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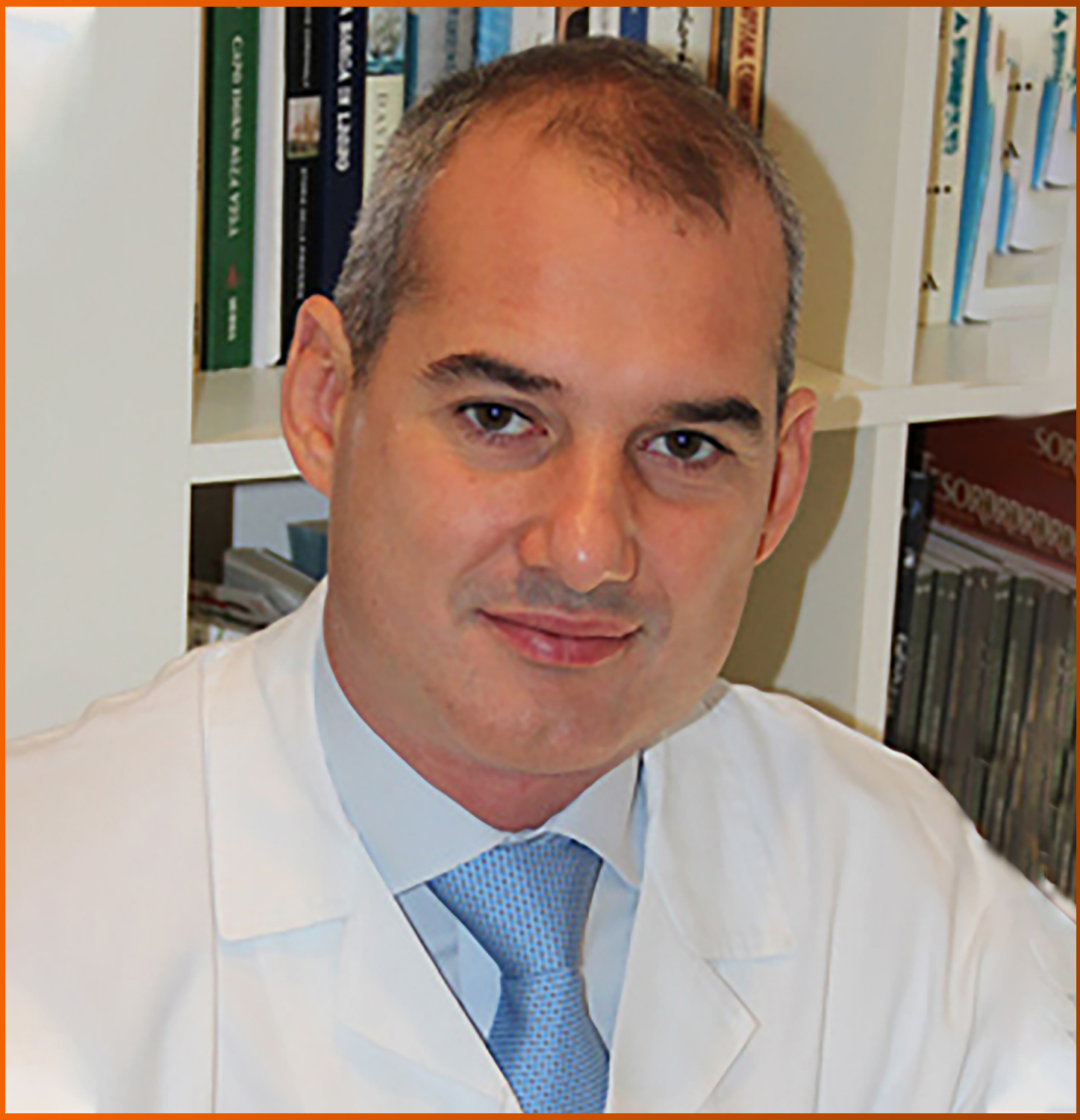

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World Journal of Clinical Cases

Contents Thrice Monthly Volume 9 Number 23 August 16, 2021

OPINION REVIEW

6582 COVID-19 pandemic, as experienced in the surgical service of a district hospital in Spain

Pérez Lara FJ, Jimenez Martinez MB, Pozo Muñoz F, Fontalba Navas A, Garcia Cisneros R, Garcia Larrosa MJ, Garcia Delgado I, Callejon Gil MDM

