Cancer Management and Research

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REVIEW

Gut Microbiota: A Potential Target for Cancer Interventions

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Abstract: The gut microbiota plays a crucial role in many physiological processes in the human body. Dysbiosis can disrupt the intestinal barrier and alter metabolism and immune responses, leading to the development of diseases. Over the past few decades, evidence has accumulated linking changes in the composition of the gut microbiota to dozens of seemingly unrelated conditions, including cancer. Overall, the gut microbiota mainly affects the occurrence and development of cancer by damaging host DNA, forming and maintaining a pro-inflammatory environment, and affecting host immune responses. In addition, the gut microbiota can also affect the efficacy and toxicity of chemotherapy, radiotherapy, and immunotherapy. Scientists attempt to improve the efficacy and decrease the toxicity of these treatment modalities by fine-tuning the gut microbiota. The aim of this review is to assist researchers and clinicians in developing new strategies for the detection and treatment of tumors by providing the latest information on the intestinal microbiome and cancer, as well as exploring potential application prospects and mechanisms of action.

Keywords: intestinal flora, carcinogenesis, mechanism, therapy, fecal bacteria transplantation

Introduction

Currently, cancer is the leading cause of death worldwide, and its morbidity and mortality rates continue to rise in parallel with the increasing and aging population.[1] It is estimated that ≤20% of the global cancer burden is caused by microorganisms, such as *Helicobacter pylori, Clostridium difficile*, Epstein–Barr virus, human papillomavirus, and other pathogens associated with cancer.[2] As the largest microbial reservoir in the human body, a balanced gut microbiota is positively associated with health. However, dysbiosis (ie, alterations in microbial diversity and/or function) can contribute to the development of diseases, including various types of cancer.[3,4] Further research on the mechanisms by which the gut microbiota influences the occurrence and development of cancer is warranted. Nevertheless, available evidence suggests that changes in the microbial composition of the specific gut microbiota increase host cell mutagenesis. This is achieved either by influencing metabolism and/or immunity to create an immunosuppressive environment that promotes cancer, or through an inflammatory cascade that leads to the initiation and progression of cancer.

The development of a precursor disease into cancer often requires years. Hence, screening and early identification are key to preventing the progression of disease. Evidence has shown that changes in the gut microbiome that occur in the early

Received: 7 July 2021
Accepted: 19 October 2021
Published: 3 November 2021

stages of colorectal cancer (CRC) may be used to identify individuals at risk of developing colorectal adenoma (a precursor lesion of CRC).[5] Therefore, changes in the gut microbiome may serve as biomarkers for precancerous lesions or the early detection of cancer. Moreover, the gut microbiome can influence the efficacy or toxicity of a variety of treatments, including immunotherapy.[6] Researchers are conducting clinical trials to improve the outcomes of cancer treatment by manipulating the gut microbiome. Therefore, the study of changes in the intestinal microbiota is of great importance for the evaluation of human health status, in-depth study of the pathogenesis of cancer, and search for new therapeutic targets and drugs. At present, there have been some reviews on the relationship between microbes and cancer, with varying emphasis. Garrett retrospected how the microbiome affects cancer, responsiveness to cancer treatments, and cancer-related complications.[7] Helmink et al mainly reviewed the effects of the gut microbiota on cancer development and treatment,[8] while Gopalakrishnan and colleagues focused on immunity.[9] This review summarizes the latest research progress on the gut microbiota and cancer in a comprehensive way, which includes mechanisms, treatments, biomarkers, interventions, clinical trials and so on, hoping to help researchers and clinicians develop new cancer diagnosis and treatment strategies.

Gut Microbiota in a Healthy State

Gut Microbiota

The microbial community in the gastrointestinal ecosystem is termed the gut microbiota.[10] The gut microbiota consists of $>10\times10^{14}$ microbes, including bacteria, viruses, fungi, and archaea. Bacteria constitute the majority of the gut microbiota; the dominant species are fairly stable, representing four main phyla, namely *Bacteroidetes, Firmicutes, Actinobacteria*, and *Proteobacteria*.[11] Notably, there are significant differences in bacterial composition between the small intestine and the colon. Due to host features such as mucus, pH, bile acids, regional oxygen levels, gastrointestinal transport time, and immune factors, as well as microbial community dynamics, the diversity and abundance of the gut microbiota normally increases from proximal to distal. The jejunal microflora is estimated to be 10^4–10^7 CFU/mL, and is mainly represented by Firmicutes, but also includes Actinobacteria, Proteobacteria, and Bacteroidetes. The ileum microbiota is mainly a facultative and compulsory anaerobes that include *Bacteroides, Enterobacteria, Clostridium, Enterococcus, Veillonella*, and *Lactobacillus*. The microbial load is approximately 10^3–10^8 CFU/mL. Colonic microbiota can reach 10^{10}–10^{12} CFU/mL and includes Firmicutes, Bacteroidetes, *Lachnospiraceae, Bacteroidaceae*, and *Prevotellaceae*, as well as strict colonic anaerobes, such as *Eubacteria, Clostridium*, and *Roseburia*.[12–14] Overall, the structure of the gut microbiota is determined by host genetics, initial microbial exposure, sex, diet, environmental factors, stress, and disease.[15,16] Polysaccharides (in the form of plant fibers) and their metabolites and short-chain fatty acids (SCFAs) have a positive influence on the of the gut microbiota.[17,18]

A Balanced Gut Microbiota is Critical for the Host

The establishment of an intestinal microbial ecosystem consisting of a variety of native symbiotic species is crucial for the host.[19] Colonization of the intestine by microorganisms synchronizes with maturation of the immune system and plays a fundamental role in the induction, training, regulation, and function of the host immune system.[20] Throughout the lifetime of an individual, the peaceful co-existence of intestinal symbiont microorganisms is destroyed, leading to serious immune deficiency and increased risk of disease.[21] Moreover, the gut microbiota regulates a series of processes at the cellular and molecular levels, leading to the maturation, differentiation, and proliferation of the intestinal mucosa.[22] Interestingly, studies have determined that the gut microbes also play a significant role in processes of neurogenesis, such as blood–brain barrier formation, myelination, neurogenesis, neurotransmitter production, and microglial cell maturation, as well as regulating numerous aspects of animal behavior.[23,24] *Lactobacillus* and *Bifidobacterium* produce the main inhibitory neurotransmitter, aminobutyric acid, by metabolizing glutamate, the most abundant free amino acid and excitatory neurotransmitter in the brain.[25]

