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Review Article

The interaction between gut microbiome and anti-tumor drug therapy

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Abstract: A large number of symbiotic gut microbiome exists in the human gastrointestinal micro-ecosystem. The daily diet, lifestyle, and body constitution influence the type and quantity of gut microbiome in the body. Increasing evidence demonstrates that the gut microbiome can affect tumor development and progress. We discuss in this paper how the gut microbiome impacts tumor pathology through DNA damage, production of dietary and microbial metabolites, altered cellular signaling pathways, immune system suppression, and involvement in pro-inflammatory pathways changing gut microbiome composition. The gut microbiome acts on different types of the anti-tumor drug through bacterial translocation, immuno-modulation, metabolic modulation, enzymatic degradation, and reduction of microbial diversity. This article summarized the aforementioned by reviewing recent studies on the interaction among the gut microbiome, tumor development, and antitumor drugs.

Keywords: Gut microbiome, antitumor drugs, tumors, therapy

Introduction

The micro-ecosystem of the human body includes the oral cavity, skin, urinary tract, and gastrointestinal tract, which is the most complex intestinal micro-ecosystem. Nearly 100 trillion bacteria inhabit the human intestine. The dominant gut microbial phyla are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* [1]. In the slow process of evolution, the gut microbiome has reached a harmonious and mutually beneficial symbiotic relationship with humans. The gut microbiome in the body is inextricably linked to the various physiological and pathological changes in the entire life cycle of human beings. The changes in the type and quantity of gut microbiome in the body are due to differences in age and gender [2]. Moreover, external factors such as diet [3], geographic environments, and living habits [4] exert varying degrees of effect on the gut microbiome in the body. The balance and imbalance of the gut microbiome are closely related to human health. Gut microbiome imbalance in the body can lead to diseases, such as inflammatory bowel disease [5], gastric cancer [6], breast cancer [7], liver cancer [8], and colon cancer [9].

The tumor is a type of disease that seriously endangers human life and health. According to the 2021 World Health Organization Global Oncology Report, cancer is the second leading cause of death among people aged 30-69 in most countries. Globally, the number of new cancer cases annually is expected to increase from 18 million in 2018 to 27 million in 2040, reflecting a 50% increase. The growth rate of new cancer cases in developing countries is also higher than that in developed countries. Cancer death is affected by various factors, such as age, environment, diet, and living habits. Primary antitumor treatment methods currently include surgery, chemotherapy, radiation therapy, hyperthermia, and immunotherapy. However, these commonly used treatments can cause damage to the body. Clinical studies

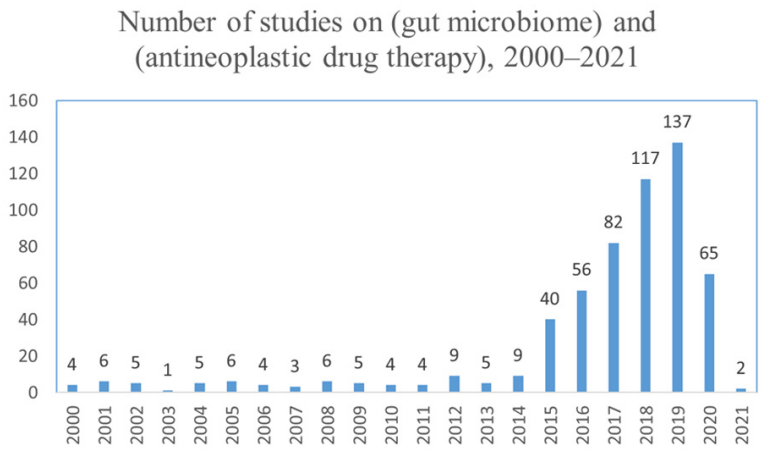

Figure 1. Number of documents published from 2000 to 2019 by Pubmed search using the keyword "antineoplastic drugs therapy and the gut microbiome".

have indicated significant differences in the type and number of intestinal microbes between cancer patients and healthy individuals. This difference is closely associated with the occurrence and development of the disease [10]. The number of studies on the gut microbiome and antitumor drug treatment has been increasing in recent years (**Figure 1**). These gut microbiomes are known to induce tumors in various models. However, the bacteria that play a key role in the occurrence and progress of each tumor, as well as the method by which gut microbiomes act on tumors and affect the occurrence and development of tumors have yet to be clarified. Understanding the interaction between the gut microbiome and the antitumor drug can elucidate the role of the gut microbiome in antitumor drug therapy, affect the occurrence and development of tumors, and discover novel antitumor drug targets to further optimize tumor treatment strategies. Therefore, this article reviews recent studies concerning the effect of the gut microbiome on the occurrence and development of tumors, as well as the interaction between the gut microbiome and antitumor drug therapy (**Figure 2**).

The effect of the gut microbiome on tumors

Preliminary research shows that in an acidic mineral water environment, the microbes themselves or their communities adjust the interaction between microbial communities via nitrogen metabolism, fatty acid metabolism, and polyamine metabolism, and so on, to achieve an improved environmental adaptation. This further reflects the view that not to mention the delicate environment in the human body, it is apparent that the gut microbiome and its micro-ecological environment will form complicated interactions [11]. Besides, studies on the potential of the gut microbiome and host metabolism have shown that dietary fiber metabolism, short-chain fatty acid metabolism, host-derived substrate metabolism, hydrogen metabolism, and vitamin synthesis occur in the host [1, 12, 13]. Therefore, when a tumor occurs and develops, the microenvironment of the gut microbiome changes, and the intestinal bacteria themselves or between the communities exert different effects on the tumor. These effects mainly induce DNA injury, diet and microbial carcinogenic metabolites, changes in cell signaling pathways, and immune system suppression and participation in proinflammatory pathways [14] (**Table 1**). A study on the interaction between the gut microbiome and tumor contributes to further research on antitumor drug treatment targets and new strategies.

Induction of DNA damage

DNA damage is an occurrence in which the DNA nucleotide sequence is permanently changed during DNA replication and leads to alterations in genetic characteristics. When DNA damage exceeds the ability of the host cell to repair, cell death or carcinogenic mutations can occur [14]. Bacterial toxins can directly or indirectly induce DNA damage in host cells.

Maddocks OD et al. found that in colorectal cancer, *Escherichia coli* can induce the complete exhaustion of host cell DNA mismatch repair (MMR) protein by secreting the effector protein EspF and relying on EspF mitochondrial targeting. Depletion of MMR protein can also be induced by increasing the reactive oxygen species (ROS) levels in host cells, independent of EspF. Simultaneously, *E. coli* infection can

