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Research Progress of Intestinal Flora and Related Diseases

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Abstract

The intestinal tract is an important digestive organ and detoxification organ of the human body, and its circling structure is vividly called the "second brain" of the human body. There are hundreds of millions of bacterium in the intestinal tract. These bacteria live in mutual benefit with the body, provide energy and nutrients for the host and themselves through fermented food, participate in the metabolism of the body, and form a metabolic mode of cometabolism between the host and the symbiotic flora. In addition, intestinal flora can also help the body resist the invasion of pathogens, promote human health, and resist diseases. More and more studies have shown that when the body is subjected to exogenous or endogenous stimuli, the microbial flora in the intestinal will change, and the disturbance of intestinal flora is closely related to the occurrence and development of inflammatory bowel diseases, metabolic diseases, immune system diseases, mental system diseases, and tumors. This article reviews the research progress of the intestinal flora affecting the pathogenesis of various diseases, aiming to provide new references and ideas for the clinical treatment of diseases.

Keywords
- intestinal flora
- metabolic diseases
- bowel diseases
- mental system diseases
- immune diseases
- tumors

Introduction

In recent years, with the increasing number of research on the composition and function of intestinal microbiota, it has become increasingly clear that microorganisms play a very important role in the maintenance of health and the occurrence and development of diseases. Microbes are important in a wide range of physiological processes, from the digestion of complex polysaccharides to the regulation of neural signaling.[1] The total number of parasitic microorganisms in the human intestinal tract exceeds hundreds of trillions, which is 10 times the number of human cells.[2] Each individual's microbiome is unique like people's fingerprints, and they are closely related to intestinal metabolic and immune functions. The biological function of the body needs energy as the basis. However, the carbohydrates in the food cannot be completely digested, absorbed, and utilized by themselves. A large part needs to be fermented and decomposed with the help of intestinal flora and then absorbed and utilized by the body. The metabolic pattern is called "host-intestinal flora cometabolism" metabolic pattern, and different intestinal bacteria have different metabolites. The composition and metabolism of the intestinal microbial community are affected by many factors, such as poor eating habits and lifestyles, overuse of antibiotics, etc., which seriously endanger the ecological balance of the intestinal flora, resulting in a decrease in the diversity of the microbiome in the body and the abundance of some bacteria. The change in this abundance will change the metabolites of the

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flora and threaten the health.[3] Studies have shown that the imbalance of intestinal flora is closely related to the occurrence and development of various diseases, such as irritable bowel syndrome,[4] acute anterior uveitis,[5] rheumatoid arthritis,[6] diabetes,[7] hypertension,[8] autism,[9] and colorectal cancer.[10] This article reviews the research on the correlation between intestinal flora and diseases in recent years, in order to provide new references and strategies for clinical treatment.

Intestinal Flora and Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an intestinal immune response caused by the interaction of multiple factors such as environment, genetics, infection, and immunity, which then causes tissue damage. Two disease subtypes of Crohn's disease (CD),[11] which often occurs in children and young adults, are incurable and associated with complications, such as infection, hospitalization, surgery, and cancer,[12,13] seriously affecting the patient's mental health and increasing the risk of depression and anxiety.[14,15] Studies based on *16S rRNA* gene sequencing have revealed significant differences between the microbiota of IBD patients and healthy individuals, suggesting a potential role of the intestinal flora not only in development but also in determining prognosis and disease progression,[16] and common changes in the intestinal flora of patients with IBD include increases in facultative anaerobes such as *Escherichia coli*[17] and reduced obligate anaerobic producers of short-chain fatty acids, such as Firmicutes.[18] The study found that the intestinal flora of healthy people had abundance of *Akkermansia muciniphila* and *Coprolococcus* regularis, while ulcerative colitis (UC) patients had abundance of *Bifidobacterium adolescentis* and *Haemophilus parainfluenzae*[19]; intestinal flora was decreased in CD patients, there was a scarcity of Firmicutes, *Bacteroides*, Rhodesia, and *Clostridium prausinii*, while there was abundance of Proteus, Actinomycetes, *Escherichia coli*, and sulfate-reducing bacteria.[20–23] As an important part of Chinese medicine, acupuncture and moxibustion have dual benefits. The study of acupuncture and moxibustion treatment of CD patients found that the clinical remission rate of the acupuncture group was significantly increased, the CD activity index and C-reactive protein levels were significantly reduced, and the CD severity degree index, histopathological score, and recurrence rate were all significantly reduced, the intestinal flora increased, Faecalibacterium prausnitzii and Roseburia faecis and Rhodesia in feces relatively increased, and relevant cytokines of plasma diamine oxidase, lipopolysaccharide, and Th1/Th17 decreased.[24] Studies have found that Gegen Qinlian decoction can improve the metabolism of fatty acids, bile acids, and amino acids by regulating the composition of intestinal flora, enhancing intestinal barrier function, repairing intestinal ultrastructural damage, relieving oxidative stress, promoting antioxidant activity, reducing the expression of inflammatory factors and chemokines, and up-regulating anti-inflammatory factors, thereby alleviating colitis in rats.[25–27]

