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Research Progress on the Correlation between Gut Microorganisms and Gastrointestinal Diseases

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Abstract: ***The intestinal microbiota refers to the complex community of microorganisms present in the human digestive tract. With the development of high-throughput sequencing technologies such as 16SrRNA gene sequencing and metagenomic sequencing, the intestinal microbiota has been shown to be closely related to gastric cancer and colorectal cancer. At the same time, a series of studies have been conducted to explore the intestinal microbiota as a new type of non-invasive biological marker. This article summarizes the research on the intestinal microbiota of gastric cancer and colorectal cancer, and explains the changes in the intestinal microbiota when the disease occurs, so as to provide new ideas for finding potential molecular targets for the prevention, treatment, and intervention of tumors.***

Keywords: Gut microorganisms, Digestive System Neoplasms, Gastrointestinal diseases**.**

1. Background

Digestive diseases have gradually become a common disease in modern life, with high incidence, high recurrence rate, underestimated risk, and obvious regional differences. Especially in recent years, with the change in lifestyle and living environment and the acceleration of the population aging process, the incidence of digestive system diseases in China has increased year by year, and it is at the forefront of the prevalence of chronic diseases. For example, gastric cancer, colorectal cancer and other diseases of the digestive tract, have long been among the forefront of China's high incidence of malignant tumors, seriously threatening people's health.

A large number of bacteria, fungi, viruses and other microbiota reside on the surface of human skin and body cavity, most of which are located in the gut, and together with their living environment constitute the intestinal microecology [1]. The intestinal microbiota is mainly in the colon. The bacterial density in the colon is about 1011 to 1012per milliliter. In terms of quantity, Bacteroidetes and Firmicutes are the main phyla, accounting for more than 90% of the entire intestinal flora. Each individual has a unique intestinal flora spectrum. Intestinal microorganisms interact with the host in various ways through the intestinal mucosal surface, playing a vital role in metabolism, maintaining the intestinal mucosal barrier structure, resisting pathogens and immune regulation [2]. However, when healthy microbial composition and function are disturbed, it can lead to dysbiosis, and changes in the intestinal microbiota can trigger the development of various gastrointestinal diseases [3].

This article summarizes the abnormal microorganisms with high abundance in the intestinal flora and analyzes the mechanism of the relationship between these species and the occurrence and development of gastrointestinal diseases, supplementing the pathogenesis of gastrointestinal diseases from a microbial perspective. At the same time, by comparing the abundance of digestive tract flora species in normal people and patients with gastrointestinal diseases, some highly specific and abundant microorganisms in patients with gastrointestinal diseases and cancer are summarized. If these microbial markers can be used, it is expected to increase the rate of early diagnosis and timely intervention, thereby improving patient survival rates.

2. Gastric Cancer

2.1 Current Status of Gastric Cancer

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of death [4]. According to the World Health Organization's International Agency for Research on Cancer (WHO-IARC), the annual burden of GC will increase to approximately 1.8 million new cases and 1.3 million deaths by 2040 [5]. GC is a multifactorial disease, and the main risk factors include environment, age, gender, diet, smoking, genetics and Helicobacter pylori (H. pylori) infection [4]. H. pylori infection is considered the major risk factor for GC, while other risk factors include Epstein-Barr virus (EBV) infection, smoking, high-salt diet, and genetics, which present a complex network of interactions. GC is considered to be the result of chronic inflammation and ulceration of the stomach.

2.2 H. Pylori and GC

H. pylori was discovered in 1982. It is a Gram-negative, flagellated, microaerophilic bacterium with catalase, urease and oxidase activities and can be transmitted through saliva, vomit and feces.H. pylori utilizes different virulence factors such as vacuolating toxin A (VacA), outer membrane proteins, peptidoglycan, and multiple adhesion factors (BABA, SABA, and OIPA) to colonize in the gastric mucosa and participate in the carcinogenesis of gastric tissue [6-7]. VacA is a multifunctional toxin that acts in different host cell types (e.g., gastric epithelial cells, antigen-presenting cells, phagocytes, mast cells, and T cells) [8].

