

Microbe-based management for colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the most prevalent, most lethal cancers in the world. Increasing evidence suggests that the intestinal microbiota is closely related to the pathogenesis and prognosis of CRC. The normal microbiota plays an essential role in maintaining gut barrier function and the immune microenvironment. Recent studies have identified carcinogenic bacteria such as *enterotoxigenic Bacteroides fragilis* (ETBF) and *Streptococcus gallolyticus* (*S. gallolyticus*), as well as protective bacterial such as *Akkermansia muciniphila* (*A. muciniphila*), as potential targets of CRC treatment. Gut microbiota modulation aims to restore gut dysbiosis, regulate the intestinal immune system and prevent from pathogen invasion, all of which are beneficial for CRC prevention and prognosis. The utility of probiotics, prebiotics, postbiotics, fecal microbiota transplantation and dietary inventions to treat CRC makes them novel microbe-based management tools. In this review, we describe the mechanisms involved in bacteria-derived colorectal carcinogenesis and summarized novel bacteria-related therapies for CRC. In summary, we hope to facilitate clinical applications of intestinal bacteria for preventing and treating CRC.

Keywords: Colorectal cancer; Intestinal bacteria; Management; Fecal microbiota transplantation

Introduction

Colorectal cancer (CRC) is one of the most common and deadliest cancers in the world, ranking second as a cause of cancer deaths in the United States.^[1] Among the new cancers diagnosed in 2018, 10.9% in males and 9.5% in females were CRC.^[2] The occurrence and mortality of CRC have increased in economically transitioning countries.^[3,4] CRC is one of the leading cancers in China, and the new cases and cancer-related deaths have increased substantially from 2015 to 2020.^[5]

CRC development is attributed to hereditary and environmental factors. Overweight and obesity, western dietary habits, smoking, and heavy alcohol consumption affect the risk of CRC and may further alter the gut microbiome.^[6] Among these environmental factors, the role of intestinal bacteria in the development of CRC has become highly important and has received widespread attention.

The human intestinal tract consists of abundant microbiota contributing to physiological or pathological functions of the host. The pathogenic mechanism by which bacteria leads to CRC involves many aspects:

chronic inflammation, genotoxins and metabolites derived from pathogens.^[7] The gut microbiota interacts with the host immune system, leading to an aberrant immune response and inflammatory environment, which further prompt the development of CRC.^[8,9] The composition of the gut microbiota influences intestinal barrier function^[10] and regulates the mucus layer of the gut.^[11] CRC-associated gut dysbiosis induces higher numbers of hypermethylated genes than are found in healthy controls, so it is considered a causal agent of host DNA alterations.^[12] Dysbiosis and abnormal metabolites may cause CRC progression and influence the therapeutic effect against CRC. Metabolites in the tumor-associated environment can stimulate immune cell-induced chronic inflammatory responses and tumorigenesis.^[13] The imbalance between pathogenic bacteria and probiotics can lead to the disruption of intestinal homeostasis. Particularly, *Bacteroides*, *Fusobacterium*, *Campylobacter*, *Escherichia*, *Streptococcus*, *Clostridium*, and *Peptostreptococcus* contribute to the pathogenesis and poor prognosis of CRC.^[14,15] In contrast, probiotics such as butyric acid-producing bacteria and *Akkermansia muciniphila* (*A. muciniphila*) can suppress tumor growth and metastasis.

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The management of CRC involves many approaches. Despite conventional therapies, including endoscopic and surgical treatment, chemotherapy, radiotherapy and immunotherapy, microbe-based management is novel but has become indispensable.^[16] The gut microbiota can serve as a biomarker for detecting tumors and can modulate the effects of CRC treatment and prevention measures.^[17] With the growing knowledge of how gut bacteria contribute to carcinogenesis and affect treatment consequences, regulation and modulation of gut bacteria have become potential strategies for CRC prevention and treatment.

In this review, we summarize the mechanisms of the pathogenic processes of CRC-related bacteria and then discuss the latest advances in the prevention and treatment of CRC, including probiotics, prebiotics, postbiotics, fecal microbiota transplantation (FMT) and dietary interventions.

