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# Role of Gut Microbiota in the Development and Treatment of Colorectal Cancer

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**Abstract**
Human guts harbor abundant microbes that regulate many aspects of host physiology. However, bacterial imbalance or dysbiosis in the gut due to the dietary or environmental changes may cause colorectal cancer (CRC). Increasing studies show that gut microbiota plays an important role in the occurrence and development of CRC, as a result of virulence factors, bacterial metabolites, or inflammatory pathways. In the future, probiotics or targeting the microbiota will probably be a powerful weapon in the battle against CRC. This review seeks to outline the relationship between gut microbiota and the development of CRC as well as the potential mechanisms of microbiota involved in treatment of CRC, so as to provide some references for research on the development, prevention, and treatment of this disease.



Colorectal cancer (CRC) is one of the most common malignant tumors, ranking in the top 3 causes of cancer-related death worldwide. In recent years, the incidence of CRC decreased slightly among adults aged $p \geq 50$ years, in contrast to the incidence that increased by about 20% among adults aged <50 years, with the mortality increased by about 10% [1]. Multiple epidemiological studies have suggested that excessive animal protein and fat intake, especially red meat and processed meat, could increase the risk of developing CRC, while fiber could protect against colorectal tumorigenesis [2]. Diet could re-shape the community structure of gut microbiota and influence its function by modulating the production of metabolites. The majority of research on the gut microbiota has focused on the colon and feces, the same as the pioneering work done by the Human Microbes Project to characterize the microbes in healthy individuals [3].

With the progress of molecular ecology and genomic research and the progress of high-throughput sequencing technology, more and more scholars pay more attention to the role of gut microbiota in the development and

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treatment of CRC. It has become clear that the interaction of a tumor with its local microenvironment and its systemic effects on the host is critical for this process. The bidirectional communication of tumor cells with their microenvironment has been demonstrated in chick and zebrafish models in which the cancer phenotype of transplanted tumor cells was reversed by the embryonic microenvironment [4]. The destruction of gut micro-ecological balance has become a hot spot in the study of the pathogenesis of CRC may provide a new direction for the treatment of CRC, besides gene mutation and genetic factors. In this review, we seek to outline the current state of knowledge on the relationship of gut microbiota and the development of CRC as well as the potential mechanisms of microbiota involved in treatment of CRC, aspects of a discussion of future prospects of microbiota in prevention and treatment.

## Mechanism of Gut Microbiota Involved in Colorectal Carcinogenesis and Development

Comparison CRC patients and normal persons, the predominant flora in CRC is some pathogenic bacteria, such as *Fusobacterium nucleatum*, *Escherichia* coli, or *Bacteroides fragilis* [5]. Especially *Fusobacterium*, has been demonstrated to be related to CRC development and pathogenicity [6], and is abundant in tumor tissue in patients with MSI-H (microsatellite instability-high) and CIMP-H (CpG island methylator phenotype-high) [7]. It suggests that *Fusobacterium* could potentially be used as a screening method for CRC and polyp detection [8, 9]. Therefore, researchers are focused on studying about gut microbiota in the carcinogenesis and development of CRC.

### *Virulence Factors Produced by Gut Microbiota*

In the progression of biological evolution, some gut microbiota has become pathogenic by virulence factors, which mainly involve invasiveness and toxin. A large number of *F. nucleatum* that lives in the gut with CRC, interacted with E-cadherin instead of β-catenin, which in turn enhances the malignant phenotype of CRC cells [10], and upregulate the expression of inflammatory genes and downregulate acquired immunity mediated by T cells [11]. Gut microbiota related to CRC, such as *E. coli*, can also invade intestinal epithelial cells through adhesin Afa and Eae, to activate similar pathways [12].