Alterations in the intestinal microbial structure can increase the secretion levels of systemic and local pro-inflammatory mediators and the expression of cancer-related genes, ultimately leading to the progression of gastric disease [9]. There have been many studies on the microbiota of GC patients and controls. However, their results vary greatly, and

some are even contradictory, probably due to different sample types, study populations, sequencing technologies, and analysis methods. Some studies have shown that the abundance and diversity of the gastric microbiota do not gradually change with the development of GC [10-11]. Other studies hold the opposite view, suggesting that the abundance and diversity of the microbiota decrease with the progression of GC, which is also the conclusion reached by most studies [12-13]. The results on the richness and diversity of microorganisms in cancerous tissues and adjacent tissues also showed great differences [14-15]. A recent meta-analysis showed that eradication of H. pylori can restore the diversity of gastric microbiota and reduce the risk of GC [16]. However, some studies contradict this result, believing that eradication of H. pylori cannot completely prevent the development of GC [17]. This suggests that other microorganisms in the stomach besides H. pylori are also related to the occurrence of GC.

2.3 Other Gut Microbes and Gastric Cancer

Different researchers have conducted 16S sequencing on biopsy tissues of GC patients and found that the intestinal flora of GC patients has changed significantly compared with normal patients. A study showed that Desulfovibrio in the feces of GC patients produces H2S, which helps release inflammatory factors that promote cancer [18]. Ding et al. also concluded that the occurrence of H. pylori-negative GC is due to the disruption of the normal microbiota, with elevated levels of some bacteria with pro-cancer activity and reduced levels of tumor-suppressive bacteria [19]. Increased abundance of the family Lactobacillaceae was detected in both H. pylori-negative and H. pylori positive GC patients. Although Lactobacillus is widely considered to be a probiotic in the intestine, it is often highly enriched in GC, especially in advanced GC [20]. Lactobacillus can upregulate pro-inflammatory genes, thereby inducing GC [21]. In addition, Lactobacillus is a potent ROS inducer, leading to DNA damage [22]. In addition to identifying potential microbial biomarkers for GC through case-control studies, a longitudinal study provided evidence that Moryella and Vibro genera are specific microorganisms for early gastric tumors [23]. This suggests that changes in the intestinal microbiota can serve as progression biomarkers, providing more options for the detection and early detection of gastric cancer.

In addition to H. pylori, various types of microorganisms are involved in the occurrence, development, prognosis, and treatment response of GC. However, in published studies, no clear microbiome and its metabolites have been identified as the main indicators of GC development. Therefore, we summarized the recent studies on the role of intestinal flora in the progression of GC and clarified its significance in the diagnosis and treatment of GC.

3. Inflammatory Bowel Disease

3.1 Current Status of IBD

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases of the gastrointestinal tract, causing long-term inflammation in the digestive tract in the form of ulcerative colitis (UC) and Crohn's disease (CRD). Currently, more than one million people are affected by IBD (including UC and CRD) worldwide, and the incidence of these digestive diseases has continued to rise over the past 50 years. Many factors, including westernization, urbanization, changes in dietary patterns, and exposure to antimicrobial agents, may affect the microecological environment in the host. The microbiome has been considered as a potential pathogenic factor or risk factor in IBD [24]. UC is characterized by diffuse inflammation limited to the colonic mucosa, which can cause recurrent symptoms, whereas CD inflammation is typically transmural, patchy, and segmental, occurring anywhere in the gastrointestinal tract [25].

3.2 IBD and Gut Microbiota

Many studies have compared the gut microbiota of IBD patients and healthy individuals. In 2020, Pittayanon et al. systematically reviewed 48 studies comparing the intestinal microbiota of IBD patients and healthy individuals. In CD, Christensenellaceae of Firmicutes, Rhodococcus of Actinobacteria, and F. prausnitzii decreased, while Actinobacteria, Veillonella, and Escherichia coli increased [26]. It has also been reported that Eubacterium rectum and Akkermansia are decreased and Escherichia coli are increased in UC patients compared with healthy subjects. At the same time, a large number of studies have shown that in addition to changes in species and quantity, intestinal microorganisms in IBD patients also show abnormal metabolic function. Certain overgrowth of microorganisms can affect the energy metabolism of intestinal epithelial cells and cause enteritis. A large number of studies have shown that the huge number of bacteria and their products in the intestine can act as intestinal antigens to induce intestinal immune responses, affect the function of the intestinal mucosal immune system, and lead to the onset of IBD. The reasons may be that, on the one hand, pathogenic bacteria in the intestine secrete immunosuppressive proteins, which damage the integrity of the mucosa; on the other hand, the increase in mucosal permeability causes the displacement of intestinal bacteria and their products, allowing substances released by pathogenic bacteria, antigens in the intestinal cavity, endotoxins and other pro-inflammatory factors to enter the mucosal lamina propria, inducing immune response [27]. In addition, bacterial products further damage the mucosal barrier after entering the liver circulation, forming a vicious cycle. Anti-inflammatory cytokine therapy can restore the body's immune tolerance to its own intestinal flora and improve IBD symptoms [28], further reflecting the important influence of intestinal microorganisms, mucosal barriers and immune responses on the occurrence and development of IBD.