Specific bacteria correlated with CRC

There are some CRC-related bacteria in the tumor microenvironment, based on the combined analysis of 526 metagenomic samples from five countries.^[18] In a retrospective analysis of patients diagnosed with CRC, *enterotoxigenic Bacteroides fragilis* (*ETBF*), *Streptococcus gallolyticus* (*S. gallolyticus*) and other intestinal microbiota entered the bloodstream and then disturbed the gut mucosal barrier, which indicated that some specific intestinal bacteria can promote colorectal carcinogenesis.^[19] Most pathogenic bacteria can produce toxins that damage the intestinal epithelial cells (IECs), leading to an inflammatory response and then to tumor growth. Some pathogens exert carcinogenesis effects by adhering to the mucosal surface of IECs or tumor cells.^[7]

Immunotherapy has a wide range of applications in CRC. Immune checkpoint inhibitors (ICIs) against programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 aim to restore and strengthen the anticancer response by suppressing intrinsic immunoinhibitory pathways. ICIs can be affected by some bacteria as well. The potential mechanisms involve the accumulation of tumor-specific T cells and intratumoral CD8⁺ T cells, as well as the maturation and activation of dendritic cells. Gut dysbiosis can influence their efficacy in an immune-mediated manner. ICI resistance results from some pathogens, but some bacteria can restore their antitumor efficacy.^[20]

By their mechanism of promoting CRC, bacteria can be divided into three groups: (1) direct carcinogenic bacteria, which can directly participate in CRC development; (2) indirect carcinogenic bacteria, which impact CRC pathogenesis via secondary metabolites, or induce immune changes in the tumor microenvironment; and (3) probiotics that are beneficial to human health and exert anticancer effects.^[15]

Recently, the use of antibiotics has become widespread and may affect the intestinal microbiota. Antibiotics can induce or exacerbate dysbiosis because they cannot differentiate pathogens from normal bacteria.^[21] A case-control study

in the UK from 1989 to 2012 suggests that oral antibiotics are positively correlated with the risk of proximal colon cancer but negatively associated with rectal tumors. This might be because oral anti-anaerobic antibiotics markedly disrupt the microbiota composition, leading to dysbiosis, and the proximal colon is the first site exposed to them. Antibiotics impact the proximal colon by disrupting biofilms, a process linked with carcinogenesis.^[22] One study in Sweden indicated that there is an association between antibiotics and a high risk of proximal colon cancer.^[23] Gut microbiota and site-specific tumorigenesis can be novel targets for CRC treatment.

Below, we cover studies on eight common bacteria related to CRC.

Enterotoxigenic Bacteroides fragilis

It has been reported that *Bacteroides* species are enriched in the gut microbiota of CRC and that the abundance of *Bacteroides* is positively correlated with intestinal tumorigenesis.^[24] *ETBF* can produce *B. fragilis* toxins (BFT), a 20 kDa zinc-dependent metalloprotease toxin that is the cause of *ETBF* pathogenicity.^[25] A study has suggested that the *bft* gene is associated with precancerous and cancerous tumors in the colon and that BFT exposure could be a potential screening marker for CRC patients.^[26] Consequently, *ETBF* or BFT exposure is considered a risk factor for advanced CRC.^[27]

Owing to the potential causality between colitis and CRC, BFT triggers a series of immune reactions, forming an inflammation-associated environment for CRC genesis. From chronic inflammation to CRC development, the activation of signal transducer and activator of transcription (STAT) 3 and regulatory T-cells (Tregs) are indispensable. After *ETBF* disrupts the balance of Tregs and T-helper (Th17) cells, interleukin (IL)-2 levels decrease, and then IL-17 is produced. Subsequently, IL-6 is generated and then activates the STAT3 pathway.^[28,29] This process causes an inflammatory environment that promotes CRC proliferation. IL-17 also triggers downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and C-X-C chemokine production by IECs in *Apc^{Min/-}* mice.^[30] After incubation with *ETBF*, exosomes containing microRNA (miRNA) 149-3p are produced by CRC cells. This miRNA can regulate the PHF5A-KAT2A axis to promote CRC development and trigger Th17 cell activation and differentiation to accelerate gut inflammation. Thus, *ETBF* has been proven to facilitate colitis and tumorigenesis.^[31] Additionally, BFT degrades E-cadherin to damage gut barrier function and change the cell morphology and thus the function of IECs.^[28]

In short, *ETBF* is linked to gut inflammation and tumorigenesis. *ETBF* and BFT are essential therapeutic targets to be further studied.

