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Research Progress of Intestinal Flora in Colorectal Cancer

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Abstract

Colorectal cancer, as a common malignant tumor, has been increasing in incidence year by year and has become one of the leading causes of death worldwide. Meanwhile, researchers have found a close relationship between dysbiosis of the gut microbiota and colorectal cancer, which has further triggered in-depth exploration of the role of gut microbiota in the pathogenesis, diagnosis, and treatment of colorectal cancer. Studies have shown that there are specific microbial changes in colorectal cancer tissues, including enrichment or depletion of certain bacterial species, which may be associated with tumor growth, invasion, and metastasis. Additionally, gut microbiota has been found to be closely linked to tumor microenvironment, tumor immune response, chemotherapy drug metabolism, and other factors. In this context, it is imperative to study the gut microbiota in colorectal cancer. A comprehensive understanding of the interaction between gut microbiota and colorectal cancer is not only helpful in revealing novel mechanisms of colorectal cancer development, but also holds promise in providing new strategies and targets for early diagnosis, individualized treatment, and prevention of colorectal cancer. This review aims to thoroughly discuss the research progress of gut microbiota in colorectal cancer, including its compositional characteristics, its role in the occurrence and development of colorectal cancer, and its potential clinical applications. The goal is to provide references and insights for further research in this field.

Keywords

Intestinal Flora, Gut Microbiota, Colorectal Cancer, Treatment

1. Introduction

Colorectal cancer (CRC) ranks third in terms of incidence and second in terms

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of mortality among all cancers worldwide [1] [2]. Due to late clinical detection, high malignancy, and poor prognosis, the incidence of CRC has been increasing in recent years, making it a common malignancy of the digestive system globally. The standard treatment methods for CRC include surgery, chemotherapy, and radiation therapy, which can be combined to treat patients. However, these treatment methods have many adverse reactions and complications due to their non-specific cytotoxicity, affecting not only cancer cells but also normal cells that are growing and dividing. Additionally, many patients experience recurrence even after a series of treatments [3]. Therefore, it is crucial to have alternative and effective treatment methods for CRC patients.

Immunotherapy is one of the new therapeutic options in cancer treatment. As an essential component of the intestinal microbiota, the gut microbiome participates in various physiological processes such as substance metabolism, digestion, absorption, and immune regulation. It plays a vital role in protecting intestinal mucosa, maintaining intestinal homeostasis, and regulating normal body functions. Increasing evidence suggests that dysbiosis of the gut microbiota plays a regulatory role in the occurrence and development of colorectal cancer.

2. Factor Analysis

Various factors such as genetic predisposition, environmental influences, dietary habits, lifestyle, and interactions among microorganisms can significantly impact the gut microbiota. The etiology of colorectal cancer (CRC) is associated with genetic susceptibility syndromes, family history of CRC, and inflammatory bowel disease, particularly in relation to obesity and dietary risk factors [4]. Certain dietary choices, such as red meat, high-fat, and low-fiber foods, may elevate the risk of CRC occurrence [5]. The presence of microorganisms can disrupt the balance of the host immune system, while specific microorganisms are capable of producing toxic metabolites, such as nitrites and polycyclic aromatic hydrocarbons, which have been demonstrated to be associated with the occurrence and development of tumors. These metabolites may directly damage the host's cell DNA, potentially leading to mutations and the onset of cancer. Microbial infections can also result in a state of chronic inflammation. Prolonged inflammatory responses can lead to tissue damage, cellular proliferation, and accumulation of mutations, thereby increasing the risk of tumor development.

Considering the impact of dietary habits on the immune response induced by intestinal bacteria, the composition of the gut microbiota, and the maintenance of intestinal homeostasis, it is plausible that the gut microbiota or its derivatives may serve as direct environmental modulators contributing to the onset of CRC. Larger scale studies are needed to explore the relationships among psychosocial stress, diet and the gut microbiome.

