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Review

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Gut microbiota as a new target for anticancer therapy: from mechanism to means of regulation

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In order to decipher the relationship between gut microbiota imbalance and cancer, this paper reviewed the role of intestinal microbiota in anticancer therapy and related mechanisms, discussed the current research status of gut microbiota as a biomarker of cancer, and finally summarized the reasonable means of regulating gut microbiota to assist cancer therapy. Overall, our study reveals that the gut microbiota can serve as a potential target for improving cancer management.

The gastrointestinal tract is the largest microbial reservoir in the human body, where a large microbial community, including bacteria, viruses, and fungi, exists. These intestinal microbes play an important role in regulating local mucosal inflammation and systemic immunity through complex cross-talk with immune cells and stromal cells in the intestine[1,2]. Gut microbiota is the largest and most complex microbial community, also known as the ' second genome '. The establishment of the human gut microbiota system began from birth, and the colonization was completed at about 3 years old. The formed gut microbiota system includes at least 1000 kinds of bacteria, which coexist with the host and constitute an important micro-ecological environment. It has an important impact on human cell metabolism, digestion and absorption, and immune regulation[3,4]. Gut microbiota disorders are associated with a variety of diseases, including hypertension, Alzheimer's disease, inflammatory bowel disease, and cancer[5–7].

The progression of cancer is believed to be the result of overlapping and complementary biological processes, including abnormal proliferation, evasion of apoptosis and autophagy, activation of invasion, enabling immunity, and inducing angiogenesis. These abnormal biological processes have been extensively studied for decades, until recently, another driver of cancer, the microbiome (including the gut microbiome) imbalance, gradually became a research focus on the impact on cancer onset, progression, and treatment response[8]. Currently, recognized anti-cancer treatments include surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, and stem cell transplantation. In addition to surgery, radiation therapy, chemotherapy and immunotherapy are the most widely used anti-cancer treatments in clinical practice, but their effects are not ideal, or they are prone to a series of unavoidable side effects that affect the quality of life of patients[9]. An increasing number of studies have shown that the gut microbiome affects the survival and development of tumors at various levels, including direct interactions between bacteria and cancer cells, the production of metabolites that affect tumor growth, and the regulation of local or systemic immune responses[10]. However, when it comes to anti-cancer treatment, can the gut microbiome continue to play a comprehensive and profound role?

In this review, we focus on the impact of the gut microbiome on the anti-cancer treatment (including radiotherapy, chemotherapy, and immunotherapy) response and side effects of various cancer types and analyze the main molecular mechanisms involved. We then reveal the feasibility of the gut microbiome as a biomarker for assisting cancer diagnosis, treatment, and prognosis. Furthermore, we explore the feasibility of assisting cancer management through fecal microbiota transplantation, probiotics, and dietary management to regulate the gut microbiome. Finally, we discuss the prospects and challenges of applying the gut microbiome to anti-cancer treatment.

The guiding significance of gut microbiota in cancer diagnosis and prognosis

Existing data suggest that the gut microbiota plays an important role in tumor pathogenesis by regulating host metabolism and immune responses, and more and more studies are beginning to explore the potential of gut microbiota and its metabolites as cancer biomarkers (Table 1).

Fusobacterium nucleatum is an important biomarker for CRC

Because gut microbiota dysbiosis is an early event in the development of CRC, a large number of studies have explored the gut microbiota as a potential diagnostic marker to assist in the diagnosis and prognosis of CRC[11]. It is worth noting that *F. nucleatum* is closely related to the occurrence of colorectal cancer, and its role as a diagnostic and prognostic marker for colorectal cancer patients has been repeatedly confirmed. Colov et al. found that high levels of *F. nucleatum* in the intestine were associated with poor postoperative prognosis in colorectal cancer patients[12]. Liang et al.

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Table 1 | The guiding significance of gut microbiota in cancer diagnosis and prognosis

Gut microbiota	Cancer type	Diagnosis/ Prognosis	Comment	References
Fusobacterium nucleatum	Colorectal cancer	Diagnosis and Prognosis	High levels of *F. nucleatum* are associated with poor postoperative prognosis in CRC patients, and the highest levels of *F. nucleatum* are found in stage IV CRC patients. The secretion of FadAc by *F. nucleatum* is a major virulence factor for the proliferation of CRC cells.	12–19
Bacteroides	Colorectal cancer	Prognosis	The enrichment of *Bacteroides* in the intestine is associated with poor prognosis in CRC patients.	180
Enterococcus, *Fusobacterium* and *Streptococcus*	Colorectal cancer	Diagnosis	The CRC enriched bacterium including Escherichia coli, Enterococcus faecalis, *F. nucleatum*, *Streptococcus gallolyticus*, *Flavoni fractorplautii* and *Eggerthella lenta* acted as promising biomarkers for early detection of CRC.	181
Prevotellaceae and *Faecalibacterium*	Colorectal cancer	Prognosis	*Faecalibacterium* and *Prevotellaceae* have been associated with better response to ICIs and are predictive biomarkers of immunotherapy in CRC patients.	182
Alistipes, *Bacilli*, *Lactobacillales* and *Pyrrolidine*	Biliary tract cancer	Prognosis	*Alistipes* is positively correlated with the survival rate, while *Bacilli, Lactobacillales and Pyrrolidine* are negatively correlated with the survival rate. Predictive models based on gut microbiota and its metabolites can predict immunotherapy efficacy with high accuracy.	183
Prevotella, *Alistipes*, *Agathobacter*, and *Parabacteroides*	Esophageal squamous cell carcinoma	Diagnosis	*Prevotella*, *Alistipes*, *Agathobacter*, and *Parabacteroides* may promote ESCC by regulating the synthesis of indole and its derivatives.	21
Bacteroides, *Parabacteroides*, *Prevotella*, and *Flavonifractor*	Lung adenocarcinoma	Diagnosis	The intestinal flora structure of patients with LUAD combined with Qi-deficiency and Phlegm-turbid stagnation (QP) is special, mainly reflected in four genera (*Bacteroides*, *Parabacteroides*, *Prevotella*, and *Flavonifractor*), which can be used as diagnostic markers.	184
Bacteroidetes, *Firmicutes*, and *Escherichia*	Breast cancer	Diagnosis	*Bacteroidetes*, *Firmicutes*, and *Escherichia* produce diβ-glucuronidase that affects levels of estrogen of non-ovarian origin through enterohepatic circulation, and elimination of β-glucuronidase may reduce the risk of BC development and facilitate treatment.	22,23,185,186
Actinomyces and *Senegalimassilia*	Hepatocellular carcinoma	Prognosis	*Actinomyces* and *Senegalimassilia* were mainly enriched in the non-durable clinical benefit group of HCC patients treated with ICI and were associated with low survival.	187
Firmicutes, *Bacteroidetes*, *Prevotella*, *Bacteroides* and *Akkermansia*	Hepatocellular carcinoma	Prognosis	Skewed *Firmicutes/Bacteroidetes* ratio and low *Prevotella/Bacteroides* ratio indicated no response to treatment, while the enrichment of *Akkermansia* indicated good therapeutic effect.	26
Prevotella and *Bacteroides*	Hepatocellular carcinoma	Prognosis	The ratio of *Prevotella/Bacteroides* can be used as a prognostic indicator of HCC treated with nivolumab. The higher the ratio, the better the efficacy.	27
Clostridiacea, *Lachnospiraceae*, *Ruminococcaceae*, *Veillonellaceae*, *Akkermansia* and *Odoribacter*	Pancreatic cancer	Diagnosis	The main features of PC patients with precancerous lesions are: the presence of *Clostridiacea*, *Lachnospiraceae*, the lack of *Ruminococcaceae*, and excessive increases in *Veillonellaceae*, *Akkermansia*, and *Odoribacter*.	188

proposed that quantification of fecal microbial DNA markers could be used as a novel assay to screen for colorectal tumors in asymptomatic subjects, either alone or in combination with fecal immunochemical testing (FIT). Targets include *F. nucleatum*, *Lachnoclostridium sp.m3*, *Bacteroides clarus*, and *Clostridium hathewayi*[13]. Subsequent studies found that combining fecal immunochemical tests with the abundance of *F. nucleatum* could significantly improve the diagnostic performance of CRC. Specifically, the AUC value of FIT for colorectal cancer was 0.86, and when the abundance of *F. nucleatum* was included in the model, the AUC value was further increased to 0.95[14,15]. Poza et al. also proposed a new diagnostic biological model composed of *Fusobacterium*, *Parvimonas*, *Bacteroides*, and *Faecalibacterium*, which can be used as an excellent non-invasive stool test for the early diagnosis of CRC[16]. Yamaoka et al. collected 100 CRC tissues and 72 matched normal mucosal tissues to determine the level of *F. nucleatum*, which can help predict the clinical prognosis of CRC patients, and the level of *F. nucleatum* was highest in stage IV CRC patients[17]. Zhao et al. also proposed that the biological model of *F. nucleatum* + *fecal occult blood* + *sex* + *age* may be the optimal combination for the diagnosis of CRC[18]. In addition, *F. nucleatum* secretes an amyloid adhesion protein FadA complex (FadAc), which is a major virulence factor that causes bacterial adhesion, induces inflammation, and colorectal cancer cell proliferation. Compared with healthy controls, circulating levels of anti-FADAC IgA were increased in patients with early and advanced colorectal cancer, but IgG levels were not, especially in patients with proximal colorectal cancer, and Han et al. suggested that anti-FADAC IgA could be developed as a serological biomarker for the early detection of colorectal cancer[19].

The role of gut microbiota in the identification of other cancers

Gut microbiota as a diagnostic biomarker. In addition to CRC, gut microbiota is a potential biomarker for a variety of other cancers. To track the changes in the gut microbiota after the onset of lung cancer, Feng et al. combined preclinical and clinical studies to thoroughly analyze the characteristics of the fecal microbiota in lung cancer, and they found that the fecal microbiota of lung cancer mice had reduced metagenomic potential for neurotransmitters (melatonin, γ-aminobutyric acid, and histamine) compared to healthy mice, which will help in the early diagnosis of lung cancer and predict the therapeutic effect, that is, the diversity, structure, and composition of the gut microbiota differ after the occurrence of lung cancer, leading to changes in functional metagenomics[20]. Esophageal squamous cell carcinoma (ESCC) is one of the most predominant subtypes of esophageal cancer, and Gao et al. have used various bioinformatics methods to fully study and discuss the characteristics of the gut microbiota and its metabolites in ESCC patients. They found that *Prevotella*, *Alistipes*, *Agathobacter*, and *Parabacteroides* may promote ESCC by regulating the synthesis of indole and its derivatives and that the microbiota and its associated metabolites can be used as diagnostic biomarkers of ESCC[21].

