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Review Article

Intestinal Barrier Function in the Pathogenesis of Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. The mechanisms involved in NAFLD onset are complicated and multifactorial. Recent literature has indicated that altered intestinal barrier function is related to the occurrence and progression of liver disease. The intestinal barrier is important for absorbing nutrients and electrolytes and for defending against toxins and antigens in the enteric environment. Major mechanisms by which the intestinal barrier influences the development of NAFLD involve the altered epithelial layer, decreased intracellular junction integrity, and increased intestinal barrier permeability. Increased intestinal permeability leads to luminal dysbiosis and allows the translocation of pathogenic bacteria and metabolites into the liver, inducing inflammation, immune response, and hepatocyte injury in NAFLD. Although research has been directed to NAFLD in recent decades, the pathophysiological changes in NAFLD initiation and progression are still not completely understood, and the therapeutic targets remain limited. A deeper understanding on the correlation between NAFLD pathogenesis and intestinal barrier regulation must be attained. Therefore, in this review, the components of the intestinal barrier and their respective functions and disruptions during the progression of NAFLD are discussed.

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Introduction

Nonalcoholic fatty liver disease (NAFLD), defined as steatosis in more than 5% of hepatocytes, also known as metabolic-associated fatty liver disease,[1] has become the most common liver disease in industrialized countries. NAFLD is an all-encompassing term for diseases including simple steatosis, nonalcoholic steatohepatitis (NASH), NASH-related liver fibrosis, cirrhosis, and hepatocellular carcinoma. Simple steatosis is considered a benign condition without features of NASH, a more advanced form of NAFLD. NASH is a progressive disease that can lead to cirrhosis and hepatocellular carcinoma.[2–4] NAFLD commonly coexists with metabolic syndrome, which also includes signs of abdominal obesity, insulin resistance, elevated blood pressure, altered fasting glucose, and dyslipidemia. NAFLD is associated with increased risk of developing comorbidities, such as systemic vascular endothelial dysfunction, atherosclerosis, and/or reproductive system disorders.[5,6] In recent decades, that supports the association between NAFLD and several extrahepatic system comorbidities such as cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, and neurological system diseases, including depressive mood disorder, anxiety, and apathy has increased.[7,8]

The mechanisms of NAFLD progression are complex and multifactorial. Historically, the pathogenesis of NAFLD has been described as a two-hit hypothesis. That is, at the onset of the disease, the first hit refers to the hepatic accumulation of lipids caused by a high-fat diet, obesity, and/or insulin resistance, and the second hit involves inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress.[9] However, the two-hit hypothesis is inadequate to explain the metabolic and molecular changes in NAFLD hepatocytes, and the pathological mechanisms of NAFLD seem to involve parallel multiple hit injuries. Therefore, the multiple hit model theory has been widely accepted to explain the pathogenesis of NAFLD.[10] In that model, the first hit is increased liver fat levels, followed by the effects of multiple factors, including insulin resistance, gut microbiota, and genetic and environmental factors. Those factors affect the hepatocyte inflammatory environment and contribute to mitochondrial dysfunction in conjunction with oxidative stress and endoplasmic reticulum stress-associated processes.[11,12] Fat accumulation, hepatocyte injury, and particularly, damage to any aspect of the intestinal barrier are vital factors in the pathophysiology of NAFLD. The intestinal barrier is essential for absorbing nutrients necessary for humans and preventing the invasion of micro-organisms into the lumen. Alteration to intestinal barrier function is associated with increased intestinal permeability, which plays a crucial role in the initiation and

Keywords: Nonalcoholic fatty liver disease; Intestinal barrier; Intestinal barrier permeability; Gut-liver axis.

Abbreviations: FMT, fecal microbiota transplantation; FXR, farnesoid X receptor; GVB, gut vascular barrier; IEC, intestinal epithelial cell; IgA, Immunoglobulin A; JAM, junctional adhesion molecule; LPS, lipopolysaccharide; MC, mast cell; MD, Mediterranean diet; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TJ, tight junction; ZO, zonula occluden.