REVIEW

6591 Beta-carotene and its protective effect on gastric cancer

Chen QH, Wu BK, Pan D, Sang LX, Chang B

6608 Liver transplantation during global COVID-19 pandemic

Alfishawy M, Nso N, Nassar M, Ariyaratnam J, Bhuiyan S, Siddiqui RS, Li M, Chung H, Al Balakosy A, Alqassieh A, Fülöp T, Rizzo V, Daoud A, Soliman KM

6624 Nonalcoholic fatty pancreas disease: An emerging clinical challenge

Zhang CL, Wang JJ, Li JN, Yang Y

MINIREVIEWS

6639 Novel mechanism of hepatobiliary system damage and immunoglobulin G4 elevation caused by *Clonorchis sinensis* infection

Zhang XH, Huang D, Li YL, Chang B

6654 Intestinal microbiota participates in nonalcoholic fatty liver disease progression by affecting intestinal homeostasis

Zhang Y, Li JX, Zhang Y, Wang YL

6663 Theory and reality of antivirals against SARS-CoV-2

Zhao B, Yang TF, Zheng R

6674 Acute acalculous cholecystitis due to infectious causes

Markaki I, Konsoula A, Markaki L, Spernovasilis N, Papadakis M

ORIGINAL ARTICLE

Case Control Study

6686 Innate immunity – the hallmark of *Helicobacter pylori* infection in pediatric chronic gastritis

Meliț LE, Mărginean CO, Săsăran MO, Mocan S, Ghiga DV, Bogliş A, Duicu C

Retrospective Study

6698 Effects on newborns of applying bupivacaine combined with different doses of fentanyl for cesarean section

Wang Y, Liu WX, Zhou XH, Yang M, Liu X, Zhang Y, Hai KR, Ye QS

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

6705 Awake fiberoptic intubation and use of bronchial blockers in ankylosing spondylitis patients

Yang SZ, Huang SS, Yi WB, Lv WW, Li L, Qi F

6717 Efficacy of different antibiotics in treatment of children with respiratory mycoplasma infection

Zhang MY, Zhao Y, Liu JF, Liu GP, Zhang RY, Wang LM

6725 Expression of caspase-3 and hypoxia inducible factor 1α in hepatocellular carcinoma complicated by hemorrhage and necrosis

Liang H, Wu JG, Wang F, Chen BX, Zou ST, Wang C, Luo SW

6734 Increased morbidity and mortality of hepatocellular carcinoma patients in lower cost of living areas

Sempokuya T, Patel KP, Azawi M, Ma J, Wong LL

SYSTEMATIC REVIEWS

6747 Safety of pancreatic surgery with special reference to antithrombotic therapy: A systematic review of the literature

Fujikawa T, Naito S

6759 What paradigm shifts occurred in the management of acute diverticulitis during the COVID-19 pandemic? A scoping review

Gallo G, Ortenzi M, Grossi U, Di Tanna GL, Pata F, Guerrieri M, Sammarco G, Di Saverio S

CASE REPORT

6768 Pylephlebitis – a rare complication of a fish bone migration mimicking metastatic pancreatic cancer: A case report

Bezerra S, França NJ, Mineiro F, Capela G, Duarte C, Mendes AR

6775 Solitary seminal vesicle metastasis from ileal adenocarcinoma presenting with hematospermia: A case report

Cheng XB, Lu ZQ, Lam W, Yiu MK, Li JS

6781 Hepatic abscess caused by esophageal foreign body misdiagnosed as cystadenocarcinoma by magnetic resonance imaging: A case report

Pan W, Lin LJ, Meng ZW, Cai XR, Chen YL

6789 2+0 *CYP21A2* deletion carrier – a limitation of the genetic testing and counseling: A case report

Xi N, Song X, Wang XY, Qin SF, He GN, Sun LL, Chen XM

6798 Psoriasis treatment using minimally manipulated umbilical cord-derived mesenchymal stem cells: A case report

Ahn H, Lee SY, Jung WJ, Pi J, Lee KH

6804 Double intussusception in a teenage child with Peutz-Jeghers syndrome: A case report

Chiew J, Sambanthan ST, Mahendran HA

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

6810 Nedaplatin-induced syndrome of inappropriate secretion of antidiuretic hormone: A case report and review of the literature