Gut microbiota can also regulate host physiological functions by metabolizing dietary components. Butyric acid is mainly generated by *Faecalibacterium prausnitzii* (*F. prausnitzii), Roseburia intestinalis, Eubacterium rectale*, and *Roseburia* spp. by fermentation of dietary fiber.[26] It provides energy to colon cells, exhibits anti-inflammatory properties, induces cell differentiation and apoptosis of cancer cells, protects histone hyperacetylation activity, and inhibits angiogenesis.[27,28] Biogenic amines

are another class of metabolites produced by gut microbes through the decarboxylation of dietary amino acids. These metabolites play a role in DNA stabilization and act as precursors of hormones, alkaloids, proteins, and nucleic acids.[29] Furthermore, the gut microbiota is a major donor of acetyl groups in acetylation reactions, responsible for regulating gene expression.[27]

The human gut microbiota can synthesize at least eight B vitamins. Vitamin B12, which has a complex structure, is produced only through bacterial fermentation, while the absorption of vitamin K also requires the transformation of intestinal bacteria.[30]

In general, the gut microbiota can metabolize indigestible ingredients in food, synthesize nutrients such as vitamins, control energy homeostasis, detoxify metabolites, regulate immune responses, promote the development of the nervous system, provide signals for epithelial cell renewal and maintenance of mucosal integrity, and secrete antibacterial products.[18]

Dysbiosis and Cancer

A balanced gut microbiota benefits host health, while ecological imbalance promotes the development of diseases, including cancer.[3,31] Dysbiosis can be caused by a variety of factors, such as diet, antibiotics and stress.[32] It is usually manifested by loss of symbiosis, pathogen proliferation, and/or reduction in alpha diversity, resulting in a shift of the metabolome to an inflammatory state conducive to carcinogenesis.[32,33] Moreover, dysbiosis renders individuals vulnerable to opportunistic pathogens that can release toxins, resulting in genomic instability and potentially carcinogenic effects.[34,35] It has been confirmed that *Streptococcus bovis, Helicobacter pylori, Fusobacterium nucleatum* (*F. nucleatum*), and *Enterococcus faecalis* (*E. faecalis*) are related to cancer.[36–38]

Gut Microbiota in the Context of Cancer

Notably, researchers have reported significant changes in gut microbes in various types of cancer. Jing et al reported that, compared with healthy controls, the proportions of *Firmicutes* and *Proteobacteria* were increased in patients with thyroid carcinoma, whereas that of *Bacteroidetes* was decreased. At the genus level, the abundance of *Bacteroides megamonas* and Trichoricaceae genera was decreased in patients with thyroid carcinoma.[39] Goedert et al reported that the alpha diversity of the gut microbiota in postmenopausal women with breast cancer was lower than that observed in pairs of healthy controls. Moreover, the relative abundance of *Clostridiaceae, Faecalibacterium* and *Ruminococcaceae* was relatively high, whereas that of *Dorea* and *Lachnospiraceae* was relatively low.[40] Vernocchi et al observed that numbers of symbiotic bacteria, such as *Akkermansia muciniphila, Rikenellaceae, Bacteroides, Peptostreptococcaceae, Mogibacteriaceae*, and *Clostridiaceae* were reduced in patients with non-small cell lung cancer.[41] In another cohort study of early-stage lung cancer, Proteobacteria, including many harmful microorganisms, were significantly enriched in cancer groups. Firmicutes and actinobacteria, which promote the production of short-chain fatty acids and regulate inflammation and tumorigenesis, were dramatically reduced. At the genus level, *Ruminococcus*, an uncharacterized genus of *Lachnospiraceae* and an uncharacterized genus of Enterobacteriaceae were obviously increased in the cancer group, while *Veillonella, Faecalibacterium, Bifidobacterium*, and *Streptococcus* were markedly enriched in the healthy controls.[42]

In previous gastric cancer (GC) studies, *Peptostreptococcus stomatis, Dialister pneumosintes, Streptococcus anginosus, Parvimonas micra* (*P. micra), Slackia exigua, Clostridium colicanis*, and *F. nucleatum* were significantly enriched, whereas *Helicobacterium* was depleted.[43–45] A recent study showed that GC patients presented notably different gut microbiota from healthy controls. At the phylum level, *Chloroflexi, TM7, Acidobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria, Nitrospirae*, and *Planctomycetes* increased in the stool of GC patients. At the genus level, 27 genera were enriched, including *Leptotrichia, Fusobacterium, Lactococcus, Prevotella*, and *Porphyromonas*, while *Megamonas* decreased.[46] Interestingly, comparing GC and CRC, there was no remarkable difference in the bacterial diversity between the cancer types. Among the 8 phyla enriched in GC, 5 phyla were enriched in CRC, 25 of the 28 genera showed the same trend.[46] These results indicated that the overlap of dysbiosis in different cancers may be a common basis for the occurrence and development of various cancers, which points out a new direction for further research on the mechanism of cancer. *Proteobacteria, Synergistetes*, and *Euryarchaeota* were abundant in the intestines of patients with pancreatic ductal adenocarcinoma (PDAC). *Proteobacteria* accounted for approximately 50% and 8% of the gut microbiota of patients and healthy controls, respectively.[47]