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progression of hepatic and extrahepatic damage.[13]

Composition and function of the intestinal barrier

The physical intestinal barrier is a complex structure consisting of mechanical, chemical, immunological, and microbial barriers. In the lumen, a mixture of gastric acid, bile acid, pancreatic digestive juice, commensal bacteria, and even pathogens are in contact with the epithelial layer, which is lined by intestinal epithelial cells (IECs) that are connected by intracellular junctions. In addition, below the epithelial layer, the gut vascular barrier is critical for maintaining the water and molecules in the intestinal microcirculation to portal circulation and finally to the liver.[14,15]

Mechanical barrier

The mechanical barrier is formed by a mucus layer, epithelial cells, intercellular tight junctions (TJs), and the lamina propria.[16–18] As the first line of defense to resist invasion by harmful pathogens and microbes in the gastrointestinal lumen, the mucus layer overlies the epithelium and consists of proteins, glycans, and mucins with hydrophobic and surfactants that are primarily secreted by goblet cells.[19,20] The gut mucosa has a large surface area exposed to the luminal environment, and it prevents harmful content from entering the systemic circulation.[21] The epithelial layer is the main barrier that preserves the integrity of the intestinal barrier.[22] Three intercellular junction complexes including TJs, adherens junctions, and desmosomes characterize the epithelial layer.[23] TJs are composed of transmembrane proteins and related proteins involved in vesicle trafficking and intramembrane linkages. TJ transmembrane proteins include the TJ-associated proteins, claudins, and junctional adhesion molecules (JAMs). In addition, intracellular scaffold proteins such as zonula occludens (ZO)-1, ZO-2, and ZO-3, linking TJs through transmembrane proteins and to the actin cytoskeleton for exerting regulatory functions.[16,24,25] The gut vascular barrier (GVB) under the epithelium is the innermost layer of multiple intestinal barriers, and it resists the entry of bacteria-derived substances moving from the lumen into the systemic circulation. The GVB is composed of vascular endothelial cells, pericytes or fibroblast cells, and enteric glial cells. These cells are united by intercellular TJs and adherens junctions.[26,27]

Chemical barrier

The intestinal chemical barrier protects the intestinal mucosa from invasion by micro-organisms and enzymes.[28] Substances in this layer include secreted gastric acid, mucus, mucin, bile, bile acids, glycoproteins, mucopolysaccharides, digestive enzymes, lysozymes, and antimicrobial peptides. Antimicrobial peptides are microbicidal peptides that are resistant to host bacteria and pathogen element-induced barrier erosion, preventing gut barrier disruption and dysfunction.[29] Gastric acid separates bacteria from the intestinal tract and prevents microbial colonization of the small intestine.[30] Bile acids not only balance the metabolism of glucose, lipids, and energy but also protect the gastrointestinal environment by inactivating pathogenic bacteria.[28] Furthermore, bile acids regulate intestinal epithelium cell proliferation and the gut microbiome. By modulating the functions of various species in the microbiome through their antimicrobial properties, bile acids, which are mainly deconjugated, influence the microbiome population by weakening the integrity of bacteria, particularly bacterial cell membranes.[31]

Immunological barrier

In addition to its barrier function that safeguards the body against pathogens, the components of the intestinal barrier, including immune cells, interact with the gut microbiome to establish an immune system that prevents microorganisms, antigens, and pathogens in the luminal space from moving into the inner environment.[20,32] The epithelium contains various IECs that trigger innate immunity. Surface goblet cells synthesize mucin on the apical barrier layer, whereas goblet cells respond to inflammatory stimuli and cooperate with IECs, mononuclear phagocytes, innate lymphoid cells, B and T lymphocytes, microbiota derivatives and metabolites to form innate and adaptive intestinal immune systems.[33–36] As the first line of immune defense, antigens (i.e., self-antigens, microbiome, food molecules, and toxins) are recognized by the innate immune system. Once invading pathogens pass through the intestinal mucosa barrier, they are recognized and eliminated by immune cells such as dendritic cells, macrophages, and natural killer cells.[37] These cells and pattern recognition receptors, such as toll-like receptors and nucleotide-binding oligomerization domain receptors, recognize pathogen-associated molecular patterns released from bacteria, viruses, and fungi. Additionally, a diverse population of T lymphocytes in the intestine form an essential part of the adaptive immune system.[38] Goblet cells are antigen-presenting cells that deliver antigens to dendritic cells in the lamina propria, promoting the development of T regulatory cells.[32,39]