Besides that, toxins produced by gut microbiota are also involved in the development of CRC. Enterotoxigenic *B. fragilis*, which can produce *B. fragilis* toxin (BFT), is a potential microbe that can promote carcinogenesis. BFT can activate the Wnt/β-catenin and nuclear factor-κB pathway to promote cell proliferation, induce the production of inflammatory mediators, and become CRC eventually [13]. Boleij et al. [14] recently reported that BFT gene is a risk factor for CRC, and is more closely related to advanced CRC. Many gut microbiota can also produce genotoxic toxins, induce DNA damage, interfere with cell cycle and apoptosis. Among them, cytolethal distending toxin (CDT) and polyketide peptide toxins, such as Colibactin, can directly damage DNA and cause genomic instability [15, 16]. Most gram negative bacteria related to CRC can produce CDT, and can promote CDT B in cytoplasm transferring to nucleus by interacting with host cells through CDT A and CDT C, so as to damage the host cell DNA as deoxyribonucleic acid [17].

The study also found that *E. coli* of CRC patients contains polyketide synthase gene, this gene can not only induce inflammation, epithelial cell injury, and cell proliferation [15] but also encode Colibactin, damage DNA, and finally promote carcinogenesis. And this *E. coli* can enhance the activity of tumor promoting macrophages by inducing cyclooxygenase-2 [18]. Although these toxigenic bacteria occupied a small proportion, the analysis of CRC samples revealed that these virulence factors were highly expressed when the intestinal flora was destroyed [19].

### *Gut Microbial Metabolites*

In addition to bacterial virulence factors, some microbial metabolites produced by gut microbial damage also strongly affect the development of CRC [20], mainly including secondary bile acid, glucuronic acid, and acetaldehyde. The study found that people with high fat diet were susceptible to CRC, and changing the high fat diet into a high fiber diet reduced the risk of cancer greatly [21]. This may be because high fat diet leads to an increase in intestinal primary bile acid secretion, while microbiota can transform this primary bile acid metabolism into secondary bile acid. When researchers fed mice with secondary bile acids, intestinal tumor formation and inflammatory damage were greatly increased [22]. It is found that this kind of bile acid can be used as the source of microbial energy, and promote the development of CRC by participating in cell proliferation, apoptosis, and DNA damage [23].

Moreover, studies have shown that fecal glucuronidase activity is higher in CRC patients than in normal subjects [24]. In the mice model of CRC, the inhibition of the ac-

tivity of glucuronide can effectively reduce the number of tumors [25]. The mechanism involved in tumorigenesis may be that the liver can inactivate toxic carcinogens through the covalent binding mediated by glucuronide. However, this process in colon is reversed by bacterial glucuronidase. Gut microbiota can also produce some carcinogenic metabolites directly through protein digestion, including sulfides, ammonia, and nitrosamines.

It has been reported that a high protein and low carbohydrate diet increases the production of toxic metabolites, decreases the production of anti-cancer metabolites, and therefore increases the risk of carcinogenesis [26]. These oncogenic metabolites can cause mutations in DNA and formation of oxygen free radicals, leading to tumors [27].

*Host Immunity and Inflammation*

Innate immunity of gut mucosa can resist gut microbial invasion and maintain gut homeostasis. Toll-like receptors (TLRs) and NOD-like receptors play an important role in identifying specific molecular patterns of pathogenic gut microbes [28]. Host immunity can both inhibit tumor formation, and promote the development of tumor. Early studies have shown that myeloid differentiation factor 88 (MyD88) plays a key role in CRC induced by spontaneous or carcinogenic agents [29], as a critical adaptor protein in the TLRs and interleukin-1 (IL-1)/IL-18 signaling pathways. Adenomatosis polyposis coli (APC) gene is a tumor suppressor gene. In the APC$^{Min/+}$ mice treated with azoxymethane (AOM), the inactivation of MyD88 gene resulted in a reduction in the number of tumors [30], and in the same model, *F. nucleatum* promotes colonic neoplasia development by downregulating antitumor T cell-mediated adaptive immunity [31]. These results suggest that MyD88 can promote the progression of CRC in TLRs pathway. However, in the MyD88 gene knockout (MyD88–/–) mice treated with AOM/dextran sulfate sodium (AOM/DSS), it is also found that MyD88 has anticancer properties [30, 32]. This may be because MyD88 activates the IL-18 signaling pathway to anti-tumor [33]. In NOD1 or NOD2 deficient APC$^{Min/+}$ mice model, the number of CRC increased significantly [34]. In AOM/DSS treated mice, the same results were observed after the absence of NOD1 or NOD2 [35]. All the above information suggests that activating NOD-like receptors pathway may inhibit the development of CRC.