In a study of 52 CRC patients and 55 healthy family members, metagenomic sequencing showed that compared with controls, *Coprobacillus, Peptoniphilus, Burkholderia, Paracoccus, Synechococcus, Porphyromonas*, and *Cyanothece* were significantly enriched in colorectal cancer patients. At the species level, patients accumulated *Clostridium ramosum, Roseburia inulinivorans, Porphyromonas gingivalis, Gemella morbillorum*, and *F. nucleatum*. In addition, microbial genes were also reduced in CRC patients, with 624,404 genes found in the control group and only 585,092 genes found in CRC. The proportion of amino acid metabolizing bacteria in the gut microbiota of patients decreased.[48] In 2019, the University of Trento analyzed five open datasets and two new cohorts, totaling 969 fecal metagenomes, and found that the gut microbiota of CRC was more abundant than that of the control group, partly because of the expansion of oral microbes. *F. nucleatum, Porphyromonas asaccharolytica, Solobacterium moorei, Peptostreptococcus stomatis, Parvimonas micra, Clostridium symbiosum, Streptococcus dysgalactiae, Streptococcus tigurinus, Streptococcus gallolyticus*, and *Gemella morbillorum* were enriched in patients, while *Bifidobacterium catenulatum* and *Gordonibacter pamelae* were enriched in the healthy control group.[49] Kostic et al compared the enrichment of *F. nucleatum* in the colonic tumor-related microbiota of patients with CRC compared with levels recorded in adjacent normal mucosa.[50] Other researchers found that the colonization rate of *F. nucleatum* in the lumen of patients with colorectal adenoma was higher than that observed in healthy controls. Furthermore, the colonization of *F. nucleatum* in adenoma was increased compared with that noted in adjacent normal mucosa.[51] These data strongly suggest that *F. nucleatum* is associated with CRC and may play a role in the early stages of disease.[52] Another study involving patients with CRC showed an increase in *F. nucleatum* and *Campylobacter* and a decrease in butyrate-producing bacteria in fecal samples.[53]

The Mechanism of Gut Microbiota Promoting the Development of Cancer

The occurrence and development of cancer is a complex process involving genetic mutations, the tumor microenvironment, and inflammatory mediators, in which gut microbes play an important role. Herein, we present the available evidence and discuss the mechanisms involving microorganisms causing cancer from the aspects of metabolism, immunity, inflammation, etc. Various mechanisms interact and form a network to jointly promote the occurrence and development of cancer. Broadly speaking, mainly by affecting host metabolism, cell proliferation, inflammatory response, and the immune status, the gut microbiota regulates cancers in terms of susceptibility to genetic instability, initiation, progression of immune responses, comorbidities, and response to treatment.[3,54]

Increase in Host Cell Mutagenesis

At present, it is known that the gut microbiota produces genotoxins, free radicals, and reactive oxygen species (ROS) that can damage host DNA, alter cell cycle control, accelerate cell proliferation, and disrupt the normal process of controlled cell death, thereby increasing the risk of cancer.[55] For example, *Helicobacter pylori* colonizing the gastric mucosa produces a cytotoxin-associated gene A (CagA) oncoprotein, which leads to reprogramming of gastric epithelial cells, thus participating in the pathogenesis of gastric cancer.[37] *Porphyromonas gingivalis* secretes peptide-arginine deaminase that may induce p53 and KRAS point mutations, which are major genetic drivers of pancreatic cancer.[56] Colibactin produced by polyketide synthetase-positive *Escherichia coli* (*E. coli*) and *Enterobacteriaceae* breaks the double-strand DNA of host cells, while *Porphyromonas spp* produce ROS that damage the host DNA.[57,58] Direct interactions of bacterial structural components and their metabolites (eg, hydrogen sulfide and para-cresol) with epithelial mesenchymal cells and hematopoietic cells may exert direct genotoxic effects and promote cancer progression.[59,60] Numerous microbes, including *B. fragilis, F. nucleatum*, and *E. faecalis*, produce toxins that alter the normal adhesion between cells, thereby facilitating the transformation of resting epithelial cells into moving mesenchymal cells. Of note, epithelial-to-mesenchymal transformation is a key step in the transformation of benign tumors to malignant tumors.[55] *F. nucleatum* is often enriched in patients with CRC and is related to DNA methylation in inflammatory colon mucosa.[61]

Promotion and Maintenance of a Pro-Inflammatory Environment

It is well-established that inflammation is involved in carcinogenesis through mutations, genomic instability,

and epigenetic modifications.[62] For instance, chronic inflammation caused by infection with *Helicobacter pylori* leads to abnormal DNA methylation in gastric mucosa and activation-induced cytidine deaminase through the activation of nuclear factor-κB (NF-κB) in gastric epithelial cells, thereby leading to mutations.[63] A large number of studies have shown that the gut microbiota plays an important role in the inflammatory response. For instance, *Lactobacillus, Proteobacteria, Clostridium difficile, Enterococci*, and *B. fragilis*, can impact on different immune cells and play pro- and anti-inflammatory roles.[64] Microorganisms activate the inflammatory response, increase the recruitment of pro-inflammatory cells, and the secretion of cytokines, enhance oxidative stress, change energy dynamics, and lead to DNA damage. These effects eventually result in molecular changes and tumor transformation, as well as promote tumor growth, invasion, and metastasis.[65] Liam et al colonized APC^{Min} mice with enterotoxigenic *B. fragilis* (ETBF) and found that the *B. fragilis* toxin (BFT) triggered a multistep inflammatory cascade in colic epithelial cells (CECs).[35] This cascade is required to promote carcinogenesis through the interleukin-17 receptor (IL-17R), NF-κB, and STAT3 signaling pathways. Notably, the activation of IL-17-dependent NF-κB in CECs induces proximal-to-distal mucosal gradients of C-X-C chemokines, including C-X-C motif chemokine ligand 1 (CXCL1).[66] This mediates the recruitment of immature myeloid cells expressing the C-X-C motif chemokine receptor 2 (CXCR2) and is parallel to ETBF-mediated distal colonic tumorigenesis.[66] Thus, BFT induces pre-oncogenic signaling from CEC to the mucosal T-helper 17 (Th17) response and selectively activates NF-κB in the distal colon CECs, which together trigger myeloid cell-dependent distal colon tumorigenesis.[66]