Microbial barrier

The human body contains a complex community of more than one hundred trillion micro-organisms, collectively referred to the microbiota.[18,40] The normal microbiota includes bacteria, fungi, protozoa, archaea, and viruses.[41] The gut microbiota defends against the invasion of pathogens and balances the luminal environment to maintain homeostasis.[42] In addition, the host needs the microbiota to maintain the vitamin production, energy generation, cholesterol metabolism and bile deconjugation, and regulate immune functions through its interaction with mucosal immune cells and intraepithelial cells.[43] The key metabolites generated from gut microbiota, including short-chain fatty acids, bile acids, trimethylamines, carotenoids, and phenolics, are regulators of intestinal metabolism and immunity.[44,45] Recent research has suggested that perturbation of the gut microbiota is linked to increased intestinal permeability and host immune deficiencies, which are vital for the translocation of bacterial derivatives and contribute to the development of NAFLD.[46] Studies have shown that dysbiosis or microbe-associated bacterial metabolites are harmful to the liver, contributing to the progression of liver steatosis and fibrosis. Some bacteria-derived products are pro-inflammatory stimuli that lead to increased gut permeability and are linked to systemic inflammation.[47]

Damaged intestinal barrier in the pathogenesis of NAFLD

The pathogenesis of NAFLD, including disease initiation and progression, involves disruption of the intestinal barrier, alteration of intracellular junction proteins, increased intestinal permeability and disturbance of gut microbiome (Fig. 1).