3. Colorectal Cancer and the Mechanisms Related to Intestinal Microbiota

The disruption of the intestinal microbiota is a prominent feature of colorectal

cancer (CRC), with studies indicating a significant reduction in the abundance and diversity of intestinal microbiota in CRC patients [6]. However, the specific mechanisms of the intestinal microbiota in the occurrence and development of CRC are not fully understood. Known microbial species that can promote the onset and progression of CRC primarily include *Fusobacterium nucleatum* (Fn), *Escherichia coli*, Lactobacillus, *Bacteroides fragilis*, *Bacteroides vulgatus*, *Bifidobacterium fragilis*, and Streptococcus. To improve the reliability of the results, larger studies could be conducted with a more diverse sample to validate previous findings.

Research by Yang *et al.* [7] confirmed that Fn promotes colorectal cancer cell proliferation and enhances invasiveness by upregulating the expression of microRNA-21. Studies by Miyasaka *et al.* [8] suggested that pks-positive *E. coli* may contribute to CRC carcinogenesis, as it is more abundant in stage 0-I tumor tissue compared to normal mucosal tissue or stage II-IV tumor tissue. Tang *et al.* [9], in a mouse model, discovered and validated that endogenous Lactobacillus La.mu730 can interfere with Cori.ST1911 colonization and restore intestinal barrier function. Furthermore, Cori.ST1911 increased acylcarnitine levels by activating CPT1A, demonstrating the involvement of the CPT1A-ERK axis.

In addition to the bacteria themselves, the toxins produced by the intestinal microbiota may also participate in the onset and development of CRC. Research by Rubinstein *et al.* [10] revealed that Fn produces *Fusobacterium nucleatum* adhesin A (FadA), a highly invasive factor that drives inflammation, activates the β-catenin signaling pathway, and promotes epithelial cell growth, thus contributing to inflammation and tumor development. Moreover, studies have shown that *F. nucleatum* promotes CRC metastasis through the miR-1322/CCL20 and M2 polarization pathways. It has been documented that the abundance of enterotoxigenic *Bacteroides fragilis* (ETBF) in CRC patients is significantly higher than in normal individuals [11]. ETBF can induce colorectal cancer by releasing a genotoxic compound, *Bacteroides fragilis* toxin, which activates the NF-κB signaling pathway and the Wnt/β-catenin pathway, leading to excessive epithelial cell proliferation, induction of intestinal inflammation, and promotion of CRC [12]. *Campylobacter jejuni* can bind to and invade intestinal epithelial cells. Studies have suggested that the cell-damaging cytolethal distending toxin secreted by *C. jejuni* can cause host cell DNA double-strand breaks, leading to cell cycle arrest and promoting the onset of CRC [13]. Furthermore, *C. jejuni* 81-176 activates the NF-κB signaling pathway, promoting IL-6 expression and exacerbating intestinal inflammation [14]. *Bacteroides fragilis* secretes virulence factors, such as *Bacteroides fragilis* toxin, which promote epithelial cell proliferation, induce the production of inflammatory mediators, and lead to mucosal inflammation and even CRC development [15].

In addition to directly influencing colorectal cancer through toxins and metabolites, the intestinal microbiota can regulate intestinal barrier function and affect the differentiation and function of immune cells, thus affecting tumor progres-

sion. Butyric acid-producing bacteria are probiotics that inhibit intestinal tumor development by regulating the Wnt signaling pathway and the intestinal microbiota [16]. Butyric acid salts improve mucosal inflammation and oxidative status, enhance epithelial defense barriers, regulate visceral sensitivity, and intestinal motility [17]. Zhang *et al.* [18] confirmed in a mouse model that Akkermansia muciniphila (*A. muciniphila*) protects mice from colorectal cancer development by specifically inhibiting tryptophan-mediated AhR/β-catenin signaling. Luo *et al.* [19] found *C. tyrobutyricum* improved high-fatdiet-induced lipid metabolism disorders, preserved the intestinal barrier's integrity, and modulated the structure of the intestinal microbiome.

