sup>[134]</sup> brought to the formulation of this hypothesis<sup>[130]</sup>. 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*<sup>[62]</sup> reported gut barrier dysfunction, tested as higher epithelial permeability to horseradish peroxidase in obese mice, both genetically deficient in leptin (C57BL/6Job/ob) and functionally deficient for the long-form leptin receptor (C57BL/6Jdb/db). Immunohistochemistry 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

(IL-1, IL-6, INF- $\gamma$ , and TNF- $\alpha$ ) were significantly higher both in ob/ob and in db/db mice compared to controls. Interestingly, HSC isolated from obese mice showed enhanced sensitivity to LPS and produced higher levels of cytokines.

Junctional adhesion molecule A (JAM-A) is a constituent of the TJ encoded by the murine gene *F11r*. It modulates the epithelial barrier function, regulating IP and inflammation<sup>[135-138]</sup>. *F11r*<sup>-/-</sup> mice, fed a diet high in saturated fat, fructose and cholesterol (HFD) for 8 weeks, developed a severe steatohepatitis, assessed by the presence of histological features of liver inflammation (hepatocyte ballooning and inflammatory cells infiltration) and fibrogenesis and increase in serum transaminases compared to controls<sup>[123]</sup>.

In a recent study, male C57BL/6 mice were fed with dextran sulfate sodium (DSS), a chemical compound able to determine gut inflammation, and a high-fat diet (HFD) for 12 wk. Fat vacuoles and leukocyte infiltration in the liver were higher in DSS and HFD-fed mice compared to HFD-fed mice. Concordantly, levels of hepatic mRNA coding for inflammatory cytokines (IL-1, IL-6, TNF- $\alpha$ , MCP-1) were increased as well. Moreover, DSS + HFD showed higher expression of collagen I and profibrogenic factors mRNA (TGF- $\beta$ , Actin  $\alpha$ 2, tissue inhibitor of metalloproteinase-1 and plasminogen activator inhibitor-1). Although there were no significant differences in the levels of serum endotoxin, an upregulation of TLR4 and TLR 9 was observed in DSS HFD mice. Finally, the downregulation of ZO-1 and Claudin-1 and the increased expression of PV1 confirmed both the intestinal and gut-vascular barrier dysfunction after DSS treatment<sup>[139]</sup>.

As for human models, the first strong evidence of increased IP in NAFLD patients emerged from a study testing the intestinal absorption and urine excretion of orally administered <sup>51</sup>Cr-EDTA<sup>[45]</sup>. Indeed, <sup>51</sup>Cr-EDTA is normally not metabolized and poorly absorbed (1%-3%) from the gastrointestinal tract and it crosses the intestinal barrier through the paracellular pathway in the presence of TJ disruption<sup>[27,140,141]</sup>. <sup>51</sup>Cr-EDTA excretion levels were significantly higher than values of healthy volunteers in a fashion that resulted proportional to the degree of liver steatosis. Furthermore, duodenal histology showed reduced ZO-1 expression in patients with NAFLD. In this population of patients, the prevalence of SIBO was about three times compared to controls, an observation that confirmed findings of previous studies<sup>[142]</sup>. However, increased IP was not associated with the severity of liver inflammation, fibrosis and the presence of NASH<sup>[45]</sup>. Similarly, in children with NAFLD liver damage has been linked to alterations of the gut barrier. The ratio between urinary excretion of lactulose and mannitol (L/M ratio) after oral administration was used to measure the degree of IP<sup>[27,127,143]</sup>. L/M ratio was significantly higher in NAFLD children and further increased in NASH patients. In order to ascertain the presence of BT, serum LPS was quantified and resulted significantly higher in children with confirmed liver damage. Interestingly, the extent of hepatic inflammation and fibrosis was proportional to the degree of IP<sup>[127]</sup>. The association between SIBO and NAFLD and the finding of increased endotoxemia across the studies underlines the role of the gut microbiota in the initiation and development of metabolic liver disease<sup>[45,127,142,144]</sup>. Once increased IP is established, dysbiosis affects liver homeostasis through different mechanisms. Gut microorganisms directly cause liver damage either by means of MAMPs and PAMPs (*e.g.*, LPS) or by products of their metabolism (*e.g.*, ethanol, short-chain fatty acids (SCFAs) and trimethylamine)<sup>[145]</sup>.

*Proteobacteria*, particularly *Enterobacteriaceae*, can ferment carbohydrates to ethanol<sup>[146]</sup>. In the presence of adequate conditions, the amount produced can be remarkable<sup>[147]</sup>; indeed, a significant correlation between ethanol-producing bacteria abundance, blood ethanol concentration and liver inflammation has been demonstrated<sup>[146]</sup>. Besides causing direct toxic effects to the liver, this overproduction determine the activation of hepatic ethanol metabolic pathways and increases liver oxidative stress<sup>[148]</sup>. 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<sup>[149]</sup>. 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<sup>[145,150,151]</sup>. Interacting with Gprotein 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<sup>[152]</sup>. Another important consequence is the release of glucagon-like peptide-1, which enhances glucose-dependent insulin release<sup>[153]</sup>. Altogether, these effects may favor the development of NAFLD and NASH<sup>[145]</sup>.