Intestinal Flora and Metabolic Diseases

Obesity

With the continuous improvement of living standards, people's eating habits have undergone tremendous changes. The number of obese people in the world is increasing, and their age is getting younger and younger, which seriously threatens human's health.[28] The root cause of obesity is an imbalance between energy intake and expenditure, but changes in genetics, epigenetics, and intestinal microbial composition all contribute to obesity,[29–31] which in turn increase the risk of diseases such as cancer, atherosclerosis, and diabetes.[32–34] The study found that after feeding resveratrol to mice for 16 weeks, fecal bacteria were transplanted to mice that had been fed a high-fat diet (HFD), and it was found that the obesity of the high-fat-fed mice was significantly improved and insulin sensitivity was significantly increased. Alcohol-induced intestinal flora can regulate lipid metabolism in white adipose tissue and brown adipose tissue, reduce inflammation and improve intestinal barrier function.[35] Huanglian (Coptidis Rhizoma) and berberine were administered to C57BL/6J mice fed a HFD, and both Huanglian (Coptidis rhizoma) and berberine were found to significantly reduce the levels of Firmicutes and *Bacteroidetes* in the feces of HFD mice, decrease body and visceral fat mass, decrease blood glucose and blood lipid levels, and degrade dietary polysaccharides in HFD mice.[36] The researchers used genetic and diet-induced two obese mouse models, orally administered *Parabacteroides distasonis* (PD), and found that PD can improve the metabolism of obese mice, control the weight of obese mice, reduce hyperglycemia and lead to fatty liver.[37] After taking *Bifidobacterium animalis* milk subsp . *CECT 8145* (Ba8145) and heat-inactivated Ba8145 for obese patients for three consecutive months, the patients' waist circumference, waist circumference/height ratio, taper index, body mass index, and visceral fat area were significantly reduced, and AKK bacteria in intestinal flora increased.[38] Through the above studies, it is found that the intestinal flora is closely related to the occurrence and development of obesity disease, and the intestinal flora may be a potential target for the treatment of obesity.

Diabetes

Diabetes mellitus (DM) refers to a metabolic disorder syndrome dominated by sugar and lipids caused by insulin deficiency or insulin resistance and is characterized by elevated blood sugar. The main feature of diabetes is elevated fasting blood sugar, which is mainly divided into diabetes mellitus type 1 (T1D) and DM type 2 (T2D), etc.T1D is insulin-dependent DM, which is an autoimmune disease. Due to the destruction of pancreatic islet B cells, insulin secretion is absolutely insufficient, and patients need to use insulin to maintain blood sugar levels. In recent years, the incidence of T1D in children has been increasing year by year, and it has become a major basic disease affecting the health of children and adults in China. Studies have shown that the structure and function of intestinal flora in T1D children are disordered, and the transplantation of flora in T1D children can