In addition to host immunity associated with CRC, inflammation is also an important factor. In patients with inflammatory bowel disease (IBD), gut microbial homeostasis has changed [36], and this population is more likely to be affected by CRC. The following study demonstrated that the mechanism of gut microflora disorders in IBD causing CRC contains the mutation of tumor protein p53, activation of β-catenin and Wnt pathway, action of cytokines, and damage of DNA [37]. Therefore, host immunity and inflammation play an important role in the development of CRC.

## Gut Microbiota in Treatment of CRC

Recent studies have reported that the effectiveness of the immunosuppressive agent in the antitumor immunotherapy depends on the gut microecology. The anticancer efficacy of the chemotherapeutics commonly used in the chemotherapy is regulated by the gut microbiota. In addition, 5-fluorouracil can enhance the killing effect on CRC cells under the influence of the gut microbial metabolites. Probiotics are used to prevent CRC through a variety of ways.

*Chemotherapy*

CRC chemotherapy is commonly used in postoperative adjuvant therapy or advanced CRC patients. Commonly used drugs include platinum, fluorouracil, and its derivatives. Recently, more and more studies have shown that the antitumor activity of various chemotherapeutic drugs is affected by gut microbiota. For example, 2 individual studies published in Science authorized by Viaud et al. [38] and Iida et al. [39] have proved that in cancer microenvironment, gut microbiota can respond to alkylated anticancer agent cyclophosphamidethe used in other tumor chemotherapy and platinum chemotherapeutic drugs oxaliplatin used in CRC, which mediates immune activation and affects the antitumor activity of drugs. Other studies [40] suggested that gut microbial metabolites could enhance the killing effect of 5-Fu on CRC.

Cyclophosphamide, a chemical drug, mediates its antitumor activity by stimulating the antitumor immune response, and controls tumor growth by inducing immune source cancer cell death, destroying immunosuppressive T cells, or promoting Th1 and Th17 cells [41]. Viaud et al. [38] further studied the effect of cyclophosphamide on gut microbiota and the subsequent effect on tumor immune reaction. Through mice models, researchers confirmed that cyclophosphamide can change the composition of gut microbes – a reduction of lactobacilli and enterococci, and induce gram-positive bacteria transfer to secondary lymphoid organs, and the microbes in the sec-

ondary lymphoid organs can stimulate host to produce a group of special "pathogenic" Th17 cells (pTh17) and immune reaction of Th1 memory cells. Finally, in sterile mice or in the mice that killed Gram-positive bacteria with antibiotics, researchers found the reaction of pTh17 weakening, and the mice were resistant to cyclophosphamide, and when pTh17 transferred to these mice, the anti-tumor effect of cyclophosphamide was improved. This study showed that gut microbiota is helpful to the antitumor immune reaction of cyclophosphamide.

Iida et al. [39] showed that the disruption of gut microbiota impairs the response of subcutaneous tumors to platinum chemotherapy. The mechanism of oxaliplatin has not been totally elucidated, but some studies have shown that oxaliplatin can inhibit DNA synthesis, produce cytotoxic and anti-tumor activity by acting on DNA to form adducts and cross-linking. In addition, the production of reactive oxygen species (ROS) after oxaliplatin is also one of the causes of DNA damage and apoptosis. In mice, researchers found that antibiotic cocktail therapy could prevent DNA damage and apoptosis induced by oxaliplatin, by reducing ROS after some of the DNA adducts have been formed. Specially, data showed that most of ROS required for oxaliplatin genotoxicity come from tumor-related inflammatory cells. This indicates that gut microbiota influences the antitumor activity of oxaliplatin through affecting the related inflammatory cells and the production of ROS. Researchers speculated that, in addition to platinum chemotherapeutics, other chemotherapeutic agents, such as anthracycline, alkylating agents, pavonlotoxin, and camptothecin, which generate ROS as part of anti-tumor activity may be affected by the same regulation.