4. Colorectal Cancer

4.1 Current Status of Colorectal Cancer

Colorectal cancer (CRC) is a common malignant tumor of the digestive tract epithelium, with the third-highest incidence and the second-highest mortality rate among malignant tumors [29]. Compared with other tumors, the heritability of CRC is not high, but it also reflects that environmental factors may play a greater role in the occurrence of CRC. When CRC is diagnosed, it is mostly in the middle and late stages.

Although medical treatment has made some progress, the treatment effect is still poor, so it is very important to prevent the occurrence of CRC. Recent studies have found that certain pathogenic bacteria in the intestinal flora can cause damage to the intestinal barrier, produce tumorigenic toxins that can act on intestinal epithelial cells and cause cell proliferation, and shape a special immune microenvironment. At the same time, these toxins can produce carcinogenic metabolites, reactive oxygen species, and other free radicals, causing DNA damage in host cells and inducing mutations. These mechanisms together promote the development of colorectal tumors [30].

4.2 CRC and Gut Microbiota

Due to the development of microbiome analysis technologies such as 16S rRNA and shotgun metagenomics, it has been gradually found that the intestinal flora composition of CRC patients is significantly different from that of healthy individuals. Higher levels of Fusobacterium nucleatum, Escherichia coli, Bacteroides fragilis, Enterococcus faecalis, Streptococcus gallolyticus and Peptostreptococcus were detected in CRC tissues, while the intestinal probiotic groups such as Bifidobacterium, Lactobacillus and Bacteroides decreased [30]. The study found that tubular adenoma and sessile serrated adenoma are two primary precancerous lesions of CRC, and changes in the microbiome of CRC have already occurred at this stage [31]. The study of the microbiome characteristics of CRC precancerous lesions and their pathogenic mechanisms will be beneficial to the early warning and early diagnosis of CRC.

Fn is a Gram-negative obligate anaerobic bacterium that is widely present in the human gastrointestinal tract. Its detection rate in tumors is gradually increasing. It is involved in the occurrence and development of tumors and is expected to become a biological marker for CRC warning, early diagnosis and prognosis [32]. Fn participates in the occurrence and development of CRC by promoting the proliferation and metabolism of CRC cells, reshaping the anti-tumor immune microenvironment, inducing genetic and epigenetic changes of CRC, and promoting the migration and drug resistance of CRC cells [33]. Pickles in our daily diet can generate nitrites during the production process, which can be metabolized by bacteria to synthesize nitrosamines. Nitrosamines can act on the colon mucosa, causing mucosal damage, and their oxidation can change intestinal permeability, leading to inflammatory reactions, thereby increasing the risk of CRC.

In addition to the potential risk of carcinogenesis, some intestinal microorganisms also have a protective effect on CRC. Clostridium butyricum can inhibit the development of intestinal tumors, and its mechanism is related to the regulation of the Wnt signal [34]. Zhang et al. found that bacteria from the Lachnospiraceae family that parasitize in intestinal tissue can inhibit tumor growth by reducing the level of glycerophospholipids in the colorectal tumor microenvironment and thereby enhancing the activity of CD8+T cells [35].

5. Conclusion

In summary, intestinal microorganisms are closely related to gastrointestinal diseases. In recent years, the method of using intestinal microorganisms to treat digestive system diseases has also been gradually introduced into clinical practice. For example, fecal microbiota transplantation is mainly used in diseases related to gastrointestinal dysbiosis. At present, research on intestinal microorganisms has been fully launched in the United States and Europe. Modern genome projects, high-throughput gene sequencing technologies and other means have made it possible to unlock the code of intestinal microorganisms. Human digestive system diseases are becoming increasingly prominent, and research on various pathological mechanisms is still needed. However, the development of new treatment technologies such as fecal microbiota transplantation provides more possibilities for curing diseases. Traditional Chinese medicine, which has rich historical experience, should keep pace with the times and combine modern scientific health research to contribute to human microecological research.

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