In postmenopausal women, an increase in circulating estrogen levels is associated with an increase in susceptibility to BC. Metabolites produced by the gut microbiota (such as Bacteroidetes, Firmicutes, and Escherichia), β-glucuronidase, affect the levels of estrogen of non-ovarian origin through the enterohepatic circulation. Specifically, the estrogen glucuronate excreted into the intestine through bile is catalyzed by β-glucuronidase into free estrogen, which is then absorbed by the intestinal mucosa into the enterohepatic circulation, and then distributed to various organs such as the mammary gland. Therefore, the elimination of β-glucuronidase can reduce the risk of BC development and facilitate treatment, in other words, microbiota metabolites such as β-glucuronidase may serve as biomarkers for clinical prediction of BC[22–25].

Gut microbiota as a prognostic biomarker. Zhu et al. explored the status and characteristics of the gut microbiota in patients with hepatocellular carcinoma (HCC) treated with ICI and discovered a prediction model consisting of 18 gut bacterial species to predict whether immunotherapy has a sustained benefit (area under the curve=75.63%), *Actinomyces* and *Senegalimassilia* and their metabolite galanthaminone were screened as prognostic biomarkers to predict the survival of ICI-treated HCC patients. They observed that *Actinomyces* and *Senegalimassilia* were predominantly enriched in the non-durable clinical benefit (NDB) group of HCC patients treated with ICIs, suggesting that they were associated with low survival, so targeting and reducing the abundance of these specific gut microbiota may help improve the efficacy of ICIs[26]. In addition to immunotherapy, Chung et al. demonstrated that gut microbiota is also associated with the prognosis of HCC patients treated with nivolumab, specifically, skewed *Firmicutes*/*Bacteroidetes* ratio and low *Prevotella*/*Bacteroides* ratio can be used as predictive markers of non-response, while the enrichment of *Akkermansia* indicates a good therapeutic effect[27].

Not only that, the gut microbiota also plays a unique biomarker value in the early diagnosis, treatment guidance, and prognosis prediction of pancreatic cancer, prostate cancer, melanoma, cervical cancer, and other cancers, which may be another exploration direction to overcome cancer problems in the future[28–31].

The role of gut microbiota in anti-cancer immunotherapy

The gut is the largest site of immune activity in the body, where about 70% of the body's immune cells are present, and several studies have shown that the gut microbiota can modulate anti-tumor immunity and affect the efficacy of cancer immunotherapy, especially immune checkpoint inhibitors (ICIs). Unraveling the underlying mechanism suggests that the gut microbiota reprograms the immunity of the tumor microenvironment (TME) by engaging in innate and/or adaptive immune cells[32]. As early as 2007, in a study of mouse melanoma models, translocated microbiota in mesenteric lymph nodes was found to enhance the function of adoptively transferred CD8 Akkermansia muciniphila T cells through TLR4 signaling, suggesting that the microbiota can stimulate the body's anti-tumor immune response[33]. Later, in 2015, the gut microbiota was first identified as being associated with anti-PD-L1 therapy in melanoma mice, and subsequent studies also found that the diversity of gut microbiota can predict the efficacy of immunotherapy with ICIs, Sivan et al. 's data suggest that *Bifidobacterium* can enhance DC function and improve anti-PD-L1 efficacy[34].

The gut microbiota affects the efficacy of a variety of immunotherapies

The microbiotas that can enhance ICIs reactivity mostly belong to *Firmicutes*, *Bacteroides*, *Actinomycetes*, *Proteobacteria*, and *Verrucomicrobia*[35]. During anti-PD-1/PD-L1 therapy, antibiotic-naïve melanoma patients have significantly higher survival rates than those treated with antibiotics, and responders have shown greater diversity in their gut microbiota compared with non-PD-1 inhibitor responders[36–38]. *Akkermansia muciniphila* induces immunoglobulin G1 (IgG1) antibodies and antigen-specific T cell responses in lymphoma mice, and its massive colonization of the gut greatly enhances the efficacy of PD-1 inhibitors, a process that appears to rely solely on T follicular helper cells[39]. Another study showed that the combination of IL-2 and *Akkermansia muciniphila* had a strong antitumor effect on the tumor tissue of colorectal cancer patients in a CRC mouse model, due to enhanced anti-tumor immune monitoring. This indicates that the combination of IL-2 and other immunomodulators with *Akkermansia muciniphila* is a new method with application value for cancer treatment[40]. Notably, pMMR (also known as microsatellite stable) CRC patients are relatively resistant to PD-1 inhibitors. Xu et al. evaluated the effect of gut microbiota on PD-1 antibody immunotherapy response in pMMR CRC mice treated with different antibiotics. It was demonstrated that gut microbiota such as *Akkermansia muciniphila* played a key role in the treatment of CRC tumor bearing mice with PD-1 antibody[41]. Such evidence suggests that Akkermansia muciniphila plays an active role in the immune effects and treatment of cancer, and the combination of related microbiota agents and immune-targeting drugs will be a new direction for personalized cancer therapy (Fig. 1).

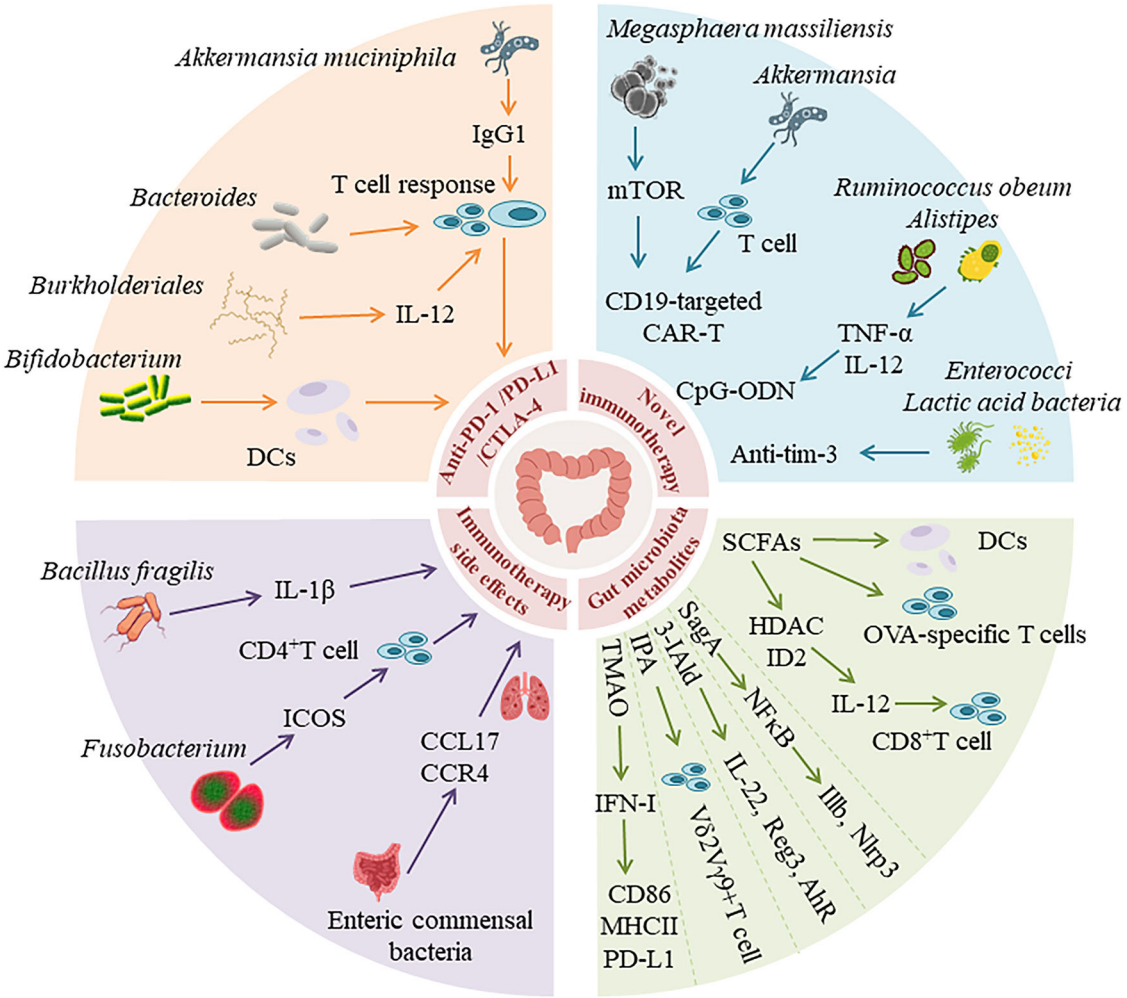

Fig. 1 | Multifaceted mechanisms by which gut microbiota influences anti-cancer immunotherapy. A large number of current studies have revealed a strong link between gut microbiota and the efficacy of anti-cancer immunotherapy, according to a further summary. In this paper, gut microbiota and its metabolites regulate anti-PD-1 /PD-L1/CTLA-4, novel immunotherapy (including anti-TIM-3 therapy, CpG-ODN, and CD19-targeted CAR-T cell therapy), and the detailed mechanisms of immunotherapy side effects are summarized. In the figure, we classify them by different color blocks.

For anti-CTLA-4 treatment, it was initially observed that gut microbiota such as *Burkholderiales* promoted anti-tumor effects by activating the IL-12-dependent Th1 immune response[42]. In addition, *Bacteroides* have also shown the potential to enhance the therapeutic effect of CTLA-4 blockers in melanoma patients, and the mechanism may involve specific T-cell responses to *B. thetaiotaomicron* or *B. fragilis*[43]. The combination of anti-CTLA-4 and anti-PD-1 (CICB) has significant immune efficacy against different tumors, and due to subsequent immune dysfunction, the incidence of immune-related adverse events is also high, especially the strong side effects such as intestinal inflammation, which is accompanied by high upregulation of IL-1β in the mucosa[44], and artificial colonization of *Bacillus fragilis* can improve the toxicity and side effects associated with this immunotherapy[45]. Similarly, the presence of *Bacteroides* in the gut significantly reduces the incidence of colitis after anti-CTLA-4 therapy in melanoma patients, while the presence of *Fusobacterium* and other *Firmicutes* makes immunotherapy-associated colitis more frequent in such patients, this is mediated by ICOS-induced increases in CD4 + T cell levels and sCD25 levels[46,47]. *Phascolarctobacterium*, which belongs to *Firmicutes*, and *Parabacteroides*, *Bacteroides*, which belong to *Bacteroidetes*, have lower abundances in lung cancer patients who develop immunotherapy-associated diarrhea, while *Veillonella*, which belongs to *Proteobacteria*, have higher abundances[48]. Notably, the influence of the gut microbiota on the immune function of the lungs may lie in the activation of gut immunity by the gut microbiota, resulting in the migration of these activated immune cells to the lungs and participation in pulmonary immunity, the so-called lung-gut axis, a process in which chemokines and their receptors play an important role (CCL17 and CCR4, among others)[49,50]. Because of the profound impact of the gut microbiota on the immune barrier of the lungs, some scholars have proposed that the gut microbiota may be a novel biomarker for predicting the sensitivity and adverse effects of immunotherapy in lung cancer patients[51] (Fig. 1).