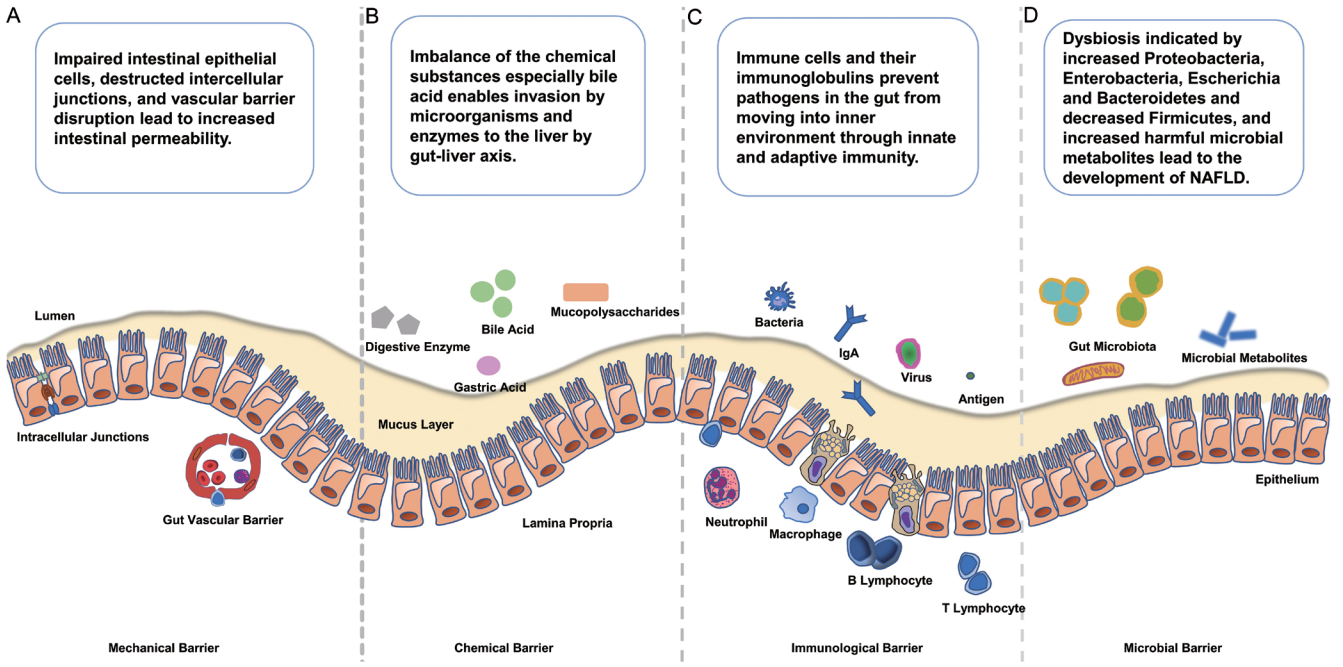

Fig. 1. Intestinal barrier components and the pathophysiological changes in NAFLD. (A–D) The intestinal barrier is composed of a complex combination of mechanical (A), chemical (B), immunological (C) and microbial barriers (D). The mechanical barrier comprises the mucus layer, epithelial cells, intercellular tight junctions, and the lamina propria. The gut vascular barrier under the epithelium is composed of vascular endothelial cells, pericytes or fibroblast cells, and enteric glial cells. The chemical barrier includes gastric acid, mucus, bile and bile acids, mucopolysaccharides, digestive enzymes, lysozymes, antimicrobial peptides, and other molecules. The immunological barrier is composed of intestinal epithelial cells, mononuclear phagocytes, innate lymphoid cells, B and T lymphocytes and goblet cells. The microbial barrier includes bacteria, fungi, protozoa, archaea, and even viruses. Impaired intestinal epithelial cells, damaged intercellular junctions, and vascular barrier disruption lead to increased intestinal permeability. Imbalance of the chemical substances, especially bile acids enables invasion of the liver by micro-organisms and enzymes via the gut-liver axis. Immune cells and their immunoglobulins prevent pathogens in the gut from moving into the internal environment through innate and adaptive immunity. Dysbiosis, with increases of Proteobacteria, Enterobacteria, Escherichia, and Bacteroidetes and an decrease of Firmicutes, together with increases of harmful microbial metabolites, leads to the development of NAFLD. NAFLD, nonalcoholic fatty liver disease.

Role of the intestinal mechanical barrier in the NAFLD development

The intestinal mechanical barrier includes the intestinal mucosa and epithelial cells that are connected by junctional complexes. Destruction of junctional proteins induces intestinal inflammation and altered barrier integrity thereby inducing NAFLD.[28] Xin *et al*.[48] showed that the level of TJ protein expression in IECs was related to the occurrence and development of NAFLD. Specifically, in a group of 92 patients, ZO-1 and occludin expression was decreased in NAFLD patients and was negatively correlated with transaminase levels.[48] Loss of junctional adhesion proteins led to increased intestinal permeability in mice fed a high-fat diet by affecting the expression of the *F11r* gene, which encodes JAM-A. Colon samples in experimental mouse models had decreased JAM-A expression and a pattern of high inflammatory protein expression, leading to the development of steatohepatitis.[49] Disruption to the intestinal epithelium layer or alteration of any component in the gut barrier leads to increased intestinal permeability in patients with NAFLD.[28] A meta-analysis reported that NAFLD patients exhibited increased intestinal permeability detected by an oral dual sugar test and serum zonulin levels, compared with healthy controls.[50] Studies found that NAFLD patients exhibited remarkably increased intestinal permeability, which alters the population of flora and promotes the translocation of microbes into blood circulation.[51,52]

Vascular barrier disruption is critical for the systemic translocation of gut bacteria and bacterial products into the blood circulation.[53] As a marker of gut vascular endothelial permeability, plasmalemma vesicle-associated protein-1 expression is increased in pathogenic events, such as systemic dissemination of bacteria, celiac disease, and NASH.[14,27] Research has shown that disruption to the GVB is evident in the early stage of NASH. Enteric pathogens can cross over the vascular barrier by interfering with the WNT/β-catenin pathway in endothelial cells.[14]

Role of the intestinal chemical barrier in the NAFLD development

The liver is the primary organ to be exposed to small molecules produced by digestion, and as an excretory organ, the liver secretes materials, including antibodies, into the bile acid that enters the intestinal lumen. Bile acids then enables the reabsorption of these materials into the terminal ileum, and the molecules are trafficked back to the liver by the enterohepatic circulation.[54] The bidirectional relationship between the gut and liver is termed the gut-liver axis, and it highlights the close correlation between intestine and liver functions.[55] Thus, any substance that enters the gut barrier will interact with hepatocytes and participate in hepatic metabolic pathways.[30]

Bile acids are associated with the progression of NAFLD. Yang *et al*.[56,57] found that patients with NAFLD had significantly elevated serum bile acids, which was correlated with steatosis severity. A study reported that removal of the gut microbiota disrupted bile acid synthesis in the liver and suppressed microbial deconjugation and dehydroxylation in the intestine, which was important to regulate obesity-induced

metabolic disorders.[58] The farnesoid X receptor (FXR) is a nuclear receptor, known as a regulator of bile acid synthesis, and is expressed in adipose tissue, liver, intestine, kidney and adrenal glands.[59,60] Studies show that FXR is associated with metabolic regulation and nutrient absorption. Yang *et al*.[56] reported that FXR protein and mRNA levels were reduced in NAFLD patients. In a murine model, inhibition of intestinal FXR mediated NAFLD development.[61] FXR has become the target for the management of NASH and liver fibrosis. Obeticholic acid, an FXR agonist, was shown to reduce bacterial translocation from the gut to liver and improve the histological features of NASH patients.[62,63]