increase fasting blood sugar and reduce insulin sensitivity in antibiotic model mice.[39] Human milk oligosaccharides and prebiotics can inhibit the occurrence and development of T1D by regulating intestinal flora and controlling blood sugar.[40,41] T2D is noninsulin-dependent diabetes. The ability of the patient to produce insulin is not completely lost, but the patient is resistant to the action of insulin. Therefore, insulin in the patient's body is in a state of relative deficiency, which is the most common type of diabetes, accounting for more than 90% of diabetes, and most patients develop it after the age of 35 to 40. Microorganisms in the intestine can inhibit the levels of proinflammatory cytokines and chemokines and inflammatory proteins, regulate intestinal permeability, affect glucose homeostasis and insulin resistance in major metabolic organs such as liver, muscle, and fat, and increase fatty acid oxidation and energy consumption and reduction of fatty acid synthesis and other effects regulate glucose metabolism in T2D patients.[42] The study found that after probiotic treatment in T2D patients, the weight, body mass index, and waist circumference of the patients were significantly improved, and the fasting blood glucose, insulin concentration, and insulin resistance were significantly reduced.[42–44] In addition, Huangqi (Astragali Radix) polysaccharides and bitter gourd polysaccharides reduce blood sugar in T2D mice by regulating the intestinal environment and improving intestinal flora disorder.[45,46]

Hypertension

Hypertension is a chronic noncommunicable disease and an important risk factor for the occurrence of cardiovascular diseases. The incidence is increasing. Because of long-medication cycle and poor clinical outcomes, it seriously affects the life of patients. Recent studies have shown that hypertension is closely related to changes in the composition and function of intestinal flora,[47] the feces of hypertensive patients were transplanted into germ-free mice and the blood pressure of the transplanted mice increased.[48] High-salt diet seriously affects people's health and is one of the important factors inducing high blood pressure. It can affect the body's immune system by changing the intestinal flora, thereby changing the body's blood pressure.[49,50] High-fiber and cellulose acetate diet, supplementation of specific microorganisms, etc. can improve hypertension by regulating the structure of intestinal microorganisms.[51,52]

Nonalcoholic Fatty Liver

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by diffuse macrovesicular steatosis of liver cells without alcohol and other clear pathogenic factors, including simple fatty liver, nonalcoholic steatohepatitis, and nonalcoholic cirrhosis. NAFLD is the most common chronic liver disease worldwide, affecting about a quarter of the adult population,[53] and the prevalence is increasing, and currently, there is no NAFLD drug with significant curative effect.[54] There is an urgent need to identify modifiable risk factors that may prevent or delay its development, as well as new clinical treatment strategies. Studies have shown that intestinal microbiota imbalance is also an important factor in the development of NAFLD, playing an important role in regulating energy balance and fat deposition.[55] Intestinal bacteria were stimulated by feeding mice the fermentable dietary fiber guar gum and suppressed by long-term oral administration of antibiotics. It was found that guar gum can significantly alter intestinal microbiota composition in mice while reducing dietary obesity induced and improving glucose tolerance, but it enhanced liver inflammation and fibrosis, with significantly elevated plasma and hepatic bile acid levels. This result suggested a causal relationship between changes in the intestinal microbiota and hepatic inflammation and fibrosis in a mouse model of NAFLD and that this change may be related to the regulation of bile acids.[56] Further studies also found that the intestinal flora of NAFLD patients was significantly changed, and the level of serum fibroblast growth factor 21 (FGF21) was increased, and FGF21 can regulate bile acid metabolism by targeting intestinal flora to improve NAFLD.[57] The above studies indicate that intestinal flora and their metabolites may be new targets for the treatment or prevention of NAFLD. In addition, Chinese medicine ingredients and preparations of resveratrol, phytosterol esters, black fungus polysaccharides, Fuzhuan tea, Simiao prescription, and Jiangan Jiangzhi pills can improve NAFLD by regulating intestinal flora disorder.[58–63]