CD19-targeted chimeric antigen receptor (CAR)-T cell therapy is a new immunotherapy that provides a new therapeutic pathway for patients with refractory lymphoma, but efficacy is mixed, with less than 40 percent achieving durable disease control[52,53]. In a multicenter cohort study of lymphoma patients, the investigators demonstrated that broad-spectrum antibiotic therapy before CD19-targeted CAR-T cell therapy was associated with serious adverse outcomes and that the biosynthesis of peptidoglycan encoded by *Bifidobacterium longum* was strongly associated with CAR-T therapy, in addition to similar efficacy promotion effects of *Bacteroides*, *Ruminococcus*, *Eubacterium*, and *Akkermansia*. *Akkermansia* is associated with peripheral blood T cell counts in patients[54]. In addition, Luu et al. reported that short-chain fatty acids (SCFAs) metabolites such as valerate and butyrate produced by *Megasphaera massiliensis* increased the biological activity of mTOR and inhibited class I histone deacetylase, resulting in increased production of effector molecules such as CD25, IFN-γ, and TNF-α, significantly enhancing the antitumor activity of CAR-T cells in melanoma mice[55]. As a novel immune checkpoint, mucin domain protein-3

(Tim-3) blockade therapy is another anti-cancer immunotherapy aimed at alleviating T cell exhaustion and enhancing anti-tumor immunity, and it has recently been found that antibiotic-induced dysbiosis can reduce the effect of Tim-3 blockade therapy, while fecal transplantation in wild-type mice can increase the number of *Enterococci* or *Lactic acid bacteria*, change the composition of intestinal ecology, and restore the efficacy of Tim-3 blockade[56]. CpG-ODN is a TLR9 agonist, which can induce the activation and maturation of plasmacytoid dendritic cells, and induce cytokines such as TNF-α and IL-12 secreted by myeloid cells to activate the immune response to tumor cells, so it can be used as a new adjuvant to tumor immunotherapy, but the pro-immune effect of CpG-ODN is almost not observed in germ-free mice. There has long been evidence that TNF production in response to CpG-ODNs is closely related to gut microbiota. For example, the number of gram-negative bacteria *Alistipes* and gram-positive bacteria *Ruminococcus* were positively correlated with TNF production, while the number of Lactobacillus was negatively correlated with TNF production[57,58]. At the same time, Goldszmid et al. found that *Alistipes* re-enhanced CpG-ODN activation of TNF-α and IL-12 after exposure to antibiotics in mice, while the opposite was true for *Lactobacillus*[59] (Fig. 1).

Relationship between gut microbiota metabolites and immunotherapy

One of the main ways in which the gut microbiota modulates anti-tumor immunity is through metabolites, small molecules that can diffuse from their original intestinal location and influence local and systemic anti-tumor immune responses to promote ICI efficiency[60,61]. The gut microbiota promotes the breakdown of intestinal contents, and most of the dietary fiber and complex polysaccharides are metabolized into SCFAs, such as acetate, propionate, and butyrate, of which propionate and butyrate are considered to be key regulators of the body's anti-tumor immune response[62]. Specifically, butyric acid inhibits the expression of the transcription factor E2A by inhibiting the expression of histone deacetylase (HDAC) and DNA-binding inhibitor 2 (ID2), induces the expression of IL-12 receptor on the surface of CD8 + T cells, enhances IL-12 signaling, and improves the anti-tumor toxicity of CD8 + T cells[62]. Martini et al. compared 14 patients with CRC who received anti-PD-1 therapy and found that five patients with long-term remission (9 to 24 months) had higher levels of *Agathobacter* and *Blautia*, both butyrate-producing bacteria, compared with nine patients with shorter survival (two to six months)[63]. However, butyric acid has also been shown to reduce the efficacy of CTLA-4 in the treatment of metastatic melanoma, limiting anti-CTLA-4-induced maturation of DCs and anti-CTLA-4-induced ovalbumin (OVA)-specific T cells[64] (Fig. 1).

SagA is an NlpC/p60 endonuclease secreted by *Enterococcus faecalis* that preferentially hydrolyzes cross-linked Lys-type peptidoglycan fragments, which are further converted to muramyl dipeptide (MDP) and n-acetylglucosamine-MDP, which activate the NFκB signaling pathway in immune cells by binding to Nucleotide-binding Oligomerization Domain Containing2. This induces the expression of Illb and Nlrp3 genes, activates the immune system, and enhances the effect of anti-cancer immunotherapy[65]. Indole-3-carboxaldehyde (3-IAld) is a tryptophan catabolite of the gut microbiota, and studies have shown that 3-IAld reduces the occurrence of immune-associated enteritis and prolongs the lifespan of mice in anti-CTLA-4-treated melanoma and lung cancer mouse models and that 3-IAld does not interfere with the antitumor activity of anti-CTLA-4 antibodies, which is related to the involvement of the aromatic hydrocarbon receptor AhR. 3-IAld also induces the expression of IL-22 and Reg3γ, an antimicrobial peptide produced by intestinal epithelial cells, which contributes to the establishment of an immune barrier in the gut. On the other hand, 3-IAld maintains a normal distribution of gut microbiota in mice, which is related to the predominance of members of *Bacteroidetes* and *Firmicutes*[66,67]. 3-Indolepropionic acid (IPA) is produced by *Bacillus sporozoites* in the intestine, and studies have shown that IPA has a beneficial effect on immunotherapy for hepatocellular carcinoma, inducing Vδ2Vγ9T cells to release more granzyme B and perforin, enhancing its antitumor effects[68]. *Clostridium spp.*-related metabolite trimethylamine N-oxide (TMAO) up-regulated the antitumor effects in an IFN-I.-dependent manner, and increased the surface expression of activation markers such as CD86, major histocompatibility complex II (MHCII), and PD-L1, and its combination with ICIs (anti-PD1 and/or anti-Tim3) in mouse models of pancreatic cancer improved the survival rate of mice and showed better tumor treatment effects[69] (Fig. 1).

In addition to the above classic gut microbiota metabolites that have a significant impact on the efficacy of anti-cancer immunotherapy, there are many more gut microbiota metabolites that play an important role in the course of anti-cancer therapy, so we have summarized them and compiled a table to show them in detail (Table 2). Future research on this aspect may be another important direction for cancer treatment.

The dual role of gut microbiota in cancer chemotherapy

Chemotherapy is currently a commonly used non-surgical and post-operative treatment for cancer patients, and approximately 50 percent of patients do not respond to this treatment, and the genotype does not fully explain the difference between chemotherapy-responsive and non-chemotherapy patients, and the emerging evidence highlights the critical role of the gut microbiota in determining chemotherapy response[70,71] (Fig. 2).

The promotion of gut microbiota on the efficacy of chemotherapy drugs and the control of chemotherapy complications

Glutathione peroxidase (GPX-1 and GPX-2) is an important peroxide decomposing enzyme widely present in intestinal epithelial cells, which promotes the decomposition of H2O2, reduces the oxidative environment, and protects cells from the damage of peroxide. Experiments have shown that cancer mice with highly down-regulated Gpx1 and Gpx2 genes are highly sensitive to chemotherapy. The presence of *Helicobacter pylori* and other gut microbiota significantly inhibited the function of GPX-1 and GPX-2, and further assisted the efficacy of chemotherapy[72]. Cyclophosphamide (CTX) is widely used in the treatment of solid tumors and hematologic malignancies, and at the same time causes acute intestinal mucosal injury of varying severity. Oral administration of Lactobacillus plantarum NCU116 increased the number of *Lactic acid bacteria* and *Bifidobacteria* in the intestinal tract of mice, increased the level of short-chain fatty acids, decreased the concentration of ammonia, further improved the expression of mucin and the number of goblet cells, and had significant efficacy in improving CTX-mediated intestinal mucosal injury, regulating intestinal barrier function and metabolism[73]. In addition, CTX combined with Lactobacillus transformed naive T cells into TH17 cells, resulting in $CD8^+$ T cell effect, which improved chemotherapy effect in B16F10 melanoma and MCA205 sarcoma mice[74]. Cisplatin can be cross-linked with DNA strands, showing cytotoxic effects, and the combination with probiotics such as *Lactobacillus* improves the response to anticancer therapy in cancer mice, and the mechanism involves the activation of pro-apoptotic genes BAX and CDKN1B in tumor tissues, enhancing host immune responses, and increasing serum IL-6 and IFN-γ levels. However, in the mouse model of lung cancer treated with cisplatin combined with vancomycin and ampicillin, the growth rate of tumor volume was significantly greater than that of cisplatin alone[75,76].

Inflammatory bowel disease caused by chemotherapy drugs such as irinotecan (CPT-11) is one of the complications of chemotherapy in cancer patients. In recent years, studies have found that bile acid metabolism is closely related to the progression of inflammatory bowel disease (IBD) caused by cancer chemotherapy, and the gut microbiota may play a role in it, specifically, the bile acids in the colon can be converted into deoxycholic acid and lithoclastic acid under the action of *Bacteroides fragilis* and *Escherichia coli*, triggering subsequent immune barrier destruction, so the inactivation of such microbiota may be a new measure to solve the IBD caused by cancer chemotherapy[77–80]. CPT-11 can also induce the formation of intestinal vacuoles by triggering the innate immune response, accelerating the excretion of mucin stored in goblet cells, thereby reducing the number of adhesion sites and nutrient supply of gut microbiota, and destroying the

Table 2 | Effects of gut microbiota metabolites on anticancer therapy of different cancer types

