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Research progress in the use of bifidobacteria for the treatment of colorectal cancer

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Author contributions

Yu-Ting Zhao, Zhi-Hui Cai, Yu-Chen Yang contributed to the conception of the study; Zhi-Hui Cai contributed to the research direction and content analysis; Yu-Ting Zhao performed the data analyses and wrote the manuscript; Yu-Chen Yang contributed to the structure and content of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CRC, colorectal cancer; mCRC, metastatic colorectal cancer; NK, natural killer.

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Abstract

Colorectal cancer has high morbidity and mortality rates; therefore, developing new therapeutic drugs and methods for it is crucial. There is increasing evidence that intestinal flora plays a vital role in maintaining intestinal homeostasis and therefore, in the development of colorectal cancer. As such, therapeutic approaches using probiotics such as *Bifidobacterium lactis* to regulate intestinal flora are expected to represent a new treatment strategy for colorectal cancer. This article introduces and compares the development status of conventional therapies for colorectal cancer, primarily targeted therapy and immunotherapy, the relationship between intestinal flora and colorectal cancer, and the research and application of *Bifidobacterium bifidum* in colorectal cancer treatment to provide a reference for its clinical application.

Keywords: colorectal cancer treatment; intestinal flora; bifidobacteria

Lifestyle changes have increased the incidence of cancer in younger individuals. Colorectal cancer (CRC) is the third most common malignant tumor worldwide in terms of incidence, with the second highest mortality rate [1]. However, effective CRC treatment methods are still lacking. CRC is related to poor lifestyle habits, such as insufficient intake of fruits and vegetables and a sedentary lifestyle. In addition to lifestyle habits, intestinal diseases and intestinal flora disorders can promote CRC development [2]. The development and maturation of the intestinal flora is a dynamic and continual process, and the interactions between key flora involved in processes such as human digestion, metabolism, and immunity are important. Research has identified a very close relationship between intestinal flora and the development of CRC; therefore, several researchers have proposed the use of probiotics to regulate intestinal flora to treat CRC. *Bifidobacterium*, an intestinal probiotic, can correct and maintain the intestinal microecological balance to maintain the body's normal physiological parameters, providing possible CRC treatments based on traditional treatment modalities.

Current status of research on conventional colorectal cancer treatments

The conventional treatment modalities for CRC include surgery, radiotherapy, and chemotherapy. Surgery, the most effective local treatment method, considers various factors, including tumor location and stage, cell grading, body type, and bowel control ability. The following surgical procedures are commonly used in China: abdominal perineal resection (Miles surgery), low anterior resection (Dixon surgery), transabdominal rectal cancer resection, proximal stoma, and distal closure surgery (Hartmann surgery)[3].Regarding radiotherapy, several clinical studies reported that preoperative radiotherapy for rectal cancer could effectively reduce tumor size and control its infiltration, thereby reducing clinical stage and improving survival [4]. Nevertheless, chemotherapy remains the primary treatment modality for advanced CRC, which can improve the quality of life of patients with advanced CRC to a certain extent [5].

Research on CRC treatment has been extensively conducted, as outlined below.

Targeted drug therapy for colorectal cancer

Targeted therapies are any therapeutic modality that acts directly on cancer cells to inhibit the process of tumor cell proliferation and differentiation. Targeted therapy achieves therapeutic effects by affecting other molecules in the target molecular pathway or modulating the tumor microenvironment, including immune cells. Therefore, it has high efficiency, toxicity, and few adverse effects [2]. Examples include anti-EGFR therapy, BRAF inhibitor applications, anti-HER-2 therapy, anti-VEGF therapy, and small-molecule tyrosine kinase inhibitors [6].

In our country, most patients are diagnosed with mid to advanced stages of metastasis (metastatic CRC (mCRC)). Although chemotherapy remains the primary modality for first-and second-line systemic therapy for mCRC with continuous research on molecular oncology, multiple molecular-targeted drugs combined with chemotherapy for mCRC based on the detection of tumor *KRAS*, *NRAS*, and *BRAF* genes have achieved significant efficacy. For patients whose disease progresses despite first-or second-line standard therapy, third-line treatment with regorafenib or fruquintinib is recommended [7].