Using a hormone receptor-positive (HR+) breast cancer mouse model, Buchta Rosean et al found that a pre-established symbiotic disorder leads to enhanced tumor cell spread, and that the symbiotic disorder leads to increased inflammation and infiltration of myeloid cells in the breast.[67] These results suggest that the symbiotic disorder has a sustained effect on the spread of HR+ breast cancer, and that the increased spread in mice with symbiotic disorder is independent of tumor growth dynamics.[67] Moreover, this evidence demonstrated that dysbiosis is a pre-existing host-intrinsic regulator of tissue inflammation, myeloid recruitment, fibrosis, and tumor cell proliferation in HR+ breast cancer.[67]

Intestinal bacteria can also upregulate the levels of toll-like receptor (TLR), activate the cancer-related inflammatory signaling pathway NF-κB, lead to the release of IL-6, IL-12, IL-17, IL-18, and tumor necrosis factor (TNF) α, to trigger persistent inflammation in the cancer microenvironment, which is vital in the regulation of inflammation and cancer-related processes.[68,69] In a cancer setting, inflammatory markers are responsible for cell proliferation, invasion, angiogenesis, and suppression of certain immune functions.[70]

Disruption of Immune Stability

Under pathological conditions, when the intestinal microbiota is disturbed or the intestinal mucosal barrier is disrupted, microbial-related molecules stimulate macrophages and dendritic cells to produce pro-inflammatory cytokines. Subsequently, these cytokines activate adaptive immune cells and lead to the disruption of immune stability.[71] Dysbiosis may also lead to the inappropriate release of cytokines (eg, IL-17 and IL-22) from innate lymphoid cells, resulting in chronic inflammation and susceptibility to cancer. Furthermore, abnormal innate lymphoid cell responses to dysbiosis may also influence T cell responses, further promoting chronic inflammation and cancer.[72]

F. nucleatum stimulates anti-inflammatory myeloid cells, interferes with natural-killer and T cells functions by activating T cell immunoreceptor with Ig and ITIM domains (TIGIT) and CEA cell adhesion molecule 1 (CEACAM1) inhibitory receptors, and induces Wnt/catenin (catenin beta 1) modulator annexin A1, thereby creating a tumor-promoting immunosuppressive environment. This process leads to the initiation and progression of CRC.[73–75] *B. fragilis* drives the differentiation of IL10-secreting regulatory T (Treg) cells. Treg cells impair anti-cancer Th1 immunity and participate in the progression and aggressiveness of gliomas.[70] The gut microbiota can also induce the expression of immunosuppressive chemokines in liver cells, leading to the accumulation of myeloid-derived suppressor cells (MDSCs) and ultimately promoting the development and growth of cholangiocarcinoma.[76] Molecular patterns associated with pathogenic microorganisms are also recognized by innate immune system cells through pattern recognition receptors, including TLRs and NOD-like receptors, chronic activation of TLRs, promotion of cancer cell proliferation, and an increase in invasion and metastasis by regulating cytokines, metalloproteinases, and pro-inflammatory

integrins.[77] For example, in the early stages of pancreatic tumors and in established PDAC, microbial-induced TLR activation suppresses both the innate and adaptive immunity of the host.[78,79] Specifically, in addition to inducing the transformation of pancreatic cancer stellate cells into fibrocytes, TLR9 also attracts immunosuppressive Treg cells and MDSCs into the tumor environment.[80] Lipopolysaccharide and TLR4 ligation through dendritic cell-dependent Th2 immune response aggravates pancreatic inflammation and expedites the development of pancreatic tumors. Microbial-mediated ligation of TLR2 and TLR5 limits T-cell-mediated immunity by inducing a macrophage immunosuppressive phenotype.[28]

Metabolic Changes

Gut microorganisms are involved in a series of metabolic activities of the host, and dysbiosis may alter the expression of lipid metabolism-related microRNAs, leading to obesity and cancer.[81] It has been hypothesized that dysregulation of the microbiome and microRNAs may be involved in the pathogenesis of cancer in the central nervous system through the microbial-enteric-brain axis.[82] Furthermore, during cancer development, gut microbes may undergo metabolic reprogramming. For example, Zheng et al in a study of early non-small cell lung cancer found that 19 of 328 metabolic pathways detected were enriched in the cancer group, including steroid biosynthesis, cell antigens, transcription-related proteins, the ubiquitin system, and bile secretion. However, 12 pathways related to bacterial chemotaxis, G protein-coupled receptors, bacterial motility proteins, flavone, flavonol biosynthesis and apoptosis were all reduced.[42] Microbial metabolites or co-metabolites produced by host and microbial contributions can cause inflammation and affect the balance of cell proliferation and death in tissues.[83] Several bacterial metabolites (eg, SCFAs or secondary bile acids) and microbial-related molecular patterns (eg, lipopolysaccharides and peptidoglycan) influence host nutrient uptake, metabolism, intestinal barrier, and systemic inflammatory responses.[84] For example, members of *Clostridium* bacteria XI and XIVa convert primary bile acids (deoxycholic acid and cholic acid) into secondary bile acids (lithocholic acid and deoxycholic acid), which exert potential DNA damage and carcinogenic effects.[85] Lithocholic acid and deoxycholic acid, trigger colon cancer development through the regulation of M3R and Wnt/β-catenin signaling in order to convert normal colon epithelial cells convert into CSC.[86] *Clostridium* IV and XIVa, which include the genera *Eubacteria, Rosa*, and *Cofaecium*, metabolize dietary fiber and polysaccharides in the colon to produce acetic acid, which is converted to acetyl-coenzyme A (acetylCoA) by acetylCoA synthetase short-chain family member 2 expressed by cancer cells.[87] This process stimulates the anabolic response of cancer cells and supports the growth of numerous types of cancer, including glioblastoma, breast cancer, ovarian cancer, and lung cancer.[88–90]

Hydrogen sulfide (H_2S) is mainly produced by the colo-intestinal bacteria, such as *E. coli* and *Salmonella*, by degrading sulfur-containing amino acids. Studies have reported the anti-inflammatory activity of H_2S in the gut, while others have shown harmful effects, suggesting that these results may be related to the environment.[91] H_2S exhibits deleterious reactions in intestinal epithelial cells. Relative levels of H_2S in the colon directly regulate oxidative phosphorylation in epithelial cells and elevated H_2S levels inhibit the electron transport chain complex IV.[92] In addition, H_2S induces genotoxic damage in epithelial cells, inhibits the metabolism of SCFAs, and induces rupture of the mucous barrier, thereby exposing the contents of the lumen to the underlying tissues.[93]

A better understanding of the mechanism through which specific microbial pathogens cause specific carcinogenic effects may lead to the discovery of valuable biomarkers for the diagnosis and treatment of cancer.