Another report showed that *F. nucleatum* promoted CRC resistance to chemotherapy. Mechanistically, *F. nucleatum* targeted TLR4 and MYD88 innate immune signaling and specific microRNAs to activate the autophagy pathway and alter CRC chemotherapeutic response [42]. And oral probiotic Lactobacillus casei variety rhamnosus (Lcr35) prevented FOLFOX-induced intestinal mucositis in CRC-bearing mice [42]. This suggests that immune may serve as a bridge between the gut microbiota and various cancer interventions.

*Immunotherapy*

Modern cancer immunotherapy mainly includes nonspecific immunomodulators, tumor vaccines, adoptive immunotherapy, and immuno-binding site blocking therapy. The immunotherapy of cancers treated with microorganisms was reported as early as the end of the 19th century: Treatment of sarcoma patients with a heat-killed mixture of *Streptococcus pyogenes* and *Serratia* can effectively increase their survival rate, and the 5-year survival rate of 80% of 1,000 patients is increased. Researchers hypothesize that the mixture induces a persistent immune response and exerts an antitumor effect [43]. Recent studies have shown that the composition of the intestinal flora can well predict the efficacy of allogeneic stem cell transplantation, confirming that intestinal microbes play an important role in the formation of systemic immune responses [44]. All the above studies showed that the regulation of patients' immune system through microbiota is one of the key mechanisms of tumor immunotherapy.

Current studies on tumor immunotherapy and research focus on the treatment of blockade, and more mature intervention mechanisms include antibodies against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), and antibodies against CD8+ T-cell programed death factor programmed death-1 (PD-1)/PD-L1, which are often known as the immune checkpoint inhibitors [45]. Sivan et al. [46] found that bifidobacteria are associated with antitumor effects in mice. Oral bifidobacteria alone can achieve tumor control equivalent to the use of PD-L1 inhibitors, and combined bifidobacteria and PD-L1 inhibitors almost completely inhibit tumor growth. Further studies found that enhanced dendritic cells increase CD8+ T-cell activation and aggregation in the tumor microenvironment and mediate these effects, but the specific mechanism remains to be explored. This study confirms that Bifidobacterium can enhance anti-tumor immunity and promote the efficiency of anti-PD-L1 immunotherapy. The researchers further hypothesized that: In solid tumors, a possible element of enhanced T-cell infiltration is gut microbiota. Vétizou et al. [47] demonstrated that CTLA-4 inhibitors are antitumor dependent on Bacteroides. In mice and humans, the response of T cells to *Bacteroides* or *B. fragilis* is related to the antitumor efficacy of CTLA-4 inhibitors. In addition, tumors in antibiotic-treated mice or sterile mice did not respond to CTLA-4 inhibitors but responded when fed with *B. fragilis*, using polysaccharides for immunization or transplanted of specific T cells. Finally, researchers transplanted fecal bacteria from melanoma patients to mice and demonstrated that CTLA-4 inhibitors promote the growth of *B. fragilis*. This study illustrates the immunostimulatory effects of Bacteroides bacteroides in CTLA-4 inhibitor therapy.

Above-mentioned studies have shown that enteric microorganisms play a key role in the treatment of cancer by immune checkpoint inhibitors, but the target tumor is melanoma, not CRC. The main reason may be that CRC

is considered not sensitive to immunotherapy. Recently, however, Lee and Le [48] demonstrated that cancers with defective gene mismatch repair respond to PD-1 inhibitors well. CRC patients with chromosomal defect repair have a control with 62% rate of PD-1 inhibitors, compared with 16% of patients with complete chromosomal mismatch repair. Above-mentioned studies provide ideas for the use of gut microbiota in cancer treatment, that regulating the composition of gut flora may enhance the efficacy of cancer immunotherapy and lay the foundation of treatment of CRC patients with defects in mismatch repair.