Metabolites	Cancer type	Model	Mechanism	References
SCFAs	Melanoma and pancreatic cancer	Mouse models of melanoma and pancreatic cancer	SCFAs increased strong mTOR function, inhibited class I histone deacetylase activity, increased the production of effector molecules such as CD25, IFN-γ, and TNF-α, and significantly enhanced the antitumor activity of T cells.	55
	Colorectal cancer and lymphoma	MC38 and EG7 cells C57BL/6 J mouse tumor model	Butyric acid inhibits transcription factor E2A through the expression of HDAC and ID2, enhances IL-12 signaling, and enhances anti-tumor toxicity of CD8 + T cells.	62
	Melanoma	Melanoma mouse models and patients	High butyrate and propionate levels inhibit the upregulation of CD80/CD86 on DC cells and ICOS on T cells, limiting anti-CTLA-4 therapeutic activity.	64
	Non-small cell lung cancer	NSCLC patient Lewis cells Mouse cancer model	The response of non-small cell lung cancer to immunotherapy was enhanced with increased levels of SCFAs.	117
	Hepatocellular carcinoma	HCC patients	Enhancing the efficacy of tyrosine kinase inhibitor sorafenib in the treatment of HCC by regulating intracellular calcium homeostasis.	189
SagA	Melanoma	Mouse model created by B16-F10 cells	Activate the NFκB signaling pathway of immune cells, induce the expression of Illb and Nlrp3 genes, and activate anti-tumor immunity.	65
3-IAld	Melanoma	Melanoma mouse model	Based on AhR/IL-22 signaling, 3-IAld alleviated ICI induced intestinal injury without impairs the antitumor activity of ICI.	66
IPA	Hepatocellular carcinoma	HepG-2 cells C57BL/6 J liver cancer mouse model	Vδ2Vγ9T cells were induced to release more granzyme B and perforin, which enhanced their antitumor effect.	68
TMAO	Pancreatic ductal adenocarcinoma	2838c3、6419c5 cells PDAC mouse model	In IFN-I dependent manner, the antitumor effect of the body is up-regulated, and the expression of CD86, MHCII and PD-L1 is increased.	69
CDDL	Colorectal cancer	RKO cells	Metabolize the chemotherapy drug gemcitabine (2', 2'-difluorodeoxycytidine) to the inactive form 2', 2'-difluorodeoxyuridine.	85
Dihydropyrimidine dehydrogenase	Colorectal cancer	HCT-116 cells Mouse and patients with colorectal cancer	The conversion of 5-FU to inactive dihydrofluorouracil reduces the effect of 5-FU chemotherapy.	89
β-glucuronidase	Colorectal cancer	Balb/cJ colorectal cancer mouse model	Metabolize SN-38G to enterotoxic SN-38, causing CPT-11 to produce delayed diarrhea upon treatment.	190
	Breast cancer	Breast cancer mouse model	The level of estrogen of non-ovarian origin is affected by enterohepatic circulation.	22,23
Hippurate	Melanoma	B16F10 melanoma mouse model	The bifidobacterium metabolite hippurate enhances the killing ability of NK cells and improves the efficacy of anti-PD-1 antibody.	171
Tyrosol	Colorectal cancer	CRC patients and mouse models	Demonstrated antitumor effects by inhibiting HIF-1α/NF-κB signaling pathway activation, resulting in decreased levels of ROS and inflammatory factors.	191
2'-deoxyinosine	Colorectal cancer	HT-29, HCT-116, Caco-2, and SW-620 cell lines CRC mouse model	AY01 secreted by probiotic lactic acid bacteria has anticancer ability, and its active substance 2'-deoxyinosine induces apoptosis of colorectal cancer cells by activating p38/MAPK pathway.	192
3-methylxanthine	Ovarian cancer	ID8 cells Ovarian cancer mouse model	Promoting apoptosis of ovarian cancer cells through dopamine receptor D1-dependent pathway, amplifying the efficacy of cisplatin.	193
Sodium butyrate	Colorectal cancer	HCT-116, SW-480 and DLD-1 cells CRC mouse model	Enhancing the antitumor efficacy of 5-fluorouracil in colorectal cancer by modulating PINK1/Parkin signaling.	194
Urolithin A	Colorectal cancer	HCT-116(R) and SW-480(R) cells CRC mouse model	Modulating the FOXO3-FOXM1 axis sensitizes drug transporters to resist the resistance of colon tumors to 5-fluorouracil.	195

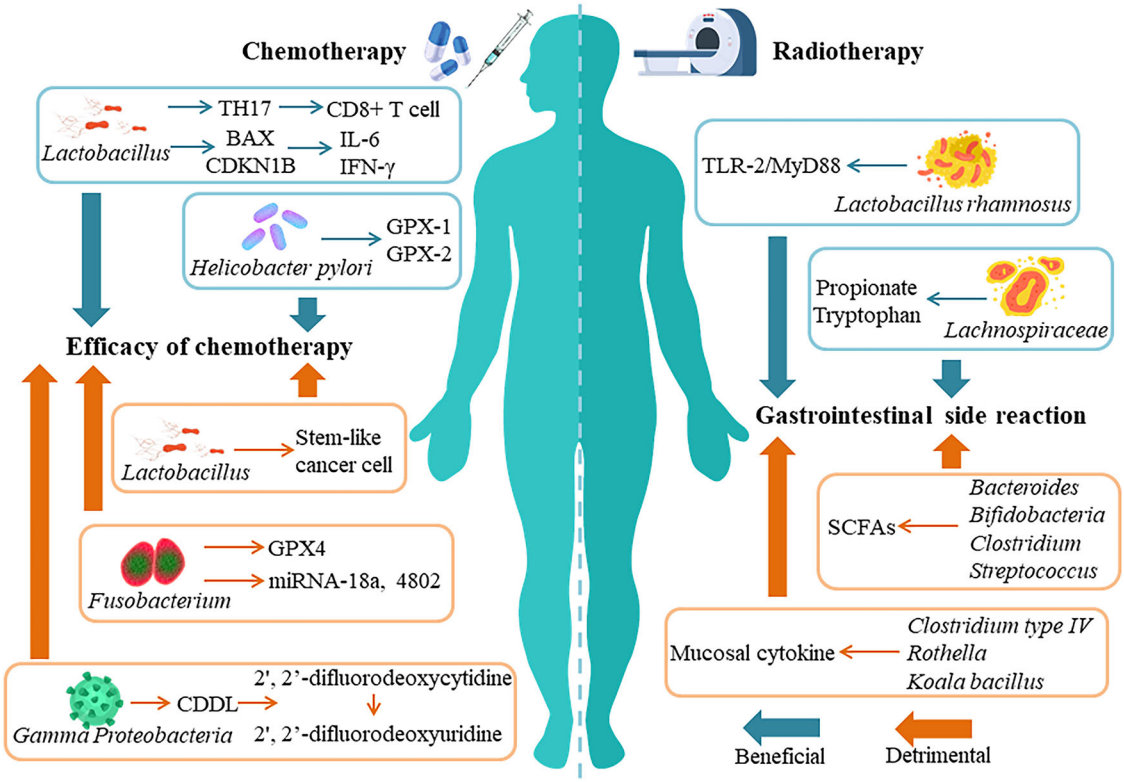

Fig. 2 | Effects of gut microbiota on chemoradiotherapy. Chemoradiotherapy is the most important treatment for cancer except surgery. There is evidence that gut microbiota has a profound influence on the efficacy and side effects of chemoradiotherapy. This figure compares the effects of several typical gut microbiotas on chemoradiotherapy, among which the effects of gut microbiota on chemotherapy are mainly focused on improving curative effect, while the effects on radiotherapy are mainly focused on reducing complications.

ecological balance of intestinal microbes[81]. In addition, researchers in Redinbo's laboratory found that CPT-11 enhances the activity of β-glucuronidase (GUS) expressed by intestinal bacteria, activating the inactive glucuronide (SN-38G) to become the enterotoxin SN-38, which causes severe delayed diarrhea. The results of this study show that CPT-11 increases GUS activity within 1 day and decreases the proliferation of intestinal epithelial cells within 5 days and can be blocked by GUS inhibitors. In tumor xenograft models, GUS inhibition prevented enterotoxicity and maintained the antitumor efficacy of irinotecan. However, the efficacy of irinotecan could be significantly improved by increasing the dose. They also found that a compound called SBX-1 protected mice from CPT-11-induced diarrhea by blocking bacterial GUS[82,83].

Chemotherapy resistance and toxic side effects caused by gut microbiota

However, due to the complexity of the gut microbiota, people have not achieved a good balance between specific gut microbiota and stable chemotherapy efficacy. For example, in an in vitro model of colorectal cancer, *Lactobacillus plantarum* amplifies the cytotoxicity of 5-fluorouracil (5-FU) by reducing the number of stem cell-like cancer cells[84]. Certain gut microbiomes, such as *Proteus*, can stimulate resistance to commonly used anticancer drugs such as CPT-11, oxaliplatin, cyclophosphamide, etc., and can reduce the anticancer activity of gemcitabine by producing bacterial enzyme isoforms of cytidine deaminase, a phenomenon that can be reversed with the antibiotic ciprofloxacin[85].

Fusobacterium nucleatum is a major oncogenic microbiota of intestinal origin in colorectal cancer, and there is increasing evidence that *F. nucleatum* induces the development of chemotherapy resistance. Recent studies have shown that *F. nucleatum* induces oxaliplatin resistance in colorectal cancer both in vitro and in vivo. Mechanically, *F. nucleatum* promotes oxaliplatin resistance by overexpressing GPX4 and inhibiting iron death. During this period, the GPX4 overexpression of *F. nucleatum* was mediated by the E-cadherin/β-catenin/TCF4 pathway[86]. On the other hand, *F. nucleatum* also induces oxaliplatin resistance by activating TLR and stimulating the expression of microRNA18a[87]. *F. nucleatum* also targets innate immune signaling of TLR4 and MYD88, and specific microRNAs (miRNA-18a* and miRNA-4802), activate the autophagy pathway, and increase the therapeutic resistance of colorectal cancer cells to 5-FU[87]. In addition, inhibition of pyroptosis death based on Hippo pathway is also an important mechanism of *F. nucleatum* induced oxaliplatin and 5-Fu resistance[88]. In view of the key role of *F. nucleatum* in cancer chemotherapy resistance, the targeted therapy of *F. nucleatum* will be a new adjunct to cancer therapy. For cancer patients with high concentrations of *F. nucleatum*, the combination of chemotherapy and anti-*F. nucleatum* drugs (including antibiotics) may be a feasible treatment strategy to reduce chemotherapy resistance.

In addition to *F. nucleatum*, dihydropyrimidine dehydrogenase in *Escherichia coli* converts 5-FU into inactive dihydrofluorouracil, which is closely related to the preTA operon, which catalyzes the reduction reaction that inactivates 5-FU, suggesting that the *E. coli* metabolite dihydropyrimidine dehydrogenase can reduce the response of 5-FU chemotherapy by inactivating drugs[89]. Through the expression of the long subtype of the bacterial enzyme cytidine deaminase (CDDL), *Gamma Proteobacteria* can metabolize the chemotherapy drug gemcitabine (2', 2'-difluorodeoxycytidine) to the inactive form 2', 2'-difluorodeoxyuridine, which shows that gemcitabine resistance is closely related to *Gamma Proteobacteria*[85].

The relationship between gut microbiota and cancer radiotherapy

Radiotherapy has long been an important treatment for tumors, inducing DNA damage in tumor cells and normal epithelial cells through energy transfer, which involves the production of reactive oxygen species and nitrogen. Among them, gastrointestinal epithelial cells have high

proliferative properties and high sensitivity to radiation, so they become the main objects of injury during radiotherapy, which significantly affects the quality of life of patients[90].