Tian L, He LY, Zhang HZ

6816 Nasal metastases from neuroblastoma-a rare entity: Two case reports

Zhang Y, Guan WB, Wang RF, Yu WW, Jiang RQ, Liu Y, Wang LF, Wang J

6824 Nocardiosis with diffuse involvement of the pleura: A case report

Wang P, Yi ML, Zhang CZ

6832 Prenatal diagnosis of triphalangeal thumb-polysyndactyly syndrome by ultrasonography combined with genetic testing: A case report

Zhang SJ, Lin HB, Jiang QX, He SZ, Lyu GR

6839 Blue LED as a new treatment to vaginal stenosis due pelvic radiotherapy: Two case reports

Barros D, Alvares C, Alencar T, Baqueiro P, Marianno A, Alves R, Lenzi J, Rezende LF, Lordelo P

6846 Diverse microbiota in palatal radicular groove analyzed by Illumina sequencing: Four case reports

Tan XL, Chen X, Fu YJ, Ye L, Zhang L, Huang DM

6858 Autism with dysphasia accompanied by mental retardation caused by *FOXP1* exon deletion: A case report

Lin SZ, Zhou XY, Wang WQ, Jiang K

6867 *FGFR2-TSC22D1*, a novel *FGFR2* fusion gene identified in a patient with colorectal cancer: A case report

Kao XM, Zhu X, Zhang JL, Chen SQ, Fan CG

6872 Trismus originating from rare fungal myositis in pterygoid muscles: A case report

Bi L, Wei D, Wang B, He JF, Zhu HY, Wang HM

6879 Retroperitoneal laparoscopic partial nephrectomy for unilateral synchronous multifocal renal carcinoma with different pathological types: A case report

Xiao YM, Yang SK, Wang Y, Mao D, Duan FL, Zhou SK

6886 Diffuse large B cell lymphoma originating from the maxillary sinus with skin metastases: A case report and review of literature

Usuda D, Izumida T, Terada N, Sangen R, Higashikawa T, Sekiguchi S, Tanaka R, Suzuki M, Hotchi Y, Shimozawa S, Tokunaga S, Osugi I, Katou R, Ito S, Asako S, Takagi Y, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M, Kasamaki Y

6900 Manifestation of acute peritonitis and pneumonedema in scrub typhus without eschar: A case report

Zhou XL, Ye QL, Chen JQ, Li W, Dong HJ

6907 Uterine tumor resembling an ovarian sex cord tumor: A case report and review of literature

Zhou FF, He YT, Li Y, Zhang M, Chen FH

6916 Dopamine agonist responsive burning mouth syndrome: Report of eight cases

Du QC, Ge YY, Xiao WL, Wang WF

6922 Complete withdrawal of glucocorticoids after dupilumab therapy in allergic bronchopulmonary aspergillosis: A case report

Nishimura T, Okano T, Naito M, Tsuji C, Iwanaka S, Sakakura Y, Yasuma T, Fujimoto H, D'Alessandro-Gabazza CN, Oomoto Y, Kobayashi T, Gabazza EC, Ibata H

6929 Sirolimus treatment for neonate with blue rubber bleb nevus syndrome: A case report

Yang SS, Yang M, Yue XJ, Tou JF

6935 Combined thoracoscopic and laparoscopic approach to remove a large retroperitoneal compound paraganglioma: A case report

Liu C, Wen J, Li HZ, Ji ZG

6943 Menetrier's disease and differential diagnosis: A case report

Wang HH, Zhao CC, Wang XL, Cheng ZN, Xie ZY

6950 Post-salpingectomy interstitial heterotopic pregnancy after *in vitro* fertilization and embryo transfer: A case report

Wang Q, Pan XL, Qi XR

6956 Ulnar nerve injury associated with displaced distal radius fracture: Two case reports

Yang JJ, Qu W, Wu YX, Jiang HJ

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 23 August 16, 2021

Contents

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MINIREVIEWS

Intestinal microbiota participates in nonalcoholic fatty liver disease progression by affecting intestinal homeostasis

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease with a pathogenesis that has not been fully elucidated. With the development of the theory of the gut-liver axis and the deepening of related research, the role of the intestinal tract in the pathogenesis of NAFLD has been investigated more. Intestinal microbiota, intestinal metabolites, and intestinal epithelial and immune-based barriers constitute the intestinal environment, which uses crosstalk to maintain the homeostasis of the intestinal environment. This paper reviews the progress in the study of intestinal microbiota, intestinal environment, and NAFLD and suggests that repair of intestinal functional balance may be a new idea for early prevention and intervention of NAFLD.