The gut-liver axis has a key role in the progression of NASH-associated portal hypertension.[64] In rat models of portal hypertension, the expression of mesenteric angiogenesis factors including vascular endothelial growth factor and endothelial nitric oxide synthase and microvascular permeability was both increased.[65] In addition, portal hypertension results in the disruption of the intestinal barrier integrity. Patients with portal hypertension had edema of the intestinal mucosa and dilation of intestinal intercellular spaces in the jejunum.[66] A study in children with portal hypertension reported villous atrophy, capillary dilation, muscularis mucosae thickening, and increased intestinal permeability.[67] In a study in Austria, patients with severe portal hypertension had increased gastroduodenal and intestinal permeability, which was correlated with the degree of the hepatic venous pressure gradient. As markers of the enteric bacteria translocation, lipopolysaccharide (LPS)-binding proteins and interleukin-6 had increased serum levels in patients with portal hypertension patients compared with controls.[68]

Role of the intestinal immunological barrier in NAFLD development

The immune function of the intestinal barrier includes plasma cells, lymphocytes, phagocytes, dendritic cells, and Paneth cells, gut-associated lymphoid tissue including Peyer's patches, mesenteric lymph nodes, and mucosa-associated lymphoid tissue.[69] Paneth cells secrete antimicrobial peptides into the gut lumen. Natural killer cells are activated by antimicrobial peptides released by lymphocytes. T regulatory cells recognize microbial and food antigens in the intestine and mediate the tolerance of non-pathogenic antigens.[31,70] Patients with NAFLD have reduced T regulatory cells and increased Th1 and CD8+ T cells in the lamina propria.[71,72] Mast cells (MCs) are immune cells in the intestinal barrier that modulate both innate and adaptive immunity. Molecules released by MCs include cytokines, histamine, and proteases that impact intestinal barrier integrity. As the main species of proteases, tryptase, and chymase lead to the cleavage of ZO-1, downregulation of JAM-A and increase of epithelial permeability.[73,74] Recent evidence shows that histamine increases intestinal epithelial permeability and gut bacterial translocation in a mouse model.[75] MCs release various cytokines that impact the intestinal barrier directly and also express FXR in the intestine and liver, which alters intestinal fibroblast growth factor 15 and promotes liver fibrosis.[76]

Immunoglobulin A (IgA) secreted by lymphocytes and plasma cells have a key role in barrier immune function. Secretory IgA is the major subtype in the gut to protect the intestinal epithelium from pathogenic micro-organisms and maintain the homeostasis in regulation of microbiota composition. There is evidence that serum IgA concentrations was significantly elevated in patients with severe NASH compared with those with early stage disease, and was associated with advanced fibrosis.[77,78] However, elevated serum IgA have been observed in other chronic liver diseases, and clinical studies investigating intestinal or fecal IgA levels are limited.[79] Bacteria release LPS and activate inflammatory-related cytokines in IECs. LPS is an endotoxin in the outer layer membrane of most gram-negative bacteria, and it promotes the release of signaling molecules from enterocytes, which impairs barrier function.[80,81] Moreover, LPS in liver induces steatohepatitis by activating Kupffer cells.[82]