Biomarkers

Screening and early identification of cancer correlates with patient outcomes. For example, the incidence and mortality of colorectal cancer can be significantly reduced by screening for precancerous lesions such as adenomatous polyps or early colorectal cancer and appropriate treatment, and the 5-year relative survival rate can reach about 90%.[94,95] As mentioned earlier, significantly different gut microbiota have been observed in patients with various types of cancer versus healthy individuals, and these differences may permit the use of specific bacteria as biomarkers.

In one study, bacterial DNA was extracted from the feces of 31 patients with early-stage breast cancer. Real-time quantitative polymerase chain reaction was used to amplify bacterial community specific 16S rRNA gene sequences. The results showed that the percentages and absolute numbers of *Clostridium coccoides, F. prausnitzii*, and *Blautia* differed significantly according to the clinical staging and tissue prognosis grading.[96] Among patients

with different histoprognostic grades of breast cancers, the abundance of *Blautia* spp. bacteria increased markedly in parallel with grade. The total numbers of *Bacteroidetes, Clostridium coccoides* cluster, *Clostridium leptum* cluster, *F. prausnitzii*, and *Blautia* sp. were significantly higher in clinical stage groups II/III than at clinical stages 0/I, with higher percentages observed for *Clostridium leptum* cluster.[30]

Jia et al found that patients with intrahepatic cholangiocarcinoma (ICC) had the highest α-diversity and β-diversity of intestinal flora and increased abundance of *Lactobacillus, Actinomyces, Peptostreptococcaceae*, and *Alloscardovia* versus those with hepatocellular carcinoma or cirrhosis and healthy individuals.[97] The plasma-fecal ratios of glycoursodeoxycholic acid and tauroursodeoxycholic acid (TUDCA) were significantly increased in patients with ICC. Moreover, the combination of *Lactobacillus* and *Alloscardovia* was positively correlated with the plasma-fecal ratio of TUDCA, which could distinguish ICC from hepatocellular carcinoma, liver cirrhosis, and healthy individuals.[97] Vascular invasion (VI) often leads to poor prognosis in patients with ICC. Compared with ICC patients without VI, those with VI had a richer Ruminococcaceae family, increased plasma levels of IL-4 and decreased plasma levels of IL-6 and chenodeoxycholic acid. In patients with ICC, the plasma levels of taurocholic acid were positively correlated with those of IL-4. In two mouse tumor models, plasma TUDCA was inversely associated with the abundance of *Pseudoramibacter* and survival in patients with ICC; however, it had no effect on tumor size.[97]

In a case-control study of CRC, polymerase chain reaction was performed on fecal samples obtained from 60 patients and 60 healthy volunteers using *neu* and *BFT* (*BFT-1, BFT-2*, and *BFT-3* are enterotoxin isotypes) as marker genes.[98] The frequency of *B. fragilis* in the CRC and control groups was 58.3% and 26.6%, respectively. The detection rate of the *BFT* gene in patients with CRC was significantly higher than that observed in the control group. Furthermore, the presence of the *BFT* gene was significantly higher in patients with CRC stage III than in those with stage II.[98] The detection rate of the enterotoxin isotype *BFT-2* was higher in patients with CRC versus healthy controls. This evidence suggested that the detection of ETBF may be a potential marker for the diagnosis of CRC.[98]

In two recent cohort studies, Löwenmark et al found that the abundance of *P. micra* was significantly higher in fecal samples obtained from patients with CRC than in those collected from controls.[99] In the Faecal and Endoscopic Colorectal Study in Umeå, Sweden (FECSU) cohort, the sensitivity and specificity of *P. micra* in feces for the detection of cancer were 60.5% and 87.3%, respectively. In the U-CAN cohort, these values were 56.7% and 92.6%, respectively.[99] Moreover, added microbial markers *F. nucleatum*, clbA + bacteria, and fecal hemoglobin enhanced the sensitivity of the assay; nevertheless, the specificity was reduced. Therefore, *P. micra*, as a candidate microbial marker for non-invasive screening, had the potential to improve diagnostic performance.[99]

Clinical Application of Microorganisms

In 1928, Fleming accidentally discovered penicillin (a product of mold that has antibacterial effects) in an experiment involving *Staphylococcus* bacteria.[100] This discovery introduced a new era of using microbes against disease. With the development of science and technology, the use of microorganisms or their metabolites to treat diseases was established. For example, fecal microbiota transplantation (FMT) is a common treatment for recurrent *Clostridium difficile* colitis with a good safety profile.[101] Intrabladder injection of Bacillus Calmette–Guerin has also become the standard treatment for moderate- to high-risk non-muscularly invasive bladder cancer.[102] In the following section, we focus on the influence of gut microbiota on the efficacy of treatment against cancer and its utility in this setting.