Key Words: Nonalcoholic fatty liver disease; Gut-liver axis; Intestinal microbiota; Metabolites; Intestinal homeostasis

Core Tip: Intestinal microbiota, intestinal metabolites, the intestinal epithelial barrier, and the immune barrier constitute the intestinal environment. The importance of intestinal homeostasis in the occurrence and development of nonalcoholic fatty liver disease (NAFLD) has been shown. Intestinal microbiota plays a leading role in maintaining the balance of the intestinal environment, but the complex interaction mechanism has not been elucidated fully. This article reviews the current research from the perspective of intestinal homeostasis and proposes that the repair of intestinal functional balance may be a new idea for early prevention and intervention of NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases[1], characterized by metabolic stress causing liver damage. Risk factors include insulin resistance and genetic susceptibility[2]. The primary pathological change is diffuse bullae steatosis in hepatocytes, which is similar to alcoholic liver disease but without a history of heavy drinking. NAFLD has a multifactorial and complex pathogenesis and diverse clinical manifestations[3]. The classical "two-hit" theory is not enough to explain the complex pathogenesis of NAFLD[4]. The "gut-liver axis" theory, which hypothesizes a bidirectional relationship between the intestinal tract and the liver, has become a prominent theory to explain the key role of metabolic disorders in the pathogenesis of many liver diseases[5-7]. The relationship between intestinal homeostasis and the occurrence and development of NALFD has also been gradually revealed due to this theory[8,9].

INTESTINAL ENVIRONMENT

The intestinal tract is an immune, metabolic, and nervous system organ, and its functional impairment plays an important role in the occurrence of many diseases, which can lead to death[10]. The intestinal tract is exposed to a variety of food components, antigens, symbiotic microorganisms, and pathogens. It is responsible for the digestion and absorption of nutrients and prevents harmful substances, such as pathogenic bacteria and toxins, from entering the circulation system through the intestinal tract[11]. Intestinal homeostasis constitutes a congenital protective barrier [12]. According to its composition, the intestinal barrier can be divided into an immune barrier, a mechanical barrier, a chemical barrier, and a biological barrier[13]. The immune barrier includes secretory immunoglobulin, lymphoid tissue, and mesenteric lymph node[14]. The mechanical barrier is composed of the mucus layer, intestinal epithelial cells, tight junctions between cells, and peristalsis function of the intestine. The chemical barrier is composed of gastric acid, bile, digestive enzymes, mucopolysaccharides, lysozyme, antimicrobial peptides, *etc*. The biological barrier refers to the microecosystem composed of the normal flora in the intestine. There are more than 4 billion microorganisms in the intestinal tract, and their metabolites can directly affect human health[15].

The composite barrier formed with multiple barriers is the key to keeping the dynamic balance in the intestinal environment[16]. The multiple barriers effectively resist intestinal bacterial translocation and endotoxin release and maintain normal bowel function, immune regulation, and body health[17]. Intestinal microbiota, metabolites, intestinal epithelium, and host immunity are important components of the intestinal environment. Under physiological conditions, all factors maintain a dynamic balance to ensure that the body is protected from harmful factors. Under pathological conditions, the imbalance of the intestinal environmental homeostasis leads to the destruction of the protective barrier, which causes the translocation of pathogenic microorganisms and toxic metabolites (an important cause of many diseases)[18].

INTESTINAL MICROBIOTA AND NAFLD

There are a variety of microbial communities in the human intestinal tract[19]. They function in a symbiotic relationship by promoting metabolism, digestion, and absorption[20] and by playing a role as a biological barrier. In both human and animal studies, the potential pathogenicity of intestinal microbial disorders in the development of NAFLD/nonalcoholic steatohepatitis (NASH) has been found[21-25]. However, due to the influence of multiple factors, such as age, region, diet, and obesity, no consistent results have been obtained on the characteristics of intestinal microbiota in patients with NAFLD/NASH[26].