Intestinal Flora and Immune System Diseases

Asthma

Asthma is a type I hypersensitivity disease. After exposure to allergens, atopic individuals induce mast cells and basophils to degranulate, causing them to release active mediators such as prostaglandins, histamine, and leukotrienes, triggering bronchospasm and impaired pulmonary ventilation. The intestinal flora is an important risk factor for asthma and has become a widespread concern in the pathogenesis of asthma.[64] Compared with healthy people, the levels of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* in fecal samples of asthmatic patients are reduced, and both of them can induce anti-inflammatory cytokine IL-10 and prevent the secretion of proinflammatory cytokine IL-12, further promoting the occurrence and development of inflammation.[65] Colonization of the intestine by the environmental fungus *Wallemia mellicola* exacerbated dust mite-induced asthma-like inflammation and exacerbated asthma in mice.[66] Studies showed that nasal inoculation of mice with lactobacillus rhamnosus could prevent birch pollen-induced allergic asthma in mice.[67] Similarly, after oral administration of specific Lactobacillus in severe asthma model mice, it can significantly reduce the infiltration of neutrophils and eosinophils in alveolar lavage fluid, decrease inflammatory factors in lung tissue, and have obvious protective effects for asthmatic mice.[68–70] Chinese medicine prescriptions, Chinese medicine extracts, and monomeric compounds such as Shaoyao Gancao decoction, Tingli Dazao Xiefei decoction, Sijunzi decoction, Yangfei decoction, Pipaye (Eriobotryae Folium) water extract can inhibit intestinal

inflammation by regulating intestinal flora disorder, repair intestinal mucosal barrier, and improve asthma.[71–75]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by chronic joint inflammation, bone erosion, and cartilage destruction.[76] Multiple studies suggest that intestinal flora plays a significant role in the etiology of RA.[77,78] The fecal microbial diversity of RA high-risk individuals was reduced, and the structure and function of bacterial communities were significantly altered. The intestinal permeability and expression of ZO-2 in the small intestine and Caco-1 cells of mice transplanted with intestinal flora from high-risk RA patients were increased. Th17 cells in mesenteric lymph nodes and Peyer's plaques increased, which further contributed to the development of arthritis,[6] and structurally and functionally altered gut microbiota in RA patients,[79] and the gut microbiota structure was altered after oral administration of *Porphyromonas gingivalis* in mice, aggravating collagen-induced arthritis.[80] And RA model mice can exert its protective effect on RA mice by maintaining the normal intestinal microbiota of arthritis mice after taking tuftsin-phosphocholine.[81] Intervention of Ershiwu (25) Wei Lyuxue pills, extract of Jishiteng (Chinese fevervine), and Sinomenine can significantly relieve the symptoms of arthritis in the RA model, reduce the score of arthritis, inhibit arthritis, and restore the homeostasis of intestinal flora.[82–84]

Intestinal Flora and Neurological Disease

Depression

Depression is a relatively common mental illness at present. Patients with severe depression are accompanied by severe self-harm and suicidal tendencies. Chronic stress is the main risk factor for the development of depression, with a prevalence rate of 11 to 15%. During the coronavirus 2019 pandemic, its incidence has doubled and in some countries even tripled.[85] More and more research works suggest that the intestinal microbiota may affect brain activity and behavior through neural and humoral pathways, possibly involved in causal pathways leading to depression.[86] In patients with depression, the abundance of *Bacteroides* was negatively correlated with brain depression characteristics, and potential neurotransmitter GABA-producing or metabolic bacteria in the intestine may inhibit the development of depression.[87] After transplanting fecal microbiota from patients with depression into rats, it was found that the rats exhibited behavioral and physiological characteristics of depression.[88] With probiotic supplementation in patients with severe depression, the concentration of kynurenine in plasma was significantly reduced, the ratio of 3-hydroxyanthranilic acid/kynurenine was significantly increased, and the cognitive function of patients with depression was significantly improved.[89] Extracts of Cistanche Tubulosa and Xiaoyao powder can relieve anxiety and depression by regulating intestinal flora, reducing LPS levels, and inhibiting the excessive activation of NLRP3 inflammasome in the colon.[90,91]