Fusobacterium nucleatum

Similar to *Bacteroides*, *Fusobacterium* was significantly increased in abundance in CRC tissue compared to normal samples in a single cohort.^[32] There is also a report that

Fusobacterium nucleatum (*F. nucleatum*) can promote CRC cell proliferation and increase their invasive activity. Indeed, *F. nucleatum* can recruit tumor-infiltrating myeloid cells to develop an inflammatory microenvironment leading to tumor progression in the *Apc^{Min/+}* mouse model.^[33] Adhesin FadA, a virulence factor identified from *F. nucleatum*, can bind E-cadherin to stimulate CRC cell proliferation and to regulate many inflammatory and oncogenic responses. Thus, FadA is considered a therapeutic target for CRC.^[34]

In addition, *F. nucleatum* is closely related to noncoding RNAs. A previous study found that *F. nucleatum* abundance has a positive relationship with high glucose metabolism in patients with CRC. *F. nucleatum* regulates glucose metabolism through the axis of long noncoding RNA (lncRNA) enolase1-intronic transcript 1 and KAT7 histone modification.^[35] *F. nucleatum* can activate Toll-like receptor 4 (TLR4) signaling to myeloid differential protein-88 (MyD88) to upregulate NF- κ B and miR-21 levels. MiR-21 is responsible for chronic inflammatory processes and the development of colitis-associated cancer (CAC). Both *F. nucleatum* and miR-21 could become risk markers of CRC.^[36]

Since traditional chemotherapy has been widely used in CRC patients, high tumor recurrence is becoming a problem in some patients. Many studies have suggested that that resistance to CRC therapy could be impacted by gut microbes such as *F. nucleatum*. *F. nucleatum* has a higher abundance in CRC patients with recurrence after chemotherapy. The mechanism involves TLR4 and MyD88 immune signaling with selective target loss of miR-18a* and miR-4802 targets and activation of the autophagy pathway.^[37]

These findings strongly indicate that *F. nucleatum* is a pathogen of CRC in tumorigenesis and chemotherapy resistance. These pathogenic bacteria have an adverse impact on cancer management.

Escherichia coli

Escherichia coli (*E. coli*) usually acts as a resident bacterium in the human gut. However, some specific strains of *E. coli* can produce different toxins to impair intestinal homeostasis and cause pathological processes. *E. coli* strains of group B2 have a genomic island called *pks*, which can induce cancer. Inactivation of the *pks* gene reduces tumor development in AOM/IL10^{-/-} mice.^[38] Organoid and primary IECs infected by *pks+* *E. coli* and show genotoxic aberrations that can induce multiple features of CRC.^[39] Moreover, colibactin, a DNA damage toxin, is produced by the colibactin-producing *E. coli* (*CoPEC*) strain and induces tumor growth in mice. Autophagy plays a key role in preventing tumorigenesis of *CoPEC*.^[40] The protein toxin cytotoxic necrotizing factor type 1 (CNF1) is another *E. coli* toxin that disrupts the function of transformed epithelial cells. CNF1 is considered a new carcinogenic biomarker in CRC.^[41]

Since most *E. coli* in the gut are nonpathogenic, targeting toxin-produced species will be helpful for the management of CRC.

Campylobacter jejuni

Campylobacter is enriched in CRC samples compared to nontumor adjacent tissues in some studies.^[42,43] Exposed patients with inflammatory bowel disease (IBD) had higher *Campylobacter* infection, which is a risk factor for CRC.^[44] *Campylobacter jejuni* (*C. jejuni*) virulence factors FlaA and FlaB and the major adhesin CadF contribute to the function of *C. jejuni*. A study found that FlaA and FlaB but not CadF could lead to colitis in mice.^[45] FliD of *C. jejuni* is the terminal cap protein of the flagellin subunits, through which *C. jejuni* can bind host cells. Glycosaminoglycans are thought to be a target of the interaction between *C. jejuni* and IECs, so they enhance colonization by *C. jejuni*.^[46] Cytolethal distending toxin produced by *C. jejuni* 81 to 176, can lead to DNA double-strand breaks. *C. jejuni* 81 to 176 has strong tumorigenic capability in *Apc^{Min/+}* mice and alters the microbial composition.^[47] In brief, *C. jejuni* can develop intestinal inflammation and promote tumorigenesis, so it can become a therapeutic target.