Gut microbiota affects the toxicity and side effects of cancer radiotherapy

Most radiation toxicity, especially gastrointestinal mucositis, is caused by the release of local pro-inflammatory factors, and the gut *Lactobacillus rhamnosus* regulates the TLR-2/MyD88 signal transduction mechanism, which migrates mesenchymal stem cells to the base and protects the intestine from radiation-induced cell damage[91]. In addition, enrichment of *Lachnospiraceae* and *Enterococcaceae* has been observed to significantly attenuate radiation-induced gastrointestinal injury and hematopoietic disruption, possibly due to the important contribution of their downstream metabolites propionate and tryptophan to radiation protection[92]. *Acidophilus*, *Bifidobacteria*, and certain *Streptococci* have also been shown to alleviate gastrointestinal side effects of radiotherapy, such as diarrhea, abdominal pain, and nausea, especially in gynecologic malignancies[93,94] (Fig. 2).

Intestinal epithelial inflammation and barrier dysfunction were observed in patients with radiation enteritis, with enhanced TNF-α and IL-1β expression accompanied by dysbiosis (significantly reduced α diversity and increased β diversity). This suggests that dysbiosis of the gut microbiota will also contribute to the development and progression of radiation enteritis[95]. SCFAs produced by *Bacteroides*, *Bifidobacteria*, *Clostridium*, *Streptococcus*, etc., are also closely related to radiation bowel disease[96]. In addition, higher levels of *Clostridium type IV*, *Rothella*, and *Koala bacillus* also contribute to the development of radiation enteropathy, which is associated with a significant reduction in intestinal mucosal cytokines that maintain intestinal homeostasis[97]. (Fig. 2).

Post-radiotherapy fatigue is another complication of radiotherapy, and the gut microbiota of these patients shows an increased abundance of *Streptococcus*, *Adecretsia*, and *Actinomycetes*, and upregulation of microbial sucrose degradation pathways, suggesting that intestinal dysbiosis may be one of the causative factors of radiotherapy-related fatigue[98]. In addition, whole-brain radiotherapy-induced cognitive dysfunction may also be highly associated with gut dysbiosis. It was found that the levels of *Bacteroides* (*Philum-Bacterroyd*), *Bacteroidetes* (*Klaas-Bactrodi*a), and *Bacteroides* (*Ode-Bactroydales*) decreased after whole-brain irradiation in wild-type mice, while the levels of *Bacteroides* (*Janus-Alobakulum*) increased. Strategies to improve gut microbiota may have beneficial effects on individuals with cognitive dysfunction[99].

Radiation pneumonitis and pulmonary fibrosis caused by radiation therapy are the main clinical complications of radiation therapy in patients with thoracic tumors, and modulation of gut microbiota may reduce radiation lung disease and pulmonary fibrosis. Relevant studies have shown that after radiation pneumonitis and lung fibrosis caused by X-ray single dose irradiation in lung cancer model mice, the intestinal inflammation-related microbiota increased compared with the original, such as the proportion of *Bacteroidetes* doubled, the proportion of gut microbiota tended to be normal after phycocyanin administration, and the lung damage was reduced compared with before, which can be speculated that radiation pneumonitis and fibrosis may be related to the gut microbiota imbalance caused by radiotherapy[100,101]. In addition, gram-positive bacteria may reduce the effectiveness of radiation therapy (RT) for lung cancer. One study found that radiotherapy combined with vancomycin, an antibiotic that acts primarily on gram-positive, significantly increased survival in mice with lung cancer compared to radiotherapy alone, and the process was associated with an increase in the number of tumors cell-lysing CD8 + T cells[102] (Fig. 2).

Gut microbiota disturbances induced by radiotherapy and its treatment

At the same time, exposure to ionizing radiation will also have a profound impact on the gut microbiota, and studies have shown that radiotherapy usually increases the harmful flora such as *Proteus* and *Fusobacterium* in the intestine, and decreases the beneficial flora such as *Faecalibacterium* and *Bifidobacteria*, resulting in intestinal dysbiosis[103,104]. In fact, the effects of pelvic radiation therapy on the gut microbiota of gynecological cancer patients have been known since 1992, that is, radiation causes a decreased abundance of E. coli, F. nucleatum, *Enterococcus faecium* and *Lactobacillus*, and an increased abundance of *Clostridium*[105]. There are many reports on such results, and the imbalance of gut microbiota is often accompanied by subsequent systemic toxic side effects. For example, radiation therapy can also change the bacteria that produce SCFAs, thereby causing changes in SCFAs, affecting the appearance of many diseases, and thus playing a negative role in the treatment of cancer patients[104]. The decrease in the ratio of radiotherapy-induced *Bacteroidetes* to *Firmicutes* will lead to significant changes in the lipidomic profile of the intestinal epithelial barrier, with glycerophospholipid metabolism being the most correlated with the progression of radiation enteritis[106].

In addition, a large number of studies have shown that gut microbiota is closely related to radiation-induced gastrointestinal disease, and the abundance of *Clostridium IV*, *Roseburia*, and *Phascolarctobacterium* in patients with radiation-induced intestinal disease is high, but effective fecal microflora transplantation can prevent radiation-induced gastrointestinal toxicity[97,107]. Similarly, Ding et al studied the use of FMT to treat chronic collateral damage after abdominal irradiation, and the results showed that FMT from healthy donors improved the patients' co-symptoms such as rectal bleeding, fecal incontinence, and diarrhea, but the effect was not lasting[108]. Another report showed that four courses of FMT from a healthy donor increased the diversity of the patient's microbiome and more radically improved symptoms of blood in the stool, abdominal pain and diarrhea[109]. We can conclude from this that FMT appears to have a beneficial effect on radiation therapy-induced toxicity, but this is dependent on a stable treatment cycle and attention to microbiome changes after FMT. It is worth noting that whether FMT can improve the efficacy of radiotherapy has so far been studied, which may be an interesting area for further investigation.

Overall, the changes in gut microbiota under radiotherapy may have important clinical significance for the risk assessment, prevention, and treatment of radiation-induced side effects.

Application of fecal microbiota transplantation in anticancer therapy

FMT is administered orally by oral fecal capsules or invasively via colonoscopy, which has the advantage of being able to transplant the intact gut microbiota from the donor to the recipient, and the introduced microbiota has less competition with the recipient microbiota and has a more stable survival in the recipient's intestinal environment. In fact, FMT is currently the most straightforward and effective way to restore the recipient gut microbiota to optimal health[110,111], and the unique role of FMT in anticancer therapy is increasingly being discovered (Table 3).

FMT promotes the efficacy of anti-cancer therapy

FMT has been shown to enhance the effectiveness of anti-PD-1 therapy in a variety of cancers, with melanoma, colorectal cancer, and lung cancer being the most reactive. FMT form cancer donors who respond to ICIs can improve the sensitivity of melanoma mice to PD-1 blockers, while FMT in patients who do not respond to ICIs does not, which is associated with increased recruitment of CCR9CXCR3CD4 T cells by *Akkermansia muciniphila*, which restores the efficacy of PD-1 blockade in an IL-12-dependent manner[112], and in melanoma mice receiving FMT, enrichment of a large number of CD8 + T cells and CD45 + CD11b + Ly6G+ cells was found, accompanied by a decrease in inhibitory CD11b + CD11c+ myeloid cells, which enhanced the anti-tumor immune response[38]. For melanoma patients, FMT can also alter the gut microflora, influence the local immune system and inflammatory response, and reprogram the tumor microenvironment to overcome PD-1 blocker resistance. Subsequent studies have shown that stool of melanoma patients with a good response to PD-1 blockers is rich in *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*[113,114].

Table 3 | The positive role of fecal microbiota transplantation in anticancer therapy

Transplanted microbiota	Cancer type	Model	Mechanism	References
Fecal microbiota of cancer patients who respond to ICIs	Epithelial tumor of mouse	Epithelial tumor mouse model	*Akkermansia muciniphila*, by increasing recruitment of CCR9CXCR3CD4 T lymphocytes, restores the efficacy of PD-1 blocking in an IL-12-dependent manner.	112
Fecal microbiota in patients with ICIs-responsive melanoma	Melanoma	B6 germ-free mice and 112 melanoma patients	Mice receiving FMT showed an enrichment of $CD8^+$T cells and $CD45^+CD11b^+Ly6G^+$ cells, accompanied by a reduction in inhibitory $CD11b^+CD11c^+$ myeloid cells, which enhanced the anti-tumor immune response.	38
Fecal microbiota in healthy people/patients with new CRC (combined Pectin)	Colorectal cancer	C57BL/6 mice	FMT combined with pectin can significantly increase intestinal flora diversity in CRC mice, promote immune infiltration of T cells, and enhance anti-tumor immune response.	115
Fecal microbiota of healthy people	Colorectal cancer	CRC tumor-bearing mouse model	FMT increased *B. thetaiotaomicron* and *B. fragilis*, decreased *B. ovatus*, up-regulated metabolites such as punicic acid and aspirin, and enhanced anti-PD-1 therapeutic effect.	116
Fecal microbiota of 41 NSCLC patients	Non-small cell lung cancer	C57Bl/6 mouse lung cancer model	FMT has enabled the implantation of *Faecalibacterium* and increased SCFAs levels of butanoic acid, acetic acid and hexanoic acid, which can enhance the efficacy of immunotherapy.	117
Fecal microbiota in patients with ICIs-responsive NSCLC	Non-small cell lung cancer	C57Bl/6 mouse lung cancer model	The combination of FMT, ginseng polysaccharides, and αPD-1 monoclonal antibodies will reshape the immune microenvironment and reverse the non-responsiveness of immunotherapy.	118
Fecal microbiota of healthy people	CRE due to radiation therapy	5 patients with CRE	FMT can effectively improve intestinal symptoms and mucosal damage in patients with chronic radiation enteritis (CRE).	108
Fecal microbiota of healthy people	Melanoma and other 4 types of cancer	12 cancer patients (5 types)	FMT supplemented *Collinsella* and *Bifidobacterium*, reduced CD8 T cells, and inhibited the occurrence of immune-mediated colitis.	119
Fecal microbiota of healthy mice	Colorectal cancer	CRC mouse model	Based on the TLR-MyD88-NF-κB signaling pathway, FMT mitigated intestinal mucositis in chemotherapy-induced colorectal cancer mice.	120
Fecal microbiota of bladder cancer patients and healthy donors	Bladder cancer	Bladder cancer mouse model	FMT caused *Parabacteroides distasonis* colonization, increased $CD4^+$T and $CD8^+$T cells, and enhanced anti-PD-1 immunotherapy efficacy.	196
Fecal microbiota of healthy mice	Castration-resistant prostate cancer	Prostate cancer mouse model	FMT from healthy control mice can reduce TNF-α levels, inhibit the activation of TLR4/MyD88/NF-κB signaling pathway, and slow tumor growth.	197

FMT combined with pectin in healthy people/patients with newly diagnosed CRC significantly increased gut microbiota diversity in CRC mice increased the production of butyrate, promoted the immune infiltration of T cells, and enhanced the response of CRC mice to anti-PD-1 monoclonal antibodies[115]. FMT can also significantly improve the survival rate and tumor control ability of CRC mice treated with anti-PD-1, which may be related to the improvement of gut microbiota composition and the up-regulation of metabolites including punicic acid in mice with FMT. Increased abundances of *B. thetaiotaomicron* and *B. fragilis* and decreased abundances of *B. ovatus* were observed in mice treated with FMT[116].