Autism

Autism, also known as autism spectrum disorder (ASD), is characterized by impaired communication skills and often accompanied by stereotyped behaviors, interests and activities, and abnormal living abilities. Autism has become one of the global problems. Since its pathogenesis is not entirely clear, the clinical effect is very little. The intestine microbiota plays a part not only in the development of parenchymal organ diseases but also in the development of mental disorders. Children with ASD have altered intestinal microbiota with higher levels of Proteobacteria, Actinomycetes, and Sutterella.[92,93] Intestinal bacterial metabolites can activate the atypical immune response of lymphoblastoid cell lines in autistic patients with abnormal metabolism, which has a potential protective effect on the treatment of autism.[94] Taking prebiotics or specific microbial strains can significantly improve intestinal flora, metabolism, and psychological status and alleviate the antisocial behavior of autistic children.[95] Palmitoylethanolamine can reduce the stereotyped and repetitive autism-like behaviors of autism model mice, increase their social activities, reduce intestinal permeability, change the structure of intestinal flora, and have protective effects on autism mice.[96] In addition, studies have found that fecal transplants can significantly improve the symptoms of autistic patients and have a potential therapeutic effect on autism.[97]

Alzheimer's Disease

Alzheimer's disease (AD), also known as senile dementia, is a neurodegenerative disease related to age and cognition. The main pathological manifestations include amyloid β-protein (Aβ) abnormal deposition to form senile plaques and hyperphosphorylation of tau protein in neurons to form fibrillary tangles. Studies have shown that increased intestinal and blood–brain barrier permeability caused by intestinal microbiota disturbance will increase the incidence of neurodegenerative diseases, and intestinal microbial metabolites and their impact on host neurochemical changes may increase or decrease the risk of AD.[98] Intestinal flora changes in Alzheimer's patients,[99] and the regulation of microorganisms can affect the occurrence and development of AD.[100] Daily probiotic supplementation for 12 weeks in patients with Alzheimer's disease can effectively improve cognitive and metabolic function, and the results of mental state examination were significantly improved.[101,102] Studies have shown that probiotic preparations SLAB51 and *Lactobacillus plantarum* MTCC1325 exert antioxidant and neuroprotective effects on AD mice.[103,104]

Intestinal Flora and Tumors

Colorectal Cancer

Colorectal cancer is an epithelial tumor of the colon or rectum that is considered malignant only when it penetrates the muscularis mucosae to the submucosa. Clinically, it can be manifested as blood in the stool, changes in bowel habits, abdominal mass, anemia, intestinal obstruction, etc. Malignant epithelial tumors above the dentate line to the

recto-sigmoid junction are rectal cancers, and malignant epithelial tumors from the recto-sigmoid junction to the ileocecal junction are colon cancers. Studies suggest a possible link between dysbiosis in intestinal microbiota and colorectal cancer.[105] The host can affect the structure of intestinal flora through miRNA, and colorectal cancer inducers can also change the structure of intestinal flora, and intestinal flora metabolites, especially butyrate, can affect gene transcription activity and the pathogenesis of colorectal cancer.[106] Studies have shown that Salmonella colonization in the intestinal tract significantly reduces the expression level of Wnt1 in intestinal epithelial cells and inhibits the invasion and migration of cancer cells.[107] Continuous preoperative administration of synbiotics (Simbioflora) can significantly reduce the inflammatory indicators of patients with colorectal cancer, and the incidence of postoperative infectious complications is also significantly reduced.[108] Olive oil and its metabolites, Ganoderma lucidum polysaccharides, etc., can change the structure and function of the flora, help maintain a healthy flora, and alleviate colorectal cancer.[109,110]