Furthermore, the intestinal microbiota inhibits the production and secretion of fasting-induced adipocyte factor (FIAP) by the intestinal L cells and the enterocytes. FIAP 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<sup>[154]</sup>. Hence, increased hepatic lipid storage activates the carbohydrate-responsive element-binding protein and the sterol regulatory element-binding protein 1, perpetuating fat accumulation<sup>[155]</sup>.

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<sup>[156]</sup>. Bacteria of the taxa *Erysipelotrichia* are able to metabolize choline to methylamines, toxic compounds that have been correlated to liver damage<sup>[157,158]</sup>. In NAFLD patients, augmented intestinal metabolism of choline, choline deficiency and abundance of *Erysipelotrichia* taxa have been observed<sup>[157]</sup>.

Recent studies reported qualitative alterations of the gut microbiota composition in patients with NAFLD. Particularly, *Bacteroides* genus is correlated with NASH and a parallel decrease in *Prevotella* abundance was found<sup>[159,160]</sup>. In fact, diet enriched in fat, proteins of animal origin and simple sugars, like Western one, promotes *Bacteroides* abundance, whilst an increase in *Prevotella* abundance is favored by a diet rich in fibers and vegetal carbohydrates<sup>[159,161]</sup>. *Ruminococcus* genus has been positively associated with significant liver fibrosis ( $\geq$  F2) in humans<sup>[159]</sup>, and a correlation between the abundance of this genus and the development of metabolic impairment has been observed in animal models<sup>[162]</sup>. Alcohol production, due to the ability of *Ruminococcus* to ferment complex carbohydrates, may be responsible for further liver damage<sup>[163]</sup>. An increase in *Proteobacteria*/*Enterobacteriaceae*/*Escherichia* abundance has been described in NASH and correlates with serum levels of alcohol<sup>[146]</sup>.

Furthermore, NAFLD-related liver cirrhosis patients showed a low gut microbiota diversity compared to healthy controls. At the genus level, an abundance in *Lactobacillus*, *Bacteroides*, *Ruminococcus*, *Klebsiella*, *Prevotella*, *Enterococcus*, *Haemophilus*, *Pseudomonas*, *Parabacteroides*, *Phascolarctobacterium*, *Veillonella*, *Streptococcus*, *Atopobium*, *Dialister*, *Christensenella*, and decrease in *Methanobrevibacter* and *Akkermansia* was observed<sup>[164]</sup>.

It is well known that diet *also* is a key regulator of IP<sup>[165]</sup>. In animal models of NAFLD, adaptation of a high-fat diet or high-fructose intake has been associated with increased gut permeability<sup>[166,167]</sup>. 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- $\alpha$  and other cytokines causing mucosal inflammation<sup>[168,169]</sup>. The consequence is a decreased expression of TJ proteins and a higher permeability of the gut barrier<sup>[170]</sup>. 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<sup>[171]</sup>. 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<sup>[62,172-174]</sup>. 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<sup>[175]</sup>.

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, fibres, polyphenols, antioxidants and phytochemicals; many of these components promote short-chain fatty acid-producing gut bacteria and have significant prebiotic effects<sup>[176]</sup>. As such, Mediterranean diet was an attractive tool for reducing impaired IP in patients with NAFLD. In a cross-over pilot study<sup>[177]</sup>, 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<sup>[5,27]</sup>. 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<sup>[5]</sup> and

correlates with prognosis<sup>[178]</sup>.

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 mucosa level, leading to ischemia and edema, up to the disruption of the TJ and epithelial barrier dysfunction<sup>[179,180]</sup>. 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<sup>[181-184]</sup>. 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<sup>[180]</sup>.

Endotoxemia 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)<sup>[185-187]</sup>. The result is a decrease in systemic vascular resistance and the secondary development of hyperdynamic circulation<sup>[74,75,188]</sup> that further worsen IP and BT<sup>[189]</sup>. In fact, there is evidence that intestinal decontamination improves the hyperdynamic state in liver cirrhosis<sup>[190,191]</sup>.

Furthermore, increased IP and consequent BT are fundamental pathogenic steps in the development of complications of chronic liver disease<sup>[74]</sup>. 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 *via* the increase of plasma levels of endothelin<sup>[192-194]</sup>. Furthermore, TLR4 may play a role in the pathogenesis of HRS *via* the consequent activation of NF- $\kappa$ B and TNF- $\alpha$  pathways, since it is overexpressed in the kidney during endotoxemia<sup>[195]</sup>. The importance of this pathogenic mechanism in the development of HRS is highlighted by the fact that in both animal and human studies, intestinal decontamination, achieved either by norfloxacin, paromomycin or rifaximin, showed beneficial effects on renal function<sup>[195-197]</sup>. Similarly, among the ancillary effects of albumin infusion, the scavenging of LPS is involved in the amelioration of renal hemodynamics<sup>[198]</sup>.