Peptostreptococcus anaerobius

Peptostreptococcus is considered a novel microbial driver of intestinal inflammation and cancer.^[48] *Peptostreptococcus anaerobius* (*P. anaerobius*) selectively adheres to CRC mucosa via a surface protein named putative cell wall binding repeat 2 (PCWBR2). The PCWBR2-integrin α 2/ β 1 axis is the core of the interaction between *P. anaerobius* and CRC cells. The downstream signaling pathway is PI3K–Akt–NF- κ B, which induces CRC development in *Apc^{Min/+}* mice. This specific axis might become a potential therapeutic target for CRC.^[49]

P. anaerobius is enriched in fecal and biopsy samples from CRC patients compared with healthy people. *P. anaerobius* can interact with Toll-like receptors TLR2 and TLR 4 to stimulate reactive oxidative species (ROS) production, which can promote the biosynthesis of cholesterol, resulting in tumorigenesis.^[50] These studies suggest that *P. anaerobius*, as a carcinogenic bacterium, can contribute to the CRC development.

Akkermansia muciniphila

Unlike the pathogenetic bacteria above, *A. muciniphila* serves as an anticancer probiotic that can exert anti-inflammatory effects. *A. muciniphila*, of the phylum *Verrucomicrobia*, grows on mucin as its sole carbon and nitrogen source.^[51] It has been reported that the abundance of *A. muciniphila* is decreased in biopsies of IBD patients, which indicates that it has anti-inflammatory properties.^[52] Amuc_1100 is a protein isolated from the outer membrane of *A. muciniphila*. Application of *A. muciniphila* and Amuc_1100 can block colitis and tumorigenesis through the modulation of CD8⁺ cytotoxic T lymphocytes.^[53] *A. muciniphila* can induce M1-like macrophage activation and that is mediated via TLR2/NLRP3-dependent signaling.^[54] Immunotherapy has become relatively mature and has applications in many diseases, including CRC. However, in some conditions, ICIs are often ineffective. *A. muciniphila* is targeted

by some immunotherapies, such as ICIs targeting the PD-1/PD-L1 axis. A study revealed that *A. muciniphila* is enriched in responders to PD-1 blockade treatment. FMT given to nonresponders and oral *A. muciniphila* restored the efficacy of PD-1 blockade in an IL-12-dependent manner by increasing the recruitment of CCR9⁺CXCR3⁺CD4⁺ T cells.^[55] Studies indicate that *A. muciniphila* can not only decrease the incidence of CAC but also restore the response to PD-1 blockade treatment.

Some bacterial genera have different effects on the host depending on the species. Some species can lead to tumorigenesis, while others serve as probiotics.

Streptococcus

Streptococcus. bovis (*S. bovis*) strains consist of two different biotypes on account of their ability to ferment mannitol. *S. gallolyticus* was identified as *S. bovis* biotype I, which has such biological activity.^[56] Many studies have proved that *S. gallolyticus* has a strong association with CRC.^[57,58] Colonization by *S. gallolyticus* is higher in tumor-burdened mice owing to its bacteriocin gallocin, which can kill *Enterococci* so that *S. gallolyticus* can replace it. This bacteriocin can be enhanced by secondary bile acids. The CRC environment provides *S. gallolyticus* with suitable conditions to survive.^[59] The tumorigenic effect of *S. gallolyticus* depends on the specific cell state, bacterial growth phase and interaction between it and IECs. *S. gallolyticus* promoted cancer development in an AOM-induced mouse model by upregulating β -catenin, a central signaling molecule in carcinogenic processes. In addition, the abundance of *Streptococcus* in CRC tissues was higher than that in adjacent noncancer tissues.^[60] On the other hand, *S. gallolyticus* can trigger the production of inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and IL-8. *S. gallolyticus* can also mediate overexpression of cyclooxygenase-2 to promote cellular proliferation and angiogenesis and inhibit apoptosis.^[58]

In contrast, another species of *Streptococcus* is regarded as a probiotic. *Streptococcus thermophilus* (*S. thermophilus*) can prevent gut microbiota infection and is often used in milk products. β -Galactosidase generated by *S. thermophilus* plays a critical role in reducing colon tumorigenesis in Apc^{min/+} mice and AOM-injected mice.^[61]

Thus, *S. gallolyticus* serves as a pathogen, while *S. thermophilus* is a potential probiotic that remains to be further applied.