A study of adult patients with NAFLD has shown that the occurrence of steatohepatitis is associated with an increase in the proportion of *Bacillus globulis* and a decrease in the proportion of *Bacteroides*[27]. In combination with 14C-D-xylose and lactulose breath test, researchers found bacterial overgrowth in the small intestine in approximately 50% of NASH patients, which was significantly higher than that in healthy controls[28]. Other studies found that gut microbiome samples from patients with NAFLD or NASH had a lower proportion of *Ruminococcaceae* than healthy subjects, and *Escherichia coli* was significantly disproportionate between obese children and children with NASH[29]. The proportion of *Clostridium globulae* in biopsy-confirmed adult NASH patients was significantly higher than that in NAFLD patients[27]. Obesity and insulin resistance are risk factors for NAFLD[30]. It has been confirmed by experiments that sterile mice can avoid obesity caused by a high-fat diet, indicating that the obesity caused by a high-fat diet, to some extent, requires the involvement of intestinal microorganisms[31].

The mechanism of action between intestinal microbiota and hosts is complex. The disorder of intestinal microbiota affects the levels of metabolites, such as ethanol, choline, and endotoxin, in the NAFLD inflammation progress[32-34] and damages the function of the intestinal barrier by increasing the permeability. This leads to exposure of the liver to endotoxin, which further promotes fatty liver inflammation and enhances fibrosis in NASH development[35]. Intestinal microbiota participates in the process of NAFLD, which is closely related to its influence on the intestinal environment.

INTESTINAL METABOLITES

Dietary substances enter the intestinal tract under the action of intestinal microbiota after digestion to produce a large number of metabolites, such as secondary bile acids, short-chain fatty acids, ethanol, choline, and endotoxin[36]. The metabolites that cannot be reabsorbed can be excreted through feces. If the production of metabolites exceeds the load capacity that the body is adapted to, it will cause metabolic disorders [37]. At present, the effects of bile acids and fatty acids have the most data in relation to NAFLD[38].

Bile acids

Bile acids are an important component of bile, which regulate lipid digestion and absorption and cholesterol metabolism. They also play a key role in insulin sensitivity and metabolic homeostasis[39]. Primary bile acids synthesized in the liver are transformed into secondary bile acids under the action of intestinal flora after entering the intestine, and their level is affected by the composition, abundance, and proportion of intestinal flora[40]. Bile acids can also change the structure of the intestinal flora [41]. By promoting the activation of the farnesoid X receptor, intestinal microorganisms can further induce the expression of fibroblast growth factor 15, inhibit CYP7YPA1, and affect bile acid synthesis. In addition, the intestinal flora interferes with secondary bile acid reabsorption by affecting the transport of normal tissue complication probability and automated blood sampling telemetry[42].

Studies have found that serum bile acid levels in patients with NAFLD are significantly increased[43], and the severity of steatosis is positively correlated with the level of bile acid synthesis[44]. Increased levels of key bile acids, such as taurocholic acid and glycocholic acid, were associated with steatosis, lobular and portal vein inflammation, and hepatocyte ballooning. In addition, the risk of NAFLD progression to fibrosis was positively correlated with the ratio of secondary bile acids to primary bile acids and the concentration of bound bile acids[45]. Bile acid may also damage bacterial membranes by binding phospholipids on the bacterial membrane, thus playing an antibacterial role in adhesion and neutralizing of endotoxins[46-48]. Mice fed food rich in saturated fatty acids promoted changes in the composition of bile acids, which showed significant dysregulation of intestinal microorganisms[49]. These results suggest that bile acid metabolism in the intestine is involved in the process of NAFLD, and there is an interaction between bile acids and intestinal microorganisms. The complex mechanism behind this interaction remains to be further elucidated.