Regorafenib is a multi-target inhibitor, which limits its utility, while fruquintinib is more effective and selective [8]. The advantage of targeted drugs is that their treatment is directed at specific targets and does not act systemically, meaning they induce less systemic toxicity [9]. Combined targeted therapy significantly improves the prognosis of patients with CRC.

Immunotherapy for colorectal cancer

Immunotherapy achieves tumor clearance by suppressing negative immune regulators, activating the immune system, and enhancing the recognition and killing of tumors by immune cells. Immunotherapy has improved the prognosis of patients with CRC to some extent and is a promising treatment option. However, only some CRC subtypes show a better immune response following immunotherapy. Further screening of the beneficiary population and selecting the optimal regimen in the future are still required [10].

Recent studies have shown that immune combination therapy may be a viable strategy for improving tumor response rates and prognosis. Common immune combination therapies include synergistic combinations of different immunotherapeutic agents and a combination of immunotherapy with traditional antitumor modalities, such as chemotherapy, radiotherapy, and targeted therapy [11]. Moreover, data suggest that the gut microbiota composition may further influence cancer immunotherapy's efficacy and toxicity. Thus, the gut microbiota may be manipulated by antibiotics, probiotics, prebiotics, or fecal transplants to improve the effectiveness and reduce the toxicity of anticancer drugs [12].

Colorectal cancer biomarkers

Biomarkers are biological indicators that objectively detect and evaluate normal biological processes, pathological processes, or pharmacological responses. DNA, RNA, microRNA, epigenetic changes, and antibodies may all be assessed as biomarkers and can be used primarily to identify cell types, study pharmacodynamics and dose-response, develop individualized therapeutic interventions, and predict adverse drug reactions. As such, biomarkers play an essential role in the early diagnosis, treatment, and prognostic assessment of CRC [13].

In recent years, many studies have been conducted on novel CRC biomarkers, including circulating tumor cells, circulating tumor DNA, and DNA methylation. Compared with traditional CRC tumor markers, these novel markers have better specificity and sensitivity for the early prediction and prognostic assessment of CRC. They are more convenient for postoperative disease monitoring as they have fewer side effects and higher patient compliance. As such, these treatments have a very wide application prospect [14].

Impact of intestinal flora disorders on colorectal cancer

Disturbance of the intestinal flora can cause various clinical diseases such as type 2 diabetes, obesity, inflammatory bowel disease, and chronic diarrhea [15]. Moreover, several studies have shown that patients with CRC exhibit significant ecological dysbiosis of the intestinal flora, suggesting a strong relationship between intestinal flora and CRC.

In recent years, several studies in numerous countries have shown that bacteria such as *Escherichia coli, Enterococcus faecalis, Streptococcus fragilis, Streptococcus gallotrophicus,* and *Clostridium perfringens* are closely related to CRC development. For example, *Escherichia coli* subtype B2 carries the conserved gene polyketide synthase island, which produces a genotoxic substance called polyacetyl monopeptide that reportedly causes DNA damage and carcinogenesis [16]. *E. faecalis* induces significant distal colitis, DNA damage, and cancer. These studies confirm that CRC is further induced by extracellular superoxide anion-producing *E. faecalis*, while *C. perfringens* can invade and survive in colon cancer cells, and its FadA adhesin binds E-cadherin, which in turn activates β-linked protein signaling and induces CRC cell proliferation [17]. In addition, its Fap2 protein acts on the inhibitory immune receptor of natural killer (NK) cells to promote the evasion of NK cell killing [18].

The causes of intestinal cancer triggered by intestinal flora can be broadly classified as follows: (1) action of genotoxins and other bacterial virulence factors, interfering with the cell cycle and apoptosis or stimulating tumor cell proliferation; (2) exertion of oncogenic effects by microbial-derived metabolites; (3) immune regulation and chronic inflammation; (4) involvement of the intestinal flora in the CRC signaling pathway, causing cell proliferation and inhibiting apoptosis; and (5) oxidative stress. It was conclusively shown that some enterococci could enhance CRC-related gene instability; for example, *Helicobacter pylori* has been clearly demonstrated to cause gastric carcinogenesis through the induction of oxidative stress [19].