Role of the intestinal microbial barrier in NAFLD development

Increased intestinal mucosal inflammation and disruption of the intestinal epithelial barrier result in translocation of bacteria and their metabolites in gut.[28,49] Under normal conditions, the microbiota in intestinal lumen helps the body absorb and digest nutrients and fluids. Dysbiosis, defined as an abnormal amount or imbalanced composition of intestinal bacteria, is closely associated with patients with chronic fatty liver disease or cirrhosis.[83] Studies show that dysbiosis or microbe-associated bacterial metabolites are harmful to the liver and contribute to the progression of liver steatosis and fibrosis.[30,52,71,84] Dysbiosis has been associated with inhibition of the expression of TJ proteins and increased intestinal permeability via toll-like receptors.[85] Small intestinal bacterial overgrowth is a significant characteristic in patients with NAFLD, and it increases the occurrence of complications, especially ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and portal hypertension.[28,83] Clinical data from the past two decades has convinced scientists that NAFLD patients exhibit a reduced gut microbiome signature, as indicated by increased percentage of Proteobacteria, Enterobacteria, Escherichia, and Bacteroidetes species and decreased the percentage of Firmicutes species in the gut microbiome profile.[86–88] Therefore, probiotics and prebiotics are important in maintaining a healthy intestinal microflora balance.[28] Recent studies show that modulating the gut microbiota with probiotics, prebiotics, symbiotic, and agents that regulate bile acids and fecal microbiota transplantation (FMT), are practical approaches to treat NAFLD.[89] FMT transfers fecal materials from healthy donors to recipients with disturbed gut microbiota. It has been widely used to treat refractory and recurrent *Clostridium difficile* infection.[90] FMT has also become a potential therapy for the treatment of NAFLD.[91] Craven *et al*.[92] reported that endoscopic FMT to the distal duodenum in 21 patients with NAFLD resulted in improved small intestine permeability but no significant changes in insulin resistance and hepatic proton density fat fraction.[92] Probiotics are live micro-organisms that improve the microbiota balance in the intestinal tract.[93] They are consumed in various foods such as in yogurt and other fermented milk and food products or capsules.[94] Prebiotics are fibers that are fermented by the intestinal microflora and stimulate the growth or activity of intestinal bacteria to sustain a healthy microbiome or restore balance.[95] Sixty-four obese children with sonographic NAFLD were included in a randomized triple-blind clinical trial and received probiotic capsules containing Lactobacilli, Bifidobacteria, and Bifidobacterium and Lactobacillus for 12 weeks. After the bacteriotherapy, the probiotic group showed decreased liver aminotransferase and lipid levels, without changes in weight and body mass index.[96] Probiotics are live micro-organisms that have benefits on intestinal gut and improvement of lipid profile. VSL#3, a mixture of probiotic medicinal food consisting of eight bacterial strains (four *Lactobacillus* species, namely, *Lactobacillus paracasei, L. plantarum, L. acidophilus,* and *L. delbrueckii* subspecies bulgaricus; three *Bifidobacterium* species, namely, *Bifidobacterium. longum, B. lactis, and B.*

breve; and *Streptococcus thermophiles*), has been shown to reverse NASH in a mouse model.[97,98] A randomized trial including 60 NAFLD patients reported a significant reduction in triglycerides, transaminases, and gamma-glutamyltransferase, but no change in fasting plasma glucose, total cholesterol, low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol with VSL#3 compared with controls.[99] The evidence suggests probiotics and prebiotics have a possible benefit in NAFLD, high-quality studies are still limited.

Lifestyle modification as the therapeutic target for NAFLD

Research on the role of diet components in intestinal barrier integrity and function has become increasingly popular. Recent publications have demonstrated that a high-fat diet may associate with endotoxemia and lead to barrier dysfunction.[100,101] Components in the diet are in close contact with epithelial cells and become the primary stimuli altering the gut barrier.[102] Increased consumption of high-fat or high-fructose food may alter intestinal barrier function, thereby contributing to the progression to obesity or fatty liver disease.[103] Cho *et al*.[104] team reported that fructose induced nitrosylation of intestinal barrier junction proteins leading to a leaky gut, and finally resulting in steatohepatitis with fibrosis.[104] Lifestyle modification based on a healthy diet and planned exercise is considered to be the most important management of metabolic disorders. The Mediterranean diet (MD) is characterized by high consumption of unrefined cereals, vegetables, fruit, nuts, olive oil, white meat, dairy products in moderation, limiting red meat, and moderate alcohol consumption.[105,106] Recent studies have focused on the possible association between the MD and NAFLD. In a study including 46 adults with NAFLD, Gellinet *et al*.[107] found that 6 months of a modified MD had reduced liver enzymes and lipid index at the end of treatment.[107] A clinical trial of an MD in Australia reported a significant reduction in hepatic steatosis and improved insulin sensitivity compared with a low-fat high-carbohydrate diet.[108] In a study by Vitaglione *et al*.[109] coffee consumption protected against the development of NAFLD. The coffee-drinking group had more undigested lipids in luminal feces, upregulated claudin expression in the duodenum and zonulin-1 expression in both the duodenum and colon, both of which are key for maintaining intestinal barrier integrity.[109]

Conclusion

Disruption of any part of the intestinal barrier, including destruction of the epithelial layer, reduction in intracellular junction integrity, increased intestinal permeability, overgrowth of bacteria, and/or dysbiosis, is a key event in pathological mechanism of NAFLD. As the gut barrier function is important in maintaining homeostasis, exploring the potential mechanisms implicated in the pathogenesis and progression of NAFLD is urgently required. More studies are needed to identify and characterize the mechanisms of gut barrier dysfunction in liver damage disorders. Clinicians should be aware of the potential gut barrier dysfunction in NAFLD, which may be a therapeutic target in the near future.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Writing the manuscript (LL), developing the idea for the article and critically revising it (XL, CX), technical and material support (JL, JZ), and updating the text of the manuscript (CY, MY). All authors have made a significant contribution to this study and have approved the final manuscript.

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