Fatty acid metabolism

Abnormal lipid metabolism is a key factor in the occurrence and development of NAFLD[50]. Fatty acid deposition in liver cells and the resulting insulin resistance, lipotoxic injury, oxidative stress, apoptosis, and inflammation are important

pathological mechanisms of the progression of NAFLD[51]. Fatty acids can be derived from glucose synthesis absorbed by hepatocytes, from peripheral adipose tissue release, and from intestinal metabolism into blood[52]. Under the action of intestinal microorganisms, fat is hydrolyzed and emulsified in the upper part of the small intestine to produce fatty acids. Long-chain fatty acids are absorbed by intestinal epithelial mucosal cells, transformed into triglycerides, and combined with apolipoproteins to form chylous particles that are released into circulation. Medium-chain and short-chain fatty acids enter circulation directly through the portal system. The free fatty acid levels in blood increase, and excessive intake of the fatty acids by hepatocytes leads to NAFLD[53].

The incidence of NAFLD is correlated with short-chain fatty acid levels. Short-chain fatty acids are produced by gut microbes through the glycolysis of carbohydrates. The most prevalent short-chain fatty acids are acetic acid, propionic acid, and butyric acid [54]. Acetic acid participates in body energy metabolism through acetyl-coA, propionic acid inhibits cholesterol synthesis in the liver, and butyric acid can protect intestinal mucosa barrier permeability[55,56].

Fatty acid metabolism in the intestine is affected by intestinal microbiota and regulates the intestinal barrier, which plays a complex role in the progression of NAFLD[57,58]. When the liver is overloaded with free fatty acids, a large amount of reactive oxygen species will be produced, causing oxidative stress and mitochondrial damage. A clinical study[59] related to short-chain fatty acids found that the concentration of propionate/acetate in feces of patients with NAFLD was positively correlated with the ratio of Th17/Treg cells in peripheral blood, but negatively correlated with Tregs in peripheral blood. Th17/Treg dynamic balance is an important factor in maintaining immune homeostasis, Th17 plays an inflammatory regulation role, while Tregs plays an immune tolerance role[60], suggesting that short-chain fatty acids may participate in the progression of NAFLD by affecting T cell immune function.

INTESTINAL MICROBIOTA AND INTESTINAL BARRIER INJURY IN NAFLD

The intestinal tract, as an important organ for nutrient absorption, forms an effective barrier network to avoid harmful substance intake. Normal intestinal barrier function is the key to maintaining homeostasis of the intestinal environment. The composition of the different barriers varies but they are closely related to each other. Intestinal biological barriers and chemical barriers have been described. Intestinal microorganisms stimulate intestinal epithelial cells to secrete a variety of immune mediators, including cytokines and chemokines, that play an important role in maintaining the integrity of the epithelial barrier, shaping the mucosal immune system, and regulating the host immune response[61]. In order to avoid an abnormal excessive immune response, intestinal epithelial cells isolate intestinal microorganisms from immune cells through chemical and mechanical barriers, thereby establishing host-symbiotic relationships. Intestinal immune cells are also involved in maintaining a healthy intestinal microbial community and enhancing epithelial barrier function[15]. Intestinal barrier damage has been confirmed in NAFLD, and the intestinal flora is a participant in that process[62,63].

Intestinal epithelial barrier

The intestinal epithelial barrier is the main component of the mechanical barrier. It includes columnar epithelial cells, Pan's cells, goblet cells, intestinal endocrine cells, cluster cells, and other cell populations, which play a crucial role in the stability of the intestinal environment[64]. The integrity and regenerative capacity of the intestinal epithelium are the structural basis. Intestinal bacterial metabolites, such as short-chain fatty acids and secondary bile acids, play an important role in maintaining intestinal epithelial integrity.

Short-chain fatty acids are an energy source for the host and regulate the physiological function of intestinal epithelial cells. Short-chain fatty acids can regulate intestinal adaptability and promote proliferation through activation of G-protein-coupled receptors (GPR41, GPR43, and GPR109A)[65]. Other studies have shown that short-chain fatty acids can activate the nuclear factor-κB signaling pathway through Toll-like receptors (TLRs), which regulates the integrity of intestinal epithelial cells [66]. Short-chain fatty acids can also activate the inflammatory body NOD-like receptor family pyrin domain containing 3 (NLRP3), upregulate interleukin (IL)-18, and maintain intestinal dynamic balance[67].

Primary bile acids secreted by the liver enter the small intestine and promote the digestion and absorption of fat in the small intestine. Under the action of intestinal microorganisms, most of the transformed secondary bile acids are reabsorbed by intestinal epithelial cells and return to the liver through the portal vein. Studies have shown that secondary bile acids also regulate the proliferation of intestinal epithelial cells. For example, cholic acid induces the proliferation of intestinal epithelial cells by activating Src, epidermal growth factor receptor, and extracellular signal-regulated kinase, while deoxycholic acid inhibits the proliferation of intestinal epithelial cells by activating the farnesoid X receptor[68].