Clostridium

Clostridium has been found at significant levels in the intestines of CRC patients compared with healthy controls.^[62] The abundance of fecal *Clostridium symbiosum* increases gradually from colorectal adenoma and early CRC to advanced CRC. This fecal biomarker can be a more effective way to detect *Clostridium* than *F. nucleatum* detection, CEA measurement and fecal immunochemical tests (FITs).^[63] Collagen binding protein A (CbpA), which is a cell wall anchored protein from

Clostridium difficile, is a surface-exposed adhesin that has adhesive properties toward collagen. CbpA can promote the interaction between *Clostridium difficile* (*C. difficile*) and the host and thereby contribute to *C. difficile* colonization of the gut.^[64]

Apart from the pathogenic species of *Clostridium*, *Clostridium* can also prevent CRC, as discussed next.

Strategies of microbe-based management

Probiotics

Probiotics, which are identified as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”, are widely used to treat many diseases.^[65] Probiotics can interact with host cells and other gut microbiota to regulate the intestinal micro-ecological balance, thereby exerting anticancer effects. The mechanisms of action of probiotics include inhibiting the proliferation of cancer cells, regulating the immune system, restoring the gut dysbiosis, restoring the function of the intestinal barrier, producing anticancer substances and decreasing the cancer-promoting substances.^[66]

Probiotics play a significant role in preventing and treating CRC. The advantages of probiotics involve many specific aspects: (1) Probiotics can promote mucus secretion and enhance the expression of tight junction proteins to protect the intestinal barrier. (2) Probiotics regulate immune cells and cytokines to reduce intestinal inflammation. (3) Probiotics regulate ROS to reduce IEC damage. (4) Probiotics reduce the activity of pathogenic bacterial enzymes to inhibit the actions of pathogens. (5) Probiotics play a critical role in the regulation of cell proliferation and apoptosis of tumor cells. (6) Probiotics restore the balance of the gut bacteria to enhance host homeostasis.^[67] Many studies have administered probiotics as CRC therapies.

In addition to the cancer-promoting efficacy mentioned above, *Clostridium* can also be used as a probiotic to prevent CRC development. A study found that *Clostridium butyricum* (*C. butyricum*), a butyrate-producing bacterium, can reduce the proliferation of CRC cells and suppress high-fat diet-induced gut tumorigenesis in Apc^{min/+} mice. *C. butyricum* can regulate the gut microbiota composition by inhibiting the Wnt/ β -catenin signaling pathway, causing pathogen reduction and the growth of short-chain fatty acid (SCFA)-generating bacteria.^[68] *C. butyricum* and *Bacillus subtilis* (*B. subtilis*) can inhibit CRC cell growth, cause cell cycle arrest and promote apoptosis in a mouse model. They can reduce inflammation and improve immune homeostasis.^[69] These findings indicate that *C. butyricum* can protect the host from intestinal tumorigenesis, and the scientific application of these bacteria is a strategy of microbe-based management of CRC.

Transforming growth factor- β -activated kinase-1 (TAK1) is an important signaling pathway in the immune system. Tak1^{DM/DM} mice are resistant to colitis and CAC. *Odoribacter splanchnicus* is enriched in Tak1^{DM/DM} mice, inducing IL-17A, which plays a protective role in inflammation and tumorigenesis in the murine gut.^[70]

The *Lactobacillus rhamnosus*-derived 8 kDa protein (P8) that induced apoptosis of CRC cells in a mouse xenograft model. Ring finger protein 152 (RNF152) is a downstream target of P8. Overexpression of RNF152 due to application of P8 can prevent the development of CRC.^[71] *Lactobacillus rhamnosus* GG promoted the anti-inflammatory response and exerted antitumor effects in a murine model. The mechanism by which protective bacteria increase the abundance of CD8⁺ T cells depends on TLR2 expression on dendritic cells.^[72]