Gut Microbes Influence the Treatment of Cancer

In the course of cancer treatment, the gut microbiota regulates the efficacy and toxicity of chemotherapy through various mechanisms, such as translocation, immune regulation, metabolism, enzyme degradation, and diversity reduction; these mechanisms are collectively referred to as the timer mechanism framework.[103] For example, cyclophosphamide damages the intestinal barrier and increases intestinal permeability. *Enterococcus hirae* is transferred from the small intestine to secondary lymphatic organs and increases the intratumoral CD8/Treg ratio.[104] *Barnesiella testinihominis* accumulates in the colon, increases the number of INF-γ-producing γδTcells in the tumor bed, shifts the immune system to a pro-inflammatory state, and synergically enhances the efficacy

of cyclophosphamide.[104] The Th17 response is reduced in sterile or antibiotic-treated tumor-bearing mice with cancers resistant to cyclophosphamide.[105] Oxaliplatin exerts its anti-cancer activity through ROS. Intestinal microorganisms stimulate bone marrow cells to produce ROS.[106] In the absence of intestinal microorganism involvement, the production of microbial-dependent ROS is reduced, eliminating the cytotoxicity of oxaliplatin in mice and preventing the killing of cancer cells.[107] Moreover, *F. nucleatum* promotes resistance to oxaliplatin and 5-fluorouracil (5-FU) by coordinating TLR to activate miRNA expression and the autophagy network.[38] *Bacteroides* and *Clostridium*, which produce β-glucosidase, are associated with the accumulation of diarrhea-inducing metabolites induced by irinotecan and 5-FU chemotherapy, while *Raoultella planticola* effectively inactivates doxorubicin by it deglycosylation to 7-deoxydoxorubicinol and 7- deoxydoxorubicinolone under anaerobic conditions.[108,109] Inactivation of gemcitabine, a chemotherapy drug for PDAC, depends on the expression of a specific subtype of the bacterial enzyme cytidine deaminase, which is common in gamma-proteobacteria.[110]

In addition to chemotherapy, the gut microbes also influence the effectiveness of radiation therapy. Researchers used vancomycin to treat mouse models of melanoma and lung cancer expressing the E6/7 of human papillomavirus and cervical cancer. The changes in gram-positive intestinal flora reshaped the tumor microenvironment, increased the antigen presentation of draining lymph nodes, and improved the anti-tumor effect of radiotherapy.[111] Indole-3-propionic acid (IPA) is derived from intestinal microorganisms and is a tryptophan deamination product with intracellular signaling activity.[112] Xiao et al found that IPA exerted a radio-protective effect on mice, which was attributed to the lower level of systemic inflammation, reduced myelosuppression, restoration of hematopoietic organ function, and improvement of gastrointestinal function and epithelial integrity in mice treated with IPA after irradiation.[113] Ferreira et al reported that enteropathy in patients who received pelvic radiotherapy was related to the composition of intestinal microbes, with increased abundance of *Clostridium, Rosesporium*, and *Phascolarctobacterium* in patients who had toxic reactions.[114]

The application of immune checkpoint inhibitors represents an important advance in cancer therapy. Immune checkpoint inhibitors, which bind to immune checkpoint proteins to relieve tumor-induced inhibition of T cell function, have been approved for the treatment of a variety of malignancies, including melanoma, lung cancer, stomach cancer, Hodgkin's lymphoma, ovarian cancer, and more.[115] Studies using mouse tumor models have shown that the gut microbiota composition is vital for promoting anti-tumor immune responses to anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed cell death-ligand 1 (anti-PD-L1) monoclonal antibodies.[116,117] Several mouse models of melanoma have shown that the effectiveness of programmed cell death protein 1 (PD-1) inhibitors is reduced under aseptic conditions and increased in the presence of *Bifidobacterium*.[118] This activates antigen-presenting cells, thereby promoting the accumulation of activated CD8+ T cells in the tumor microenvironment.[117] The efficacy of PD-1/PD-L1 blockade in non-small cell lung cancer, renal cell carcinoma, and urothelial carcinoma was partially offset by bacterial ablation.[119] Another study found that antibiotic-induced dysbiosis was associated with a reduced PD-1 blocking effect and poor clinical efficacy. The survival time of anti-PD-1 monoclonal antibodies was positively correlated with the relative abundance of *Akkermansia*, one of the most abundant bacteria in the ileum of healthy individuals.[120] In addition, transfer of intestinal microbes in patients with cancer who had responded to immunotherapy and oral supplementation of *Akkermansia* improved the efficacy of immunotherapy.[120] Furthermore, in a study of tumor-bearing mice, bacterial ablation significantly reduced the therapeutic efficacy of CTLA-4 blocking, while the use of *B. fragilis* showed potential to overcome resistance to anti-CTLA-4 immunotherapy in germ-free mice.[120]

A study of 39 patients with metastatic melanoma who underwent immune checkpoint therapy also showed a significant correlation between the microbial content and response to immunotherapy.[121] *Bacteroides thetaiotaomicron, F. prausnitzii*, and *Holdemania filiformis* were abundant in the intestines of responders to cancer immunotherapy.[50] Transfer of the feces of patients with melanoma into mice demonstrated that FMT could improve the effectiveness of immunotherapy and, thus, optimize existing therapies.[118]

With further research into the mechanisms of these relationships, the composition of the gut microbiota is a potential biomarker for predicting individual therapeutic outcomes and a target for improving these outcomes.[122]

Manipulation of Gut Microbes to Interfere with Cancer

Scientists have proposed several ways to take advantage of gut microbes for the prevention and treatment of cancer, as well as the mitigation of the toxic side effects of chemotherapy and radiotherapy. These approaches to achieving better clinical outcomes for patients with cancer undergoing immunotherapy include dietary modifications and use of probiotics, selected antibiotics, and FMT (Table 1).