In addition to producing toxins and metabolites, the intestinal microbiota can promote CRC development by altering the tumor microenvironment. In CRC, *F. nucleatum* can promote CRC progression by inhibiting the immune microenvironment, such as inducing T cell apoptosis by inhibiting $CD4^+$ T cell activity [20]. Enterococcus is enriched in the intestines, inducing the immune microenvironment or interacting with epithelial cells to promote inflammation and CRC development [21]. It has been found that *Bacteroides fragilis* can induce tumor proliferation by regulating the tumor immune microenvironment and also induce an increase in reactive oxygen species and DNA damage, thereby promoting the onset of colorectal cancer [22]. Dysbiosis of the intestinal microbiota leads to intestinal immune responses, and changes in the intestinal microbiota promote the onset of CRC. As previously mentioned, *F. nucleatum* activates an immune suppression signal by binding to the surfaces of immune cells with adhesion factors, recruiting tumor-infiltrating myeloid cells, altering the tumor microenvironment, and thus promoting tumor growth and infiltration.

4. Future Prospects and Application Outlook

In summary, gut flora has been shown to be closely associated with the pathogenesis of CRC. Recent studies have indicated [23] that the abundance and diversity of the gut microbiota in colorectal cancer (CRC) patients may be related to different BMI status, and the enrichment of Actinobacteria, Desulfovibrionaceae, and Bacteroidales may be associated with the overweight status of CRC patients. In order to reduce the impact of inconsistencies, a uniform study design and methodology can be established across different studies to ensure comparability and consistency of results. Furthermore, different probiotics can inhibit the occurrence and development of CRC through various mechanisms such as reducing the genotoxicity and mutagenicity of carcinogens, releasing anti-inflammatory factors, anticancer compounds (anti-angiogenesis, promoting the action of anti-PD-L1 drugs), and improving the function of the intestinal barrier, such as short-chain fatty acids [24] [25]. The two main probiotics are Lactobacillus and Bifidobacterium [26] [27]. The authors may have used only a small sample size for the analysis, which may lead to questions about the reliability of the results. To improve the reliability of the results, larger studies could be conducted with a

more diverse sample to validate previous findings.

By modulating the composition and function of the microbiota, such as using probiotics or prebiotics for treatment, it is possible to improve the imbalance of the gut microbiota, which may provide potential benefits for the prevention and treatment of CRC. Therefore, precision medicine strategies based on individual differences can be employed to utilize this information for preventive and therapeutic interventions, such as vaccination, fecal microbiota transplantation (FMT), dietary remediation and gut microbiome regulation [28]. Additionally, adjustments to diet and other methods can significantly improve the internal environment of the human body, especially playing a crucial role in the balance and health of the gut microbiota. As mentioned earlier, the standard treatment for CRC involves surgery, chemotherapy, and radiotherapy, but these approaches can lead to damage to the intestinal mucosal barrier, disruption of the gut microbiota, and the occurrence of adverse reactions such as intestinal mucositis, diarrhea, and weight loss [29]. By modulating the gut microbiota and improving the intestinal barrier function, the occurrence of adverse reactions can be reduced. Studies by Mi *et al.* [30] have found that Bifidobacterium can effectively alleviate chemotherapy-induced intestinal mucositis. Sample sources may not be diverse enough to represent the diversity of the population as a whole. This limitation may affect the accurate understanding of the relationship between colorectal cancer and the microbiome. But there is a tantalizing opportunity to find ways to live in harmony with our microbiome through the consumption of probiotics or fermented foods/supplements that have probiotics included in the matrix, which may provide large-scale health benefits [31].

In addition to therapeutic potential, the gut microbiota can also serve as a biomarker. Research has shown that bacteremia of specific bacteria in the microbial community has been associated with the diagnosis of CRC [32]. Detecting these specific bacteria or immune responses in the blood may indicate colon tumors, and for the detection of colitis-associated cancer, *Fusobacterium nucleatum* may be a potential biomarker [33]. By analyzing the composition and characteristics of the gut microbiota, predictive models of the gut microbiota can be established and used for the early diagnosis and risk assessment of colorectal cancer. It can serve as a non-invasive method in the future for searching for gastrointestinal diseases and related markers, opening up new means for tumor screening. However, the use of the gut microbiota as diagnostic and prognostic indicators for CRC requires further exploration, in order to provide new insights for the future use of the gut microbiota in the diagnosis and treatment of CRC. With the continued progress of research, we can expect the gut microbiota to play an important role in the prevention and personalized treatment of colorectal cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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