The lactic acid bacterium *Pediococcus pentosaceus* (*P. pentosaceus*) is used as a novel bacterial drug delivery system for CRC therapy. A synthetic probiotic consisting of *P. pentosaceus* and a small therapeutic protein called P8 can ameliorate CRC development in mice. This new synthetic probiotic sheds light on the treatment of CRC.^[73]

Thus, probiotics can treat CRC by producing beneficial metabolites, regulating immune signaling pathways and inhibiting colonic inflammation. Both natural and synthetic probiotics are considered promising candidates for CRC therapy.

Prebiotics and postbiotics

Prebiotics are defined as substrates that are selectively utilized by host microorganisms, conferring a health benefit.^[74] Some food ingredients, such as dietary fibers, are considered prebiotics that exert beneficial effects. The mechanisms of prebiotics include stimulating beneficial gut microbiota to modulate the gut microbiota composition, producing fermentation products such as SCFAs, increasing micronutrient absorption in the colon, and regulating xenobiotic metabolizing enzymes and the immune response.^[75] Gynostemma pentaphyllum saponins (GpS), a dietary herbal medicine, shows prebiotic properties. GpS can reduce polyps in *Apc*^{Min/+} mice, and promote the growth of *Bifidobacterium animalis* (*B. animalis*), which suppresses CRC development.^[76] These findings reveal that prebiotics can enhance the function of probiotics and the combination of them can prevent gut tumorigenesis.^[77]

Postbiotics are soluble factors secreted by live bacteria or released after bacterial lysis.^[78] Postbiotics include inactivated microbial cells, cell fractions and cell metabolites. The mechanisms of action of postbiotics are manifold: postbiotics can induce apoptosis of CRC cells, prevent pathogen translocation and restore the gut barrier, regulate immune activity to fight inflammation, inhibit pathogenic bacterial enzymes, exhibit anti-mutagenic and antioxidant effects, decrease the intestinal pH and moderate signaling pathways associated with the carcinogenic procedure.^[79] SCFAs are postbiotics that are the major products of bacterial metabolites of dietary fiber. CRC cells can use SCFAs in the process of aerobic glycolysis and show increased sensitivity to SCFAs. Butyrate is the most widely used SCFAs, displaying strong anticancer properties by regulating some signaling pathways.^[80]

Prebiotics and postbiotics encourage the probiotics to convert food components into beneficial metabolites and

exert anti-inflammatory effects. The combination of probiotics, prebiotics and postbiotics in clinical applications is eagerly awaited.

Fecal microbiota transplantation

FMT delivers feces from donors into the gastrointestinal tract of receivers via colonoscopy or oral administration. FMT can reprogram the gut microbiota composition by disrupting or restoring the gut balance to induce or treat some diseases, such as CRC. A previous study revealed that feces from patients with CRC rather than from healthy controls promoted the development of high-grade dysplasia and polyp production in mice. Moreover, feces from CRC patients can increase proinflammatory genes, immune cell infiltration and oncogenic factors in AOM and GF murine models.^[81] In line with this cancer-promoting function, another study has shown that FMT from CRC patients can lead to more tumors in *Apc*^{Min/+} mice. The mechanism of tumorigenesis involves upregulating the expression of β -catenin and cyclin D1 and further activating the Wnt signaling pathway. The gut barrier is also damaged, and the proinflammatory cytokine profile is disrupted.^[82]

FMT therapy is a novel approach to treat CRC as well. The beneficial fecal microbiota is transplanted from healthy samples to CRC patients to pursue homeostasis but does not change the natural balance of the gut. Rice bran is an agricultural byproduct of white rice milling that has been proven to exhibit efficacy in the suppression of colitis and CRC. CRC survivors who consume rice bran daily are considered a source of protective bacteria. FMT from such patients to AOM/DSS mice resulted in less tumorigenesis. In addition, *Flavonifractor* and *Oscillibacter* were enriched, but *Parabacteroides* was decreased, in the recipient mouse.^[83] Consequently, FMT is a promising option for CRC therapy.