Studies have shown that a reduction in the consumption of animal fat reduced the abundance of harmful *Bacteroidetes* species, while a high-fiber diet increased the number of microorganisms producing SCFAs, such as *Eubacterium rectale, Roseburia* species, and *F. prausnitzii*.[123] High consumption of whole grains was associated with an increase in the number of SCFA-producing microorganisms (eg, *Roseburia, Lachnospira*) and a decrease in pro-inflammatory microorganisms (eg, *Enterobacteriaceae*). Consumption of fermented foods may also contribute to a protective metabolic environment due to their probiotic content, particularly *Lactobacillus casei* CRL431.[124]

Probiotics can prevent the proliferation of pathogenic bacteria, regulate gut microbiota and metabolism, maintain the integrity of intestinal barrier, reduce intestinal inflammation, enhance immune response, bind or inactivate carcinogens, so as to protect against tumors.[125,126] For example, Lactobacillus acidophilus and Bifidobacterium bifidum both strengthen the intestinal epithelial tight junction barrier and prevent against intestinal inflammation, and the former was induced in TLR-2 dependent and a strain-specific manner, while the latter was NF-κB independent in targeting the TLR-2 pathway.[127,128] In addition, Parisa et al using in vivo and in vitro studies that bifidobacterium inhibits CRC by down-regulating HER-2, EGFR, and PTGS-2 (COX-2).[129] Chou et al used azoxymethane/dextran sulfate sodium to induce colitis-associated CRC in ICR mice. After 14 weeks of treatment with *Lactobacillus fermentum* V3 (1′108 CFU/d) (5 days/week, once a day), Compared with the control group, the levels of lactobacillus in feces were significantly increased, and the abundance of harmful bacteria, Bacteroides and Akkermansia, was markedly decreased. Pro-inflammatory factors such as IL-1α, IL-1β, and IL-6 were dramatically reduced. The infiltration of CD68+ macrophages in tumors was reduced, and tumor growth was observably inhibited.[130] More recently, Chung et al synthesized stable synthetic probiotics using *Pediococcus pentosaceus* and P8 therapy protein that ameliorated azoxyMethane and Dextran sodium sulfate-induced colitis-associated CRC impaired flora, while tumor growth and tumor volume were significantly inhibited.[131] Furthermore, *Lactobacillus kefiri* LKF01 is safe and effective in preventing severe diarrhea in cancer patients receiving 5-FU or capecitabine-based treatment.[132]

Prebiotics are usually fibers or polyphenols that cannot be digested by the host and are selectively used by gut microbes to produce health benefits.[133] Common prebiotics include fructose oligosaccharide, inulin, and galactose oligosaccharide, which in high doses can increase the abundance of *Lactobacillus* and *Bifidobacterium*.[133] In a mouse model of melanoma, supplementation with inulin or mucin enhanced anti-tumor immune activity through significant changes in intestinal flora, thereby inhibiting tumor growth.[134] In addition, inulin may limit the growth of colon tumors.[29] In mice fed with inulin, the growth of colon cancer was inhibited and *Akkermansia muciniphila* was significantly enriched. Moreover, *Akkermansia muciniphila* was also associated with a therapeutic response to anti-PD-1/PD-1 immunotherapy.[29,120]

Intriguingly, studies have shown that exercise can independently alter the gut microbiome. Among premenopausal women, those performing 150 min of moderate aerobic exercise per week (in line with the recommendations of the World Health Organization) had higher levels of *Akkermansia muciniphila, F. prausnitzii*, and *Roseburia hominis* than those who were sedentary. These species play health-promoting roles, such as maintaining the intestinal barrier.[135]

In FMT, the functional flora in the feces of healthy individuals is transplanted into the gastrointestinal tract of patients to reconstruct the new intestinal flora and treat intestinal and extraenteral diseases. As an effective means for reconstructing the intestinal flora, FMT has been used in the treatment of and exploratory research on infection with *Clostridium difficile*, inflammatory bowel disease, obesity, and other bacteria-related diseases.[2,136,137] Furthermore, it is regarded as a breakthrough in medical research. The safety profile of FMT has also been demonstrated in a number of studies. In an academic medical center, Navalkele et al performed a retention enema for fecal microbiota transplantation in 47 patients with recurrent *Clostridioides difficile* infections, including 17 immunocompromised patients, which proved safe and

https://doi.org/10.2147/CMAR.S328249 DovePress

Table 1 Clinical Trials Assessing Intervention in Cancer by Modifying the Gut Microbiota

Title	Start and End Dates	Status	Condition	Estimated Enrollment	Intervention	Location
Preventing Toxicity in Renal Cancer Patients Treated with Immunotherapy Using Fecal Microbiota Transplantation	January 2020-November 2028	Recruiting	Renal cell carcinoma	20	FMT	London Regional Cancer Program of the Lawson Health Research Institute, London, Canada
Fecal Microbiota Transplant (FMT) Capsule for Improving the Efficacy of Anti-PD-1	January 2020-December 2021	Recruiting	Gastrointestinal system cancer	10	FMT capsule	Beijing Cancer Hospital, Beijing, China
Fecal Microbiota Transplant and Pembrolizumab for Men With Metastatic Castration Resistant Prostate Cancer	October 2019-October 2023	Recruiting	Prostate cancer (metastatic)	32	FMT	VA Portland Health Care System, Portland, OR, USA
A Single Dose FMT Infusion as an Adjunct to Keytruda for Metastatic Mesothelioma	September 2018-December 2018	Completed	Mesothelioma	1	FMT	ProgenaBiome, Ventura, CA, USA
Prebiotics and Probiotics During Definitive Treatment With Chemotherapy-radiotherapy SCC of the Anal Canal (BISQUIT)	March 2019-February 2024	Recruiting	Anal cancer (squamous cell)	75	Dietary supplement: prebiotics in combination with probiotics	AC Camargo Cancer Center, São Paulo, Brazil
Effect of Probiotics Supplementation on the Side Effects of Radiation Therapy Among Colorectal Cancer Patients	November 2018-December 2022	Recruiting	Colorectal cancer	40	Dietary supplement: probiotic formula capsule	King Hussein Cancer Center, Amman, Jordan
Engineering Gut Microbiome to Target Breast Cancer	October 2017-May 2020	Completed	Breast cancer	7	Dietary supplement: probiotic	Mayo Clinic in Florida, Jacksonville, FL, USA
Mixture of Prebiotics on Intestinal Microbiota of Patients Receiving Abdominal Radiotherapy	June 2005-December 2007	Completed	Endometrial neoplasms	40	Dietary supplement: inulin; fructo oligosaccharide; maltodextrin	Nutrition Unit. Hospital General Universitario, Gregorio Marañón, Madrid, Spain
Fecal Microbiota Transplantation for Steroid Resistant/Dependent Acute GI GVHD	December 2018-December 2022	Recruiting	Hematopoietic and lymphoid cell neoplasm	30	Biological: FMT	Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai, China; Shanghai Jiao Tong University Affiliated Shanghai General Hospital, Shanghai, China