The junction of the intestinal epithelium depends on tight junction proteins, including occludin, the claudin family proteins, and zona occludens 1. The imbalance of intestinal flora in patients with NASH and excessive growth and reproduction of intestinal Gram-negative bacilli, such as *Enterobacteriaceae*, causes tight junction proteins to contract and move to the cytoplasm under the pathological conditions of hypoxia and inflammatory stimulation. This increases intestinal mucosal permeability, epithelial barrier destruction, and intestinal bacterial translocation. In addition, the metabolite lipopolysaccharide is released into the blood and liver through the portal system, promoting the release of inflammatory factors and resulting in NAFLD[69]. Studies have found that the application of intestinal microbiota regulator probiotics or synbiotics can reduce hepatic steatosis and inflammation in NAFLD[70], which may be related to the improvement of intestinal permeability and regulation of intestinal microecological balance[71].

Intestinal immune barrier

The intestinal immune barrier plays an important role in the pathogenesis of NAFLD. The intestinal mucosal immune barrier is composed of immune cells, intestinal mucosal lymphoid tissues, and immunoglobulin A (secreted by the immune cells)[72], which plays an important role in protecting the body from pathogenic bacteria and pathogens. Immune cells include T cells, B cells, dendritic cells, macrophages, eosinophils, and mast cells that are distributed in different tissue layers of the intestinal mucosa and have an inherent immune effect. These cells play a key role in maintaining immune homeostasis by inhibiting responses to harmless antigens and enhancing the integrity of the intestinal mucosal barrier function[73].

The intestinal immune function acts as a sentinel to prevent harmful substances from entering the portal system. Then, the liver can monitor enteric metabolites and pathogens and induce an immune response from harmful substances entering the liver *via* the portal vein. The function of the intestinal immune barrier is related to pattern recognition receptors, such as TLRs and nucleotide binding oligomerization domain-like receptors[74]. The intestinal epithelium can express TLRs, recognize intestinal metabolites, and further participate in the inflammatory progression of NAFLD by activating MYD88. Mice with intestinal epithelial cell-specific *MYD88* gene deletion fed a high-fat diet showed improved oral glucose tolerance and associated hepatic steatosis and triglyceride content, in contrast to wild-type mice[75]. In addition, lipopolysaccharide produced by the flora can activate NLRP3 inflammatory bodies through TLR4 and TLR9, activate caspase-1, and cleave IL-1β and IL-18 precursors into activated IL-1β and IL-18, which promotes the progression of NAFLD inflammation and fibrosis[76].

Intestinal regulatory T cells play a key role in inhibiting the immune response induced by symbiotic microorganisms and metabolites. Intestinal short-chain fatty acids can induce epithelial transforming growth factor-β production and promote regulatory T cell production to participate in the immune process[77]. Therefore, the intestinal immune system response is a key link in the occurrence and development of NAFLD.

CONCLUSION

Intestinal microbiota, intestinal metabolites, and intestinal epithelial and immune-based barriers constitute the intestinal environment. These components are all dependent on the others, requiring crosstalk to maintain the homeostasis of the intestinal environment. Current studies have shown that intestinal flora play a leading role in maintaining the balance of the intestinal environment. The balance of intestinal environmental factors is the key to maintaining a healthy state, and the importance of homeostasis imbalance in the occurrence and development of NAFLD has been shown. Although some progress has been made in all aspects of research, the complex

interaction mechanisms have not been fully elucidated. Most of the previous studies highlight a single factor. The research on the relationship between the factors must be expanded. The balance of multiple factors likely involves a variety of complex mechanisms, which also presents difficulties in the research efforts.

At present, there is no specific therapeutic drug for NAFLD. The discovery of the "gut-liver axis" and the importance of the intestinal microbiota in the pathogenesis of NAFLD suggest that focusing on the repair of intestinal functional balance may be a new drug target for prevention and intervention of NAFLD. In the future, with the further development of more studies, major mechanisms will be revealed, which will bring new treatment options for NAFLD.

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