*Probiotics in the Inhibition of CRC*

Pathogenic microbes may participate in the pathogenesis of CRC through different mechanisms when the gut microbial homeostasis is disturbed. Therefore, transformation of this disorder will become a new method for the treatment of CRC. Probiotics make a variety of biological benefit to host health, containing the anti-activity of pathogenic bacteria, regulating immune system, reducing blood cholesterol, reducing colitis, and preventing CRC [49].

Different probiotics can inhibit CRC by different mechanisms. Studies have shown that probiotics combined with carcinogenic mutagens, make a biotransformation aim to detoxification, which mainly depends on the peptidoglycan, polysaccharide, and secreted glycoproteins on the surface of probiotics. Probiotics can downregulate inflammation and reduce the carcinogenic metabolites to prevent CRC [49]. Besides, probiotics can regulate the immune system and inhibit the progression of CRC. The results showed that the incidence of tumor decreased in mice treated with Clostridium butyricum and 1, 2-two hydrazine hydrochloride, due to a decrease in the number of Th2 and Th17 cells, thereby inhibiting CD4+ and CD8+ T lymphocytes, blocking the cell cycle, reducing secretion of inflammatory factors, such as nuclear factor-κB, IL-22, and promoting tumor cell apoptosis [50].

Probiotics not only produce anti-inflammatory factors to extend the immune stimulating function, but also secrete antioxidant, anti-cancer compounds, short chain fatty acids to improve intestinal barrier function [51, 52]. Cyclooxygenase-2 can promote tumor angiogenesis, while probiotics inhibit carcinogenesis by reducing cyclooxygenase-2's expression [53]. Sivan et al. [46] found that probiotics can increase the antitumor effect of anti-PDL1 drugs.

Immunotherapy and chemotherapy are partial antitumor effects that depend on the intestinal microbiota. The difference is that probiotic therapy itself is a direct change to the intestinal microecology. In healthy people, the use of probiotics mainly plays a role in prevention of CRC, but in CRC patients, the direct supplement of probiotics can regulate the intestinal microecology on the one hand, and on the other hand, can promote the effect of CRC-related treatment methods.

## Conclusion

The classic clinical guidelines have made it clear that CRC is treated mainly by surgery, while the whole body treatment scheme is not enough. This paper mainly discusses the role and application of gut microbiota in the development and treatment of CRC. In the present study, gut microbiota plays a key role in the mechanism of common treatment on CRC, and gut microbial dysbiosis will affect immunotherapy and chemotherapy, as well as the efficacy of medicine. It may increase the possibility of adverse reactions, the economic burden of patients, reduce patients compliance, and even lead to treatment failure. Therefore, the study of gut microbiota in the treatment of CRC and other tumors suggests that clinicians should not only try to assess the intestinal microecology of patients comprehensively but also try to use medicine such as antibiotics carefully and strictly during the diagnosis and treatment of CRC to avoid destroying the normal balance of intestinal microenvironment. It is further suggested that clinicians should try to use probiotics to maintain and improve gut microbiota so as to prevent CRC. Regulating the intestinal flora or adding probiotics may be beneficial to immunotherapy and chemotherapy, and it will even destroy tumor cells in the process of carcinogenesis some day in future.

In addition, risk stratification of CRC patients can be performed based on the level of mucosa-associated bacterial symbiotic groups. The heterogeneity of colon cancer-associated bacteria can be developed as a tool for screening individuals at high risk of CRC, but further longitudinal studies are needed to assess its value as a biomarker for predicting CRC. Intestinal flora profiles can be used to predict CRC in combination with other risk factors such as age, race, and body mass index.

## Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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