FMT can also effectively delay the progression of advanced NSCLC and enhance the effect of immunotherapy, which is related to the implantation of *Faecalibacterium* and the increase of SCFA levels of butanoic acid, acetic acid, and hexanoic acid[117]. FMT, ginseng polysaccharides, and αPD-1 monoclonal antibodies (mAbs) were used to treat patients with small cell carcinoma of the lung to reshape the composition of gut microbiota and reverse the non-responders to responders, indicating that FMT can improve the sensitivity of tumor immunotherapy. The combination of FMT, ginseng polysaccharides, and αPD-1 monoclonal antibody will remodel the gut microbiota ecology of patients with pulmonary small cell carcinoma and reverse their non-responsiveness to immunotherapy alone[118].

FMT to control complications related to anticancer therapy

A 2020 clinical trial found that FMT was associated with remission of complications from anticancer therapy, with five patients with chronic radiation enteritis who received fecal microbiota transplantation from healthy donors had significant improvements in radiation side effects, including reduced blood in the stool and abdominal pain[108]. In addition, FMT also improved inflammatory bowel disease in cancer patients treated with ICI, and 92% of 12 patients with ICI-induced inflammatory bowel disease experienced remission after receiving FMT in healthy patients[119]. Triple therapy with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), a 5-FU-based chemotherapy regimen, is currently one of the most common treatment options for CRC, FMT restores the gut microbiota composition destroyed by FOLFOX without causing bacteremia and reduces the occurrence of intestinal mucositis[120].

Potential challenges and possible solutions for FMT applications

Although many studies have found that FMT plays an important role in anticancer therapy, there are still many challenges in its application. The first is the safety of FMT treatment, such as the transmission of unknown pathogenic microorganisms and pathogenic genes. Some studies have reported the infection events of patients after FMT, including viral infection and giant cell infection[121]. The use of FMT has been found to sometimes clear antibiotic-resistant bacteria from the gastrointestinal tract, complicated by norovirus gastroenteritis, acute graft-versus-host disease, and eosinophilic pancreatitis[122]. In 2019, a United States patient died of severe sepsis after receiving FMT treatment, United States the Food and Drug Administration suspended some clinical trials involving FMT until its safety profile was fully confirmed[123,124]. Two patients developed bacteremia by extend-spectrum beta-lactamase *Enterobacterales* (ESBL) after receiving FMT, and genomic sequencing revealed that both cases originated from the same donor[125]. Chuang et al. found that ESBL had a high carrying rate among healthy FMT donors. They screened 159 healthy patients for fecal screening and found that only 37 of them were qualified[126]. Another study reported adverse events in seven FMT patients due to foreign colonization of Shiga toxin-producing Escherichia coli (STEC)[127]. These studies support the effectiveness and importance of donor screening for FMT, which can be enhanced to limit the occurrence of similar events.

In addition, some unknown components in the donor's faecal preparations may lead to changes in the recipient's gut microbiota, which may induce chronic diseases, including obesity, autism, cardiovascular disease, and autoimmune diseases. For example, transplanting obese human feces into germ-free mice fed a low-fat diet induces obesity-related metabolic phenotypes[128]; Susceptibility to atherosclerosis may also be transmitted through FMT through the production of trimethylamine oxide (TMAO)[129].

Moreover, how to ensure the implantation status and function of microorganisms in the receptor after receiving FMT treatment is the key to FMT treatment, which is related to whether FMT treatment can bring sustainable benefits. It is generally believed that increasing the amount or frequency of FMT treatment may benefit sustained therapeutic effectiveness or improve implantation methods such as biocapsule and lyophilization[130]. Similarly, studies have shown that increasing the biological population richness of FMT also improves efficacy, with treatment with combined FMT products resulting in a higher overall microbial diversity of the recipient compared to FMT products from a single donor[131]. Compared with the improvement of the donor and FMT biologics, the preparation of the recipient before treatment is also crucial, and the success of implantation may depend on the compatibility or rejection between the donor and the recipient microbiota, so the gut preparation or antibiotic pretreatment of the recipient will be necessary[132].

It is also worth noting that the therapeutic effect of FMT varies among recipients. For example, FMT changes ICI treaty-induced colitis, and patients with greater ecological dysbiosis at baseline of intestinal flora have a greater response to FMT treatment. This result may be due to the greater ability of FMT-derived bacteria to transplant in malnourished hosts. Another possible pathophysiological factor driving colitis is microbiome dysregulation in patients with refractory immune-mediated colitis (IMC)[119]. This means that not all patients are suitable for FMT treatment, and this outcome may be improved by more systematic evaluation of patients before treatment. In addition, the current clinical studies on FMT generally have problems such as short follow-up time and lack of systematic research on potential confounding factors in the microbiome, which makes the persistence and repeatability of positive clinical reactions controversial. Therefore, a simple and quick detection method may be the key to solve these problems.

In summary, although FMT has made many advances in the field of cancer treatment, important challenges remain, and how to reduce receptor risk, improve the persistence of FMT therapy, and tailor treatment options to different patients are keys. Rigorous donor screening and isolation modalities may mitigate disease transmission due to FMT, but they cannot be completely eliminated for NCDS. However, changes in administration parameters such as frequency of administration, route of administration, and single or combined donor materials may determine treatment success.

Probiotics

Although FMT is currently the most direct method of remodeling the gut microbiota, complex microbiota stimulation increases the risk of intestinal injury and systemic acquired infections in patients. Compared with FMT, probiotic transplantation provides a more practical method for regulating gut microbiota in clinical treatment. Probiotics refer to a class of live microorganisms that are beneficial to the host by colonizing the human body and changing the composition of the microflora of a certain part of the host, and when given in appropriate quantities, provide a safe and beneficial effect on the health of the host. The earliest probiotic supplements were derived from single strains that were easy to culture, such as *Bifidobacterium* and *Lactobacillus*, which have shown remarkable results in treating many gastrointestinal disorders[133–135].

Probiotics are adjunct agents for anticancer therapy

Probiotics have shown great support on the road to adjuvant cancer treatment. Both prophylactic and therapeutic oral administration of *Lacticaseibacillus rhamnosus Probio-M9* has shown remarkable efficacy in ICI therapy in controlling tumor growth, producing beneficial metabolites in the gut including butyric acid, alpha-ketoglutaric acid, n-acetyl-L-glutamate and pyridoxine. Promote the infiltration and activation of cytotoxic T lymphocytes (CTL), inhibit regulatory T cells (Tregs) in tumors, and enhance immunotherapy response[136]. By colonizing melanoma, *Lactobacillus rei* can release aromatics receptor (AhR) agonist indole-3-aldehyde (I3A), thereby activating interferon-γ-producing CD8 + T cells and

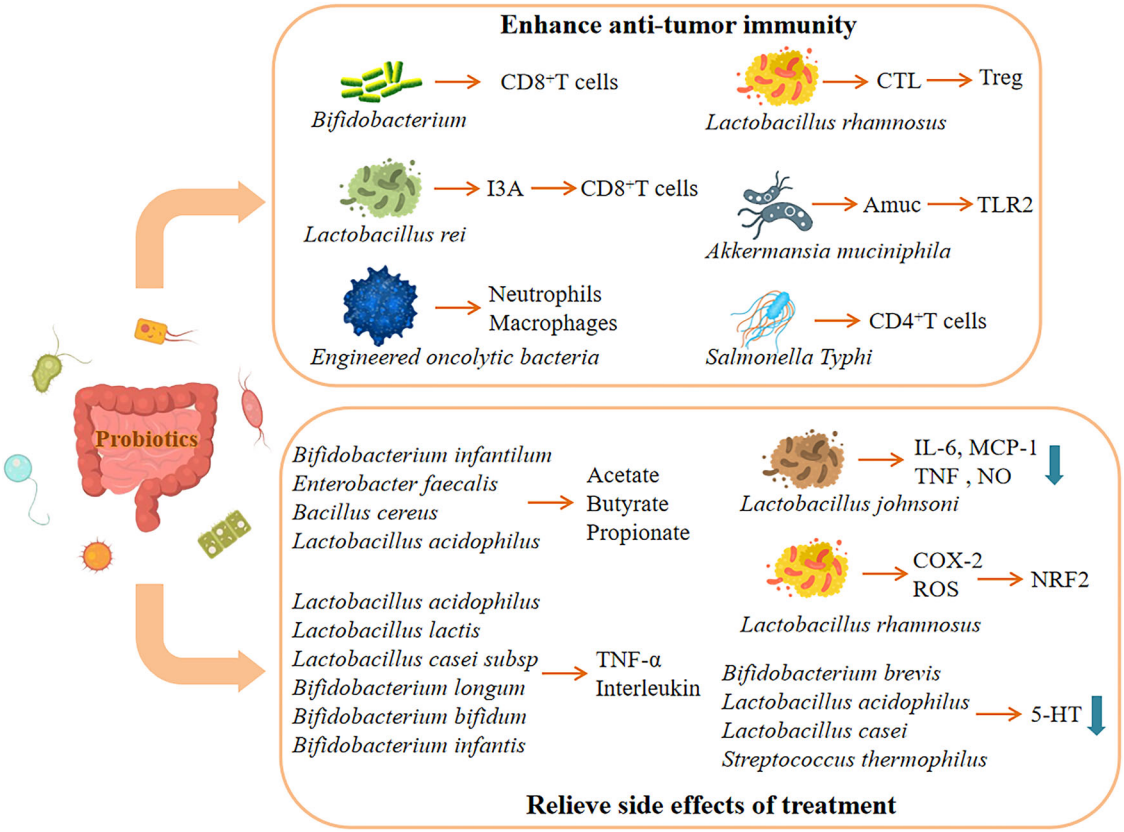

Fig. 3 | Specific mechanisms of parasite involvement in anticancer therapy. Intestinal parasites have a profound effect on the anticancer process, including improving the body's anti-tumor immunity and reducing related complications. This figure shows the specific mechanism.

enhancing the treatment response of melanoma patients to ICIs[137]. Amuc, the outer membrane protein of the symbiotic probiotic *Akkermansia muciniphila*, mediates its anti-tumor response by activating the TLR2 signaling pathway, enhancing the efficacy of IL-2-based immunotherapy for melanoma and colorectal tumor-bearing[40]. Intravenous injection of *Engineered oncolytic bacteria* can increase the level of pro-inflammatory cytokines in tumor tissue to increase tumor immunogenicity, recruit neutrophils and macrophages, and enhance immune activation response[138]. A study evaluating the inhibitory effect of the orally administered *Salmonella Typhi* vaccine strain (CVD 915) on liver metastasis in mice with breast cancer found that the oral vaccine increased CD4 + T cell and dendritic cell populations, The number and volume of liver metastases were reduced[139]. Engineered symbiotic Escherichia coli specifically binds to heparan sulfate proteoglycan on colorectal cancer cells and secretes the enzyme myrosinase, which converts glucosinolates ingested by the host into sulforaphane. Sulforaphane has anticancer activity, showing significant tumor regression and reduction in tumor incidence in mouse models of colorectal cancer[140]. Oral administration of probiotic *Bifidobacterium* enhanced anti-tumor immunotherapy response in melanoma mice. The combination of probiotics and PD-L1-specific antibodies can significantly eliminate tumors, and the related mechanism is related to the activation and accumulation of CD8 + T cells in the tumor microenvironment due to the enhanced function of dendritic cells[34] (Fig. 3).