In the first clinical reports of spontaneous bacterial peritonitis (SBP) in the 1960s, a pathogenic mechanism involving BT from the gastrointestinal tract has already been hypothesized<sup>[199-202]</sup>. However, clear scientific evidence was only produced in the 1990s. These experiments showed in murine models of liver cirrhosis a high correspondence between the isolation of bacteria from cultures of MLNs and ascites. Positive cultures were obtained from both mice with or without SBP, demonstrating that BT is a frequent event in advanced liver disease<sup>[203-205]</sup>. Another evidence that elucidates the causal association between intestinal dysbiosis, impaired IP, BT and SBP is the decrease in the incidence of SBP (-72%) in patients with ascites treated with rifaximin<sup>[206]</sup>. Similar results in SBP primary and secondary prophylaxis have been obtained with norfloxacin<sup>[207,208]</sup>.

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<sup>[209,210]</sup>. On the other hand, the formation of portosystemic shunts further decrease the part of blood depurated<sup>[211]</sup>. 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)<sup>[209,210]</sup>.

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<sup>[212]</sup>. Moreover, the systemic inflammatory state resulting from the perpetuation of BT independently affects brain functions and worsens cognitive performance<sup>[213-217]</sup>, and finally, inflammation secondarily extends to the brain, where a self-maintaining process is then established<sup>[214,218-220]</sup>. Hence, the modulation of the gut microbiota and its metabolism represents the basis for the treatment and prevention of overt HE<sup>[221-223]</sup>.

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<sup>[224,225]</sup>. Indeed, it is known that endotoxin is able to increase thrombin generation *via* the increased production of tissue factor (TF)<sup>[226]</sup>. Similarly, LPS stimulates the release of factor VIII and von Willebrand factor release, in a way that could be mediated by TLR4 activation<sup>[227]</sup>. Since the liver acts as a firewall towards BT<sup>[61]</sup>, there is a gradient between the concentration of LPS in the portal vein and in the systemic circulation<sup>[228]</sup>. Hence, this could be a significant pathogenic mechanism for the development of PVT in cirrhotic patients<sup>[224,225]</sup>. Interestingly, endotoxin-induced prothrombotic state in the portal system can cause microembolism to hepatic sinusoids, contributing to liver

damage and inflammation<sup>[229]</sup>.

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<sup>[85]</sup>. The subsequent activation of NF- $\kappa$ B signaling initiates the inflammatory cascade that favors carcinogenesis<sup>[230,231]</sup>. Indeed, in animal models, it has been demonstrated that the infusion of LPS stimulates the development as well as the growth of liver tumors<sup>[232,233]</sup>. Conversely, the lack of IKK-b, a kinase that frees NF- $\kappa$ B from inhibitory proteins, decreases hepatocarcinogenesis<sup>[234]</sup>. An inflammatory environment is crucial for the development of hepatocellular carcinoma (HCC). Cytokines modify the micro-environment by recruiting innate immune cells and altering the extracellular matrix<sup>[231,235]</sup>. Moreover, the production of ROS cause direct DNA damage<sup>[236]</sup> and inflammation stimulate cell turnover and proliferation, favoring the accumulation of DNA mutations<sup>[231,235]</sup>.

Other MAMPs and PAMPs and microbial metabolites have also been proposed as potential carcinogens<sup>[237,238]</sup>. 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.*<sup>[164]</sup> 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*, *Butyrivimonas*, *Christensenella*, *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<sup>[239]</sup>.

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*, *Veilonella*, and *Enterobacteriaceae*, may explain the frequent involvement of these bacteria in the pathogenesis of infectious complications in these patients<sup>[240,241]</sup>. 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<sup>[240]</sup>. In particular, a higher abundance of *Streptococcus salivarius* has been correlated with the minimal HE<sup>[242]</sup>. In parallel, a decrease in the abundance of potentially beneficial *Lachnospiraceae* and *Clostridium* cluster XIVa has been reported<sup>[240,241]</sup>.

## 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)<sup>[243,244]</sup>. 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.*<sup>[245]</sup> reported an increase in lactulose /rhamnose ratio (LacI/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<sup>[246]</sup>. 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<sup>[247]</sup>. 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<sup>[248]</sup>. Afterwards diversity was progressively restored<sup>[247,248]</sup>. No association was been found between intestinal dysbiosis and acute cellular rejection, post-transplant bloodstream infections and/or the recurrence of liver disease<sup>[248,249]</sup>.

## CONCLUSION

Increased IP, BT and alterations of the gut microbiota composition are important pathogenetic 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.

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