Dietary interventions

Diet is a vital environmental factor that may be involved in CRC, and an unhealthy diet might contribute to tumorigenesis. Diet plays an important role in gut microbiota and further impacts the homeostasis of the gut. People consuming different diets have significantly different intestinal microbial compositions and abundances. Long-term dependence on the same diet can lead to a relatively higher risk of specific disease.

Fiber from fruits, vegetables and grain cereals can prevent CRC development, while fat and red meat or processed meat have a positive relationship with the risk of CRC. Butyrate with anti-inflammatory and antineoplastic abilities can protect IECs from tumorigenesis.^[84] The Western diet, characterized by a high-fat/low-fiber diet, is correlated with disease recurrence after surgery. The collaboration of a Western diet and antibiotics can promote tumorigenesis by CRC cell anastomosis after surgery in mice.^[85] Along with direct interventions, diet-derived metabolites connect the microbiota to CRC. Sulfur-metabolizing microbes can produce pro-carcinogenic hydrogen sulfide, which links sulfur-rich foods with the risk of CRC. In a protective

cohort of young women, high consumption of a sulfur microbial diet was associated with an increased risk for early-onset adenomas.^[86]

Dietary intervention has advantages in CRC prevention and anticancer therapy. Changing dietary habits is a potential strategy to modulate the gut microbiota composition. Owing to the modifiable character of the diet, dietary intervention is considered the most reasonable and cost-effective method of CRC treatment.

Traditional Chinese medicine (TCM) can be a special dietary invention that can interact with intestinal bacteria and further impact the prevention of CRC. Curcumin, one of the major curcuminoids present in the root of the plant *Curcuma longa*, can ameliorate intestinal inflammation by regulating gut bacteria levels. It can increase the abundance of butyrate-producing bacteria and reduce the abundance of *Ruminococcus* species, which is related to CRC.^[87] Evodiamine (EVO) is an extract of TCM that can exert antitumor effects by inhibiting inflammation. In EVO-treated mice, the abundances of *Enterococcus faecalis* and *E. coli* were reduced, while those of *Bifidobacterium*, *Campylobacter* and *Lactobacillus* were increased. In addition, inflammatory cytokines were decreased, and the IL6/STAT3/P65 signaling pathway is inhibited.^[88] Berberine (BBR) is a component of the Chinese herb *Coptis chinensis*. BBR can rescue the *F. nucleatum*-mediated increase in opportunistic pathogens and can reduce tumorigenesis by modulating the mucosal immune system and blocking the activation of tumorigenesis-related pathways.^[89] Another study indicated that BBR could

induce alterations in the composition of the gut microbiota and bacterial metabolism in AOM/DSS mice, leading to inhibition of colorectal tumorigenesis.^[90] Sini decoction (SND) is a classic prescription of TCM. SND extract can ameliorate the degree of tumor malignancy in AOM/DSS mice. In SND-treated mice, the abundance of pathogenic bacteria decreased, while the abundance of some bacteria increased, such as *Lactobacillus*, *Bacillus coagulans* and *A. muciniphila*.^[91]

Overall, TCM can effectively prevent CRC development by regulating the intestinal microbiota and further regulating the immune system, including the inflammatory cytokines or tumor-related pathways.

Conclusion

The relationship between gut microbiota and CRC has been widely studied. Some specific pathogens have been shown to impair the gut mucus and further damage intestinal barrier function. Some pathogens disrupt the immune system to promote a tumor-associated microenvironment. However, many bacteria can serve as probiotics to ameliorate gut inflammation, restore the balance of gut microbiota and regulate immune cells and cytokines. Gut bacteria are also known to influence the efficacy of chemotherapy and immunotherapy. Both types of microbes can become the novel targets for treating and preventing of CRC. The bacteria-related mechanisms of the development and prevention of CRC are shown in [Figure 1].