Bifidobacteria in oncology treatment

Members of the intestinal flora beneficial to the human body are termed probiotics; this class includes *Lactobacillus*, *Bifidobacterium*, and *Clostridium typhimurium*. Among them, *Bifidobacterium*, an important dominant symbiotic flora in the human intestine, improves the human intestinal environment by converting fructose-6 phosphate ketone enzymes to glucose enzymes to lactic acid and acetic acid, lowering intestinal pH to inhibit the growth and reproduction of pathogenic bacteria [20]. It is also a key aspect of the microflora involved in intestinal regulation that protects the intestinal mucosal barrier, inhibits tumor growth, and promotes tumor cell apoptosis [21].

Bifidobacteria and colorectal cancer correlation

Bifidobacteria are closely associated with various diseases of the digestive system. Fifty healthy individuals were selected as the control group. Stool samples were collected from both groups, from which DNA was extracted. The number of bifidobacteria was determined by fluorescence quantitative polymerase chain reaction, and the levels of bifidobacteria in both groups were compared to analyze the correlation between bifidobacteria and the clinicopathological characteristics of CRC. *Bifidobacterium* counts were significantly lower in patients with CRC, indicating a close correlation to the occurrence and development of CRC [22]. In recent years, the use of bifidobacteria to treat CRC has become a hot research topic.

Bifidobacterial CRC treatment

Bifidobacterial immunotherapy includes the following

1. Enhanced tumor-specific CD8+ T cell activity. The symbiotic microbial composition can influence the spontaneous antitumor immune response. Bifidobacterial overexpression was positively correlated with delayed tumor growth and a good patient response to anti-PD-L1 therapy. Signals produced by symbiotic bifidobacteria stably modulate dendritic cell activation, thereby improving the effector functions of tumor-specific CD8+ T cells. 2. Activation of type I IFN signaling: CD47 is a signaling molecule that helps tumor cells escape immune system detection, and some studies reported that blocking CD47 can produce good tumor immunotherapy effects. Several researchers have further reported that members of the intestinal flora can activate the STING signaling pathway to stimulate the body further and produce anti-CD47 antibodies, while *Bifidobacterium*, an anaerobic symbiotic bacterium in the intestine, can colonize the tumor and regulate the immune response triggered by CD47 blockade. 3. Promotion of conventional dendritic cell-dependent Th1 differentiation: several studies using animal models of CRC have identified the bacteria that promote the efficacy of immune checkpoint inhibitors. For example, *Bifidobacterium pseudobacterium longum* enhanced the effect of immune checkpoint inhibitors in a mouse intestinal tumor model by enhancing the conventional dendritic cell-dependent Th1 cell circuitry [23].

Targeted therapy with *Bifidobacterium*: killing tumor cells and inhibiting tumor cell proliferation

Bifidobacterium vectors can mediate the expression of cytotoxic genes coding for proapoptotic proteins and precursor drug-active enzymes. In pre-bedside models, many *Bifidobacterium* vectors have successfully been used to transduce suicide genes, resulting in tumor-killing effects [24].

Bifidobacterium ameliorates CRC adverse reactions

Live bifidobacteria can effectively improve the intestinal flora, rebuild intestinal barrier function, reduce postoperative adverse reactions, and enhance patient satisfaction, which is clinically significance [25]. The intestinal flora can reduce intestinal inflammation, modulate the toxic side effects caused by immunotherapy, effectively reducing PD-1-induced enteritis [26].

Future perspectives

There are currently many clinical treatment options for CRC, of which modulation of the intestinal flora is rising as an important aspect of research. The intestinal flora is closely related to intestinal tumors, and intestinal flora disorders can cause CRC. In view of this finding, regulation of the intestinal probiotic flora is a new therapeutic strategy. *Bifidobacterium bifidum* counts were significantly reduced in patients with CRC, which led some researchers to propose its use as a treatment. This approach requires further investigation, and more clinical data and theoretical support are needed. As the role of probiotics in the gut is further explored, we believe that patients with CRC will benefit from the regulation of intestinal probiotics.

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