Rational use of probiotics can alleviate complications related to anticancer therapy

For potential complications caused by anticancer therapy, the colonization of probiotics has also played a certain clinical benefit. The administration of *Lactobacillus acidophilus* LAC-361 and *Bifidobacterium longum* BB-536 can alleviate the diarrhea caused by radiotherapy in patients with pelvic cancer[141]. CRC patients who received oral treatment with *Lactobacillus johnsoni* during the perioperative period had significantly fewer intestinal complications because *L. johnsoni* adheres to the colon mucosa, reduces the concentration of pathogens in the stool, regulates local immune function, and lessens the release of pro-inflammatory mediators such as IL-6, MCP-1, TNF, and nitric oxide[142]. A probiotic formulation composed of *Bifidobacterium infantilum*, *Lactobacillus acidophilus*, *Enterobacter faecalis*, and *Bacillus cereus* can regulate the imbalance of gut microbiota and its metabolites caused by chemotherapy, increase the levels of acetate, butyrate, and propionate in the body, and effectively reduce the gastrointestinal complications caused by chemotherapy[143]. A study also used probiotics composed of *Bifidobacterium infantilum*, *Lactobacillus acidophilus*, *Enterobacter faecalis*, and *Bacillus cereus* to administer to gastric cancer patients after surgery, and found that probiotics could enhance tumor immune response and reduce local inflammatory response[144]. A probiotic compound (consisting of *Lactobacillus plantarum* MH-301, *Lactobacillus rhamnosus* LGG-18, Lactobacillus acidophilus, and *Lactobacillus animalis bifidobacterium* LPL-RH) has been shown to effectively reduce postoperative inflammation in gastric cancer, enhance immunity, and restore gut microbiota composition. In vivo experiments in rats have shown that it can down-regulate the inflammatory and permeability signaling pathways in intestinal tissue, and restore the gut microbiota disorder after gastrectomy in rats[145]. Six kinds of probiotic mixed preparations (including *Lactobacillus acidophilus*, *Lactobacillus lactis*, *Lactobacillus casei subsp*, *Bifidobacterium longum*, *Bifidobacterium bifidum* and *Bifidobacterium infantis*) were used in patients with colorectal cancer after surgery longum, bifidum and Bifidobacterium infantis significantly reduced the levels of pro-inflammatory factors (TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-17C and IL-22, etc.), thereby reducing the complications associated with anticancer therapy[146]. In a study of advanced nasopharyngeal carcinoma patients treated with a probiotic mixture (consisting of animal bifidobacterium subspecies Lactis *LPL-RH*, *Lactobacillus rhamnosus* LGG-18, and *Lactobacillus acidophilus*), oral probiotic mixtures reduced the incidence of oral mucositis compared with controls. The mechanism is related to decreased rates of CD3 T cells, CD4 T cells, and

CD8 T cells[147]. *Lactobacillus rhamnosus* (LGG) reduces the toxic side effects of chemotherapy and radiotherapy on intestinal mucosa. Studies have shown that in mouse models, LGG induces reactive oxygen species (ROS) by transferring cyclooxygenase-2 (COX-2) expressing cells on intestinal villi to the base of intestinal crypts, activating the cell protective NRF2 (nuclear factor-erythroid 2-related factor-2) pathway[91]. A probiotic mixture (*Bi*do-bacterium brevis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Streptococcus thermophilus*) alleviated cisplatin treaty-induced mucositis and pica in mice by reducing intestinal pheochromocytoma secretion of 5-HT and restoring chemotherapy-induced changes in gut microbiota[148] (Fig. 3).

Challenges in the application of probiotics in cancer therapy

Probiotics have shown promise in the treatment of various cancer types and the prevention of complications associated with anti-cancer treatment, however, there are still challenges associated with the practical application of probiotics as anti-cancer treatment options. First, the efficacy of probiotics in preclinical studies and clinical applications may not be consistent. The study found that people treated with probiotics had only a temporary improvement in gut microbiota concentration, not a long-term effect[149]. Inconsistencies in the manufacturing process and storage conditions of probiotics can also affect their quality, which may lead to differences in clinical results. Therefore, strengthening quality control in the production process of probiotics is crucial for the effectiveness of probiotic products.

In addition, since probiotic products can be classified as dietary supplements, food additives or drugs, regulatory issues arise in their application process, which likewise limits the use of probiotic products[150]. And the live bacteria in probiotics or certain types of prebiotics may conflict with certain cultural or religious beliefs, which will also pose challenges in the development and application of their related products. In addition to this, due to factors such as taste, convenience, and cost, the use of probiotics may be limited due to poor patient compliance. One study found that the effects of short-term probiotic interventions on changes in the gut microbiota may be temporary, and some specific individuals or diseases may require longer treatment durations to achieve therapeutic effects[151]. Therefore, the integration of probiotic-related products into healthcare initiatives may promote overall health and minimize the burden on the healthcare system.

The interaction between microorganisms and individual differences between patients also affect the efficacy of probiotics, which may depend on the ability of different populations to absorb probiotics, the composition of intestinal flora and the type of cancer[152,153]. In clinical application, the selection of the most suitable strain for a specific situation requires more thorough research and evaluation, therefore, the strain of probiotics and the relevant factors such as the dosage need to be standardized when using, which also affects the results of comparative studies and the determination of the best treatment[154]. In addition, the safety of probiotics is also widely concerned; its use may be limited in patients with impaired or deficient immune function, critically ill patients, and children. Probiotic strains may be a causative factor in immunocompromised subjects, including systemic infections, metabolic abnormalities, and immune disorders[155–157].

Therefore, before a probiotic is developed for use, complete in vivo and in vitro safety studies should be established to ensure the health of subjects. The current direction of probiotics development should focus on personalized and targeted therapies, and advances in metagenomics and bioinformatics may be able to better help researchers understand the complex interactions between probiotics and host health, thus facilitating the development of diversified therapies.

Dietary habits-mediated changes in gut microbiota and their effects on cancer

Diet is the most accessible external factor of the gut microbiota in human daily life, and long-term dietary structure plays a crucial role in determining the composition and function of the gut microbiota, and the interaction between the two determines whether they are beneficial or harmful to the health of the host[158].

Dietary fiber is the protagonist in regulating the gut microbiota

Supplementation with dietary fiber, such as fructan and galactooligosaccharide, alters the composition of the gut microbiota, increases the abundance of bifidobacteria and lactobacillus, metabolizes the production of large amounts of butyrate, and inhibits colorectal cancer. Specifically, the accumulated butyrate acts as a histone deacetylase (HDAC) inhibitor, stimulates histone acetylation, and affects apoptosis and cell proliferation, exerting tumor-suppressive properties[159]. Dietary fiber also prolonged the progression-free survival (PFS) of melanoma patients treated with anti-PD-1, and some subjects increased the diversity of microbial α in their gut microbiota and the abundance of *Rumen coccaceae* and *Faecobacterium* species after eating high dietary fiber, and preclinical experiments showed that dietary fiber had no obvious gain effect in germ-free mice, which indicated that it had achieved an effect in the immunotherapy of cancer mice by regulating the gut microbiota[160]. Spinach contains 2.2 grams of dietary fiber per 100 grams, and eating spinach can increase the production of butyric acid, a metabolite of the gut microbiota, which, as mentioned above, plays a beneficial role in the treatment of cancer[161,162]. Inulin is a natural water-soluble dietary fiber that can hardly be hydrolyzed and digested by gastric acid and is only used by beneficial microorganisms in the colon, thereby improving the intestinal environment. Inulin can increase the beneficial flora of the gut microbiota such as *Akkermansia*, *Lactic acid bacteria*, and *Roseburia*, thereby activating whole-body memory T cells and enhancing the immunotherapy response of α-PD-1 to C57BL/6 mice harboring MC-38 colon cancer and B16F10 melanoma[163]. The results of related studies using polylactic acid-polyethyleneimine (PLA-PEI) and hyaluronic acid-inulin (HA-IN) loaded on the nanoparticles of the chemotherapy drug paclitaxel in the treatment of colon tumors have shown that it can accurately guide and prolong the action time of the drug in tumor cells, enhancing the therapeutic effect[164]. Pectin is also high in dietary fiber (FD) and regulates the gut microbiota of mice. Studies have shown that oral pectin can enhance anti-tumor IBC therapy in mice (models of mass lymphoma, breast cancer, colon cancer, and melanoma) by affecting the gut microbiota of *Akkermansia*[165].