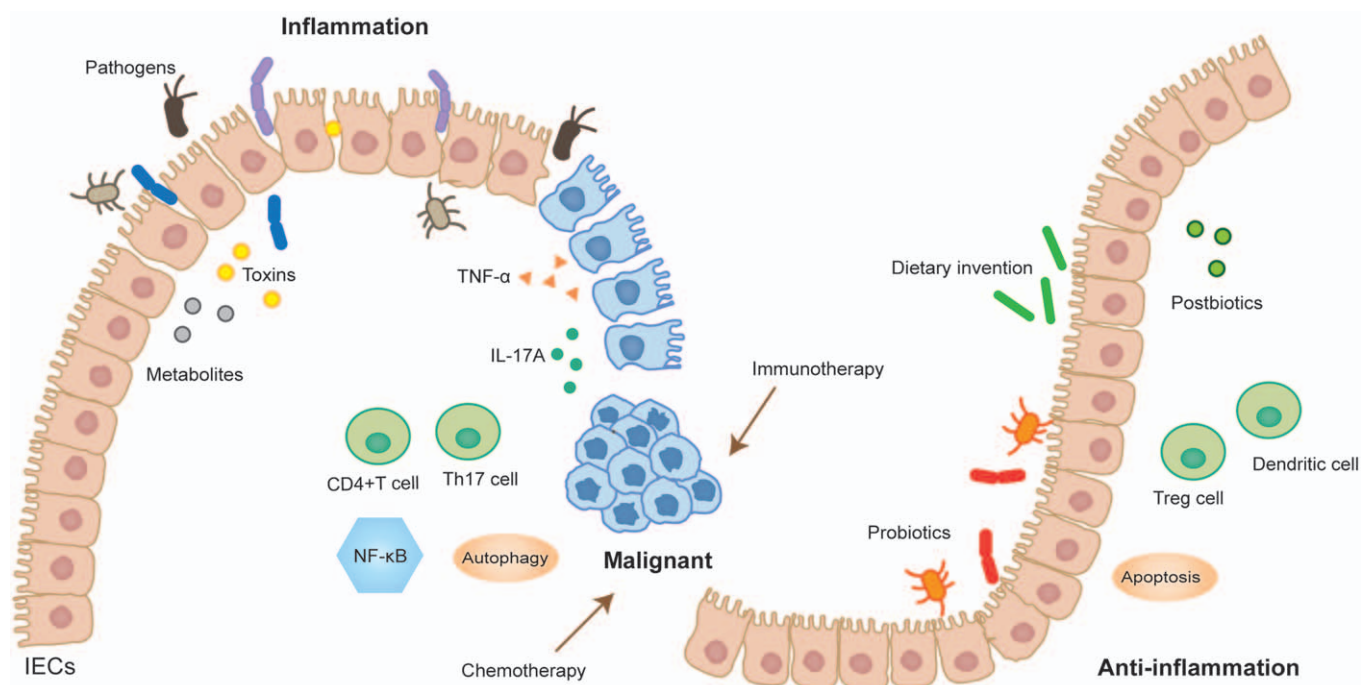


Figure 1: Bacteria-related mechanisms involved in the development and prevention of CRC. Pathogens secrete toxins and metabolites to damage the intestinal barrier and disrupt the immune system. Pro-inflammatory cytokines, such as TNF- α and IL-17A, are produced and then activate NF- κ B or autophagy which can contribute to an inflammatory environment, leading to the carcinogenesis of IECs. Microbe-based management, such as probiotics and dietary invention, can ameliorate the intestinal inflammation through generating postbiotics and other anticancer substances. Treg cells and dendritic cells can exert anti-inflammatory effects and activate apoptosis of CRC cells to restore the gut homeostasis. Gut bacteria can also influence the efficacy of the chemotherapy and immunotherapy. CRC: Colorectal cancer; IECs: Intestinal epithelial cells.

With an abundance of studies on gut microbiota modulation, microbe-based management plays a potential role in CRC management. Compared to the traditional treatment of CRC, some microbe-oriented studies are still in their early stages. However, we hope these experiments in murine models will be translated into clinical applications. The value of such therapies deserves more attention. In the future, intestinal bacteria intervention could be combined with other strategies for CRC management. Further clinical research in the microbiome should clarify more specific bacteria that are related to CRC development and focus on potential applications that will modulate the gut microbiota to broaden the scope of this treatment. Overall, gut-microbiota modulation is a promising approach to prevent and treat CRC.

Conflicts of interest

The authors declare that they have no competing interests.

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