Abbreviations: CRC, colorectal cancer; SCFAs, short-chain fatty acids; *F. prausnitzii*, *Faecalibacterium prausnitzii*; *F. nucleatum*, *Fusobacterium nucleatum*; *E. faecalis*, *Enterococcus faecalis*; GC, gastric cancer; *P. micra*, *Parvimonas micra*; PDAC, pancreatic ductal adenocarcinoma; *B. fragilis*, *Bacteroides fragilis*; ROS, reactive oxygen species; CagA, cytotoxin-associated gene A; *E. coli*, *Escherichia coli*; NF-κB, nuclear factor-κB; ETBF, enterotoxigenic *B. fragilis*; BFT, *B. fragilis* toxin; CECs, colic epithelial cells; IL-17R, interleukin-17 receptor; CXCL1, C-X-C motif chemokine ligand 1; Th17, T-helper 17; HR+, hormone receptor-positive; TLR, toll-like receptor; TIGIT, T cell immunoreceptor with Ig and ITIM domains; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; Treg, regulatory T; MDSCs, myeloid-derived suppressor cells; acetylCoA, acetyl-coenzyme A; H2S, hydrogen sulfide; ICC, intrahepatic cholangiocarcinoma; TUDCA, tauroursodeoxycholic acid; FMT, fecal microbiota transplantation; 5-FU, 5-fluorouracil; IPA, indole-3-propionic acid; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; anti-CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; anti-PD-L1, anti-programmed cell death-ligand 1.

effective.[138] In 2017, a male patient with Philadelphia-positive acute lymphoblastic leukemia had a serious infection (β-lactamase-producing *E. coli, Clostridium difficile*, and carbapenemase-producing *Enterobacteria*) that occurred before preparation for hematopoietic stem cell transplantation; the symptoms of the infection improved after undergoing FMT.[139]

Currently, research is focused on a more targeted approach, namely the precise adjustment of the gut microbiota. For instance, this approach involves the development of a drug that specifically targets *Fusobacterium*, the production of a vaccine, or the use of phage infection to precisely destroy this harmful microorganism.[118] Some researchers are concerned that toxic microbes may pass through the screening process. Therefore, they are focusing on well-characterized and laboratory-grown microbial formulations that use properly designed combinations of bacteria. In addition to their specific safety advantages, these microbial formulations can also be modified and extended by evaluating performance and other indicators.[140]

Prospects and Challenges

Over the years, numerous studies have shown that the gut microbiota is inextricably linked to cancer. Overall, researchers have found significant changes in the gut microbiota of patients with various cancers, in which specific bacteria and/or microbiota characteristics may serve as biomarkers for cancer screening and prognosis prediction. The gut microbiota influences the occurrence and development of cancer through mutation, metabolism, immunity, and other pathways. Regulating gut microbes through diet, probiotics, FMT, and more can influence cancer and response to treatment. With the development of metagenomics and metabolomics deep sequencing technology, and the establishment of multidisciplinary collaborative networks, research on the gut microbiota is continuously expanding. This lays a solid foundation for investigators to better understand the composition and function of this complex ecosystem. Meanwhile, decoding the relationships among intestinal flora, metabolism, immune system, cancer progression, and response to treatment will deepen the current understanding of the mechanism of cancer development.

Despite intensive efforts, there are numerous challenges to overcome. Most experts acknowledge that the causal relationship between the human microbiome and cancer remains to be determined. Current microbiome studies lack prospective cohort designs. Hence, it is impossible to determine the role of the gut microbiota in the initiation and development of diseases. Meanwhile, different geographic populations exhibit different microbial compositions, the fecal, luminal, and mucosal microbiota vary greatly, and many intestinal bacteria are not culturable.[141,142] Microbiome research studies have a high degree of heterogeneity in terms of descriptive methods, techniques used, depth of classification, and lack of information on confounders. Therefore, standardization of microbiome research methods (from sample collection to bioinformatics analysis) is urgently needed to improve the comparability of findings. Furthermore, current studies are not characterized by sufficiently high resolution to identify individual microbial species or communities that are carcinogenic and tumor suppressing. Thus, these investigations are frequently limited to recognizing associations between diseases and phyla and genera.[143] In addition, although probiotics are generally considered safe, sepsis has been observed in severely immunocompromised individuals following supplementation with *Bacillus subtilis*, as well as in critically ill patients who received *Lactobacillus rhamnosus* GG.[144] Therefore, the safety of usage of live bacteria for the treatment of cancer warrants further investigation. Finally, numerous experiments reported thus far were conducted on animals; hence, we should be cautious in extrapolating these results to humans.

Screening of specific gut microorganisms from different cancers as biomarkers to assess the risk and/or extent of disease in patients, as well as develop new, simple, and highly sensitive non-invasive tests has shown great potential. The prevention of cancer by fine-tuning the gut microbiota may be another adjuvant or primary therapy with great potential after surgery, radiotherapy, chemotherapy, or targeted therapy, paving the way for improved outcomes in such patients.

Funding

This research was supported by the National Natural Science Foundation of China (Grant No. 00022986) and the Natural Science Foundation of Southwest Medical University (Grant No. 2016XNYD217 and No. 2018-ZRQN-032); the Science and Technology Projects of Sichuan Province (Grant No. 2018JY0403); the Sichuan Province Returnees'Science and Technology Activities

Project (2019(76)-72); and the Scientific Research Program of Southwest Medical University (JG201977).

Disclosure

The authors report no conflicts of interest in this work.

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