Other dietary characteristics

Resistant starch is a kind of starch that cannot be absorbed and utilized by the small intestine of healthy people, but can be fermented or partially fermented by coliform bacteria (such as *Bifidobacterium*, *Akkermansia*, and *Megasphaera*) in the colon and has physiological functions such as maintaining intestinal morphology, promoting intestinal peristalsis, increasing fecal volume and moisture content, regulating immunity and anti-tumor[166]. The combination of resistant starch and *Arabinoxylan* increases the abundance of bifidobacterium, reduces the abundance of other harmful bacteria in gut microbiota, increases the concentration of SCFAs in the intestinal tract, and enhances the efficacy of anticancer treatment for colorectal cancer[167]. The type and amount of protein in the diet can also affect the composition of the gut microbiota, for example, casein is a growth factor for *Lactobacillus* and *Bifidobacteria*, which, as mentioned earlier, are beneficial for anti-cancer treatments[168]. Nitrate and inorganic sulfur are often used as preservatives in processed meat, and they are metabolized into carcinogens such as nitroso compounds and hydrogen sulfide with the participation of sulfur-reducing bacteria such as *Clostridium* in the gut. Regular consumption of such meat increases the risk of colorectal cancer in the elderly[169,170]. A high-salt diet can change the composition of gut microbiota, increase the abundance of *Bifidobacterium* and the level of metabolite hippurate, which enhances the ability of NK cells to kill tumor cells, improves the efficacy of anti-PD-1 antibody-related tumor immunotherapy, and provides ideas for enhancing tumor immunotherapy[171]. The high-fat/high-cholesterol diet can disrupt the stability of gut microbiota, resulting in a sequentially increased number of *Muconcus*, *Desulphuricobacteria*, *Anaerobic bacteria* and *Desulphuricobacteriaceae* in the gut microbiota of mice, while the abundance of *Bifidobacteria* and *Bacteroides* decreased, and the metabolic product of gut microbiota 3-indole propionic acid was reduced, which hurts the immunotherapy of cancer[172]. In one

study, the oral formulation of the chemotherapeutic drug capecitabine, composed of the prebiotic xylan-stearic acid conjugates with cap nanoparticles, acted on mice with colorectal cancer, delaying the metabolic rate of chemotherapeutic drugs in mice. This prebiotic conjugate increases the abundance of the gut microbiota of *Ackermania* and *Faffia cup* and the concentration of the gut microbiota metabolite SCFA, which is more beneficial for the treatment of cancer[173]. Ellagitannin is the active compound of polyphenol-rich berry camms. Studies have shown that oral ellagitannin can regulate *Rumen micrococcus* in the gut, increase its abundance, and improve the CD8+/FOXP3 + CD4+ ratio in the tumor microenvironment, thereby improving the resistance of αPD-1 in a mouse model of E0771 breast cancer tumor[174].

Summary and challenges

The gut microbiota is known as the "second genome" of the human body, and the intestinal microecosystem it consists of plays a key role in various physiological links of the human body through its interaction with the host. There is a large amount of evidence that the gut microbiota is closely related to the occurrence and development of various types of cancer, such as CRC, HCC, BC, and PC, and scientists regard the imbalance of gut microbiota as an important marker of cancer[175–177]. In our previous research, we have profoundly explored the multifaceted mechanisms of gut microbiota influencing human cancer[177]. Compared with the human genome, the gut microbiota does not fulfill an extremely wide range of biological functions; however, it is difficult to alter certain biological processes in the human body by regulating the human genome, especially for complex pathological changes such as cancer, where the gut microbiota may be more feasible. Therefore, this review focuses on the multifaceted impact of the gut microbiota on cancer treatment (Table 4).

While certain intestinal colonized microbiotas may be involved in the development of cancer, it is important to note that many beneficial microbiotas also play a vital role in the body's defense against cancer. In the course of our discussion, we mentioned the harmful microbiotas that contribute to cancer development and hinder anti-cancer treatment, including *Clostridium*, *Enterobacter*, *Enterococcus*, *Bacteoidetes*, and *Ruminococcus*. Relative beneficial microbiotas are also mentioned, including *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Fecalibacterium*, *Eubacterium*, *Roseburia*, *Ruminococcus*, and *Blautia*. As the protagonists of gut microbiota, their richness and colonization area greatly affect the occurrence and treatment of cancer, and it is an important research goal in the future to accurately control the existence of each or several microbiota in different patients. In addition, we have already explored the effects of diet on the gut microbiota, however, medications, the patient's living environment, and other underlying diseases also directly affect the composition of the gut microbiota, which makes it difficult to manipulate the microbiota, and perhaps there will be more stable ways to maintain the control of the gut microbiota in patients in the future.

Happily, novel therapies based on gut microbiota are also gradually playing a role in cancer treatment. For example, endostatin gene therapy delivered by oral attenuated *Salmonella typhimurium* has shown therapeutic anti-tumor effects in mouse tumor models[178]; A strain of *Salmonella typhimurium* called ST8 has high levels of accumulation in tumors and rarely spreads to the extraneoplastic anaerobic zone. The therapeutic plasmid encoding endostatin carried by ST8/pSEndo is fused with the secreted protein SopA, which can target the peritumor blood vessels, stably maintain and safely deliver the therapeutic vector, and release angiogenesis inhibitors through the type III secretion system (T3SS), thereby achieving anti-tumor effects[179].

In conclusion, there is still a big gap in the mechanism of action of gut microbiota in the occurrence and development of cancer and the regulation of anti-cancer treatment, which will greatly improve the treatment effect of cancer patients, improve the prognosis, and provide the impetus for the era of precision treatment.

Table 4 | Effects of gut microbiota on radiotherapy, chemotherapy and immunotherapy for cancer

Treatment	Gut microbiota	Assistance/Interference	Research model	Mechanism	References
Radiotherapy	*Lactobacillus rhamnosus*	Assistance	Whole-body irradiated C57BL/6 mice	Transfer mesenchymal stem cells to the base of the crypt to protect the intestine from radiotherapy-induced cell damage	91
	Lachnospiraceae and Enterococcaceae	Assistance	C57BL/6 J mice exposed to whole body radiation of 8.0 to 9.2 Gy	Propionate and tryptophan are produced to alleviate the damage of radiation to the gastrointestinal tract and hematopoietic function	92
	Clostridium type IV, Rothella, and Koala bacillus	Interference	Patients with radiation bowel disease	Reduces intestinal mucosal homeostasis factors, leading to the occurrence of radiation intestinal disease	97
	G^+ bacteria sensitive to vancomycin	Interference	C57BL/6 J mice exposed to radiation of 21 Gy	Vancomycin enhances radiation-induced anti-tumor immune responses after elimination of gram-positive bacteria	102
	Bacteroidetes	Interference	C57BL/6 mice receiving chest irradiation	After the elimination of this bacteria with phycocyanin, radiation pneumonia and pulmonary fibrosis were alleviated	101
Chemotherapy	Cyclophosphamide	*Lactobacillus johnsonii*	Assistance	C57BL/6 colorectal cancer mice	Leads to the transformation of naïve T cells to TH17 and induces the production of INF by CD8 + T cells	74
		Lactic acid bacteria and Bifidobacteria	Assistance	Mice treated with CTX	Increase the level of short-chain fatty acids, decrease ammonia concentration, increase mucin expression and goblet cell count, and alleviate intestinal mucosal injury	73
	Cisplatin	*Lactobacillus*	Assistance	Lung cancer mice	Regulate the expression of VEGFA, Bax, CDKN1B and other genes to enhance adaptive immune response	75

Table 4 (continued) | Effects of gut microbiota on radiotherapy, chemotherapy and immunotherapy for cancer

Treatment		Gut microbiota	Assistance/Interference	Research model	Mechanism	References
	5-Fluorouracil	*Lactobacillus plantarum*	Assistance	Human colorectal cancer cell line HT-29, HCT- 116	Amplifies the cytotoxicity of 5-FU by reducing the number of stem-like cancer cells	84
		Lactobacillus casei YIT 9018	Assistance	BALB/c mice model	As a nonspecific immunostimulant, reduces the lethal toxicity of 5-FU	198
		Escherichia coli	Interference	Female thymus free nude mouse and HCT-116 cell	It releases dihydropyrimidine dehydrogenase which converts 5-FU to inactive dihydrofluorouracil	89
	Oxaliplatin	*Fusobacterium nucleatum*	Interference	Human colorectal cancer cell line	Drug resistance is induced by activating the expression of TLR and microRNA18a	87
	Gemcitabine	*Gammaproteobacteria*	Interference	BALB/c colorectal cancer mice	Secretes the bacterial enzyme cytidine deaminase (CDDL), metabolizing gemcitabine from the active form to the inactive form	85
	Irinotecan	Bacteria that produce beta-glucuronidase	Interference	Mice given Irinotecan	The bacteria dissociates SN-38G into SN-38, inducing delayed diarrhea	199
Immunotherapy	CTLA-4 inhibitor	*Bacteroides*	Assistance	MCA205 Fibro sarcoma mice	Enhances IL-12-dependent TH1 immune response	43
		Firmicutes	Interference	26 melanoma patients	Induce CD4 + T cells, increase the number of CD25, and aggravate the toxic side effects	46
		Akkermansia muciniphila	Assistance	Lymphoma GF mice model	Transform mononuclear phagocytes in TME into immune-stimulated monocytes and Dirk	165
		Bifidobacterium pseudolongum	Assistance	CRC mice model	TH1 cell activation is promoted through the T cell-specific A2AR signaling pathway	200
	PD-1 inhibitor	*Bifidobacterium*	Assistance	C57BL/6 mice model	Recruit DCs to activate CD8 + T cell responses in the tumor microenvironment	34
		Akkermansia muciniphila	Assistance	MCA-205 sarcoma, RET melanoma mice model	Increase the recruitment of CCR9 + CXCR3 + CD4 + T lymphocytes in tumor tissues to restore the efficacy of PD-1 blockers in an IL-12-dependent manner	112
		Akkermansia muciniphila	Assistance	C57BL/6 J mice	Induce IgG1 and antigen-specific T cell responses to enhance the efficacy of anti-PD-1	39
		Bifidobacterium longum, Enterococcus faecium	Assistance	42 melanoma patients, GF mice model	Recruit DC cells, increase TH1 response, reduce Treg cells, enhance T cell response, and improve the efficacy of anti-PD-1 therapy	114
		Clostridium, ruminococcus, and Faecalis	Assistance	112 melanoma patients	Increases antigen presentation-mediated anti-tumor immune response and improves effector T cell function	38
	CD47 inhibitor	*Bifidobacterium*	Assistance	Bearing cancer mice model	Stimulates the STING signaling pathway to increase the cross-primer of DC	201
	CD19-CAR-T cell therapy	*Megasphaera massiliensis*	Assistance	C57BL/6 mice injected with PancOVA cells	The resulting SCFAs increase the biological activity of mTOR, upregulate CD25, IFN-γ and TNF-α, and enhance the antitumor activity of CAR-T cells	55
	Tim-3	*Enterococci and Lactobacillus*	Assistance	Patient with lung cancer	Changing the composition of intestinal ecology restores the effect of Tim-3 blockade	56
	CpG-ODN	*Ruminococcus obeum and Alistipes*	Assistance	Germ-free C57BL/6 mice	Enhance the activation effect of CpG-ODN on TNF-α and IL-12	59

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

J.S., S.S., and J.L. were the first author, to collect data, drafting and revising the manuscript. C.F., X.li and W.G. design research direction provide writing guidance and participate in the manuscript revision and supplement. All authors have agreed to the version of the manuscript for this release and have agreed to work on their respective aspects.

Competing interests

The authors declare no competing interests.

Additional information

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