Liver Cancer

The liver is an important metabolic and detoxification organ of the human body and participates in the biotransformation and metabolism of the body. According to incomplete statistics from 1999 to 2016, the number of deaths from liver cirrhosis in the United States increased by 65%, the number of deaths from hepatocellular carcinoma doubled, and the mortality rate increased by 2.1%, which seriously threatened human health.[111] The liver is profoundly influenced by the intestinal microbiota and its metabolites, and leaky gut and microbiota imbalance are triggers for liver pathological reactions.[112] The intestine–liver axis is a two-way communication pathway composed of intestinal flora, hepatic portal system, and biliary system, which is the physiological basis for the interaction between intestinal flora and liver.[113] The disordered intestinal flora can promote the progression of liver disease and the development of hepatocellular carcinoma, and regulating the intestinal flora to restore it to normal can improve liver cancer, intestinal leakage, etc. Therefore, the intestine–liver–intestinal flora becomes an ideal target to prevent chronic liver disease from developing into advanced liver disease and liver cancer. Intestinal commensal *Clostridium* bacteria suppress immune responses to liver cancer by metabolizing host-generated primary bile acids to secondary bile acids.[114] After certain probiotic combinations were administered to mice with liver cancer, anti-inflammatory bacteria such as intestinal Prevotella and Fibrobacillus increased, hepatoma decreased, IL-17 expression and the number of Th17 cells decreased, and Th17 cells migrated to the tumor from the intestinal tract and peripheral blood cell decrease.[115] Shaoyao Ruangan mixture and Supplemented Xiaoyao powder can effectively inhibit the progression of liver cancer by changing the intestinal flora composition of the incidence of liver cancer, increasing the proportion of beneficial bacteria and reducing the proportion of harmful bacteria.[116,117]

Lung Cancer

Lung cancer is a type of cancer with the highest mortality rate. In addition to genetic and environmental factors, the microbiota plays a vital role in the development of lung cancer.[118] Intestinal microbiome composition altered in lung cancer patients with lower levels *of Kluyvera*, *Escherichia-Shigella*, *Dialister*, *Faecalibacterium*, and *Enterobacter* and increased levels of *Veillonella*, *Fusobacterium*, and *Bacteroides*,[119] and some studies suggest that *Enterococcus* and *Bifidobacterium* are potential biomarkers for lung cancer.[120] The administration of *Lactobacillus acidophilus* to lung cancer mice can enhance the anti-tumor effect of cisplatin, reduce the tumor size, and improve the survival rate, suggesting that probiotics can improve the effect of cisplatin on tumor cells.[121] In addition, Bufei Xiaoji decoction can improve the NLRP3 inflammatory response and intestinal flora in mice with lung cancer complicated with qi and yin deficiency[122]; combined treatment of Xihuang pills and Anlotinib can significantly inhibit tumor growth in mice with Lewis lung cancer and increase the ratio of beneficial bacteria *Bacteroides* and *g_norank_f_Muribaculaceae*.[123]

Conclusion

The microbial genome is called the “second genome” of the human body, and the intestinal flora is also regarded as a new “organ” of the body to participate in the life process of the body. From the above explanations, we know that the homeostasis of the intestinal flora is crucial to the maintenance of health. Once the intestinal flora is disturbed, it can regulate the body’s metabolism and immunity through metabolites and cause varying degrees of damage to the body and lead to a series of diseases. Probiotics can maintain the intestinal homeostasis of the body and the development of normal physiological functions of the intestinal tract and also play a crucial role in the clinical treatment of diseases. Chinese materia medica and its preparations can be used as probiotics to regulate the structure and metabolic phenotype of host intestinal microbiota and further act as a new source of leading drugs for the treatment of intestinal microbiota-targeted diseases. With the continuous development of science and technology, people will gradually explore the relationship between intestinal flora and diseases. The analysis of intestinal flora will provide a certain basis for the clinical diagnosis of the disease and provide new targets for the clinical treatment of diseases.

CRediT Authorship Contribution Statement

Y.S. was responsible for conceptualization, funding acquisition, and writing-review & editing. X.Z. was responsible for investigation, and writing—original draft. Y.Z. was responsible for supervision. Y.S., B.C. and Z.S. were responsible for investigation.

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Conflict of Interest

The authors declare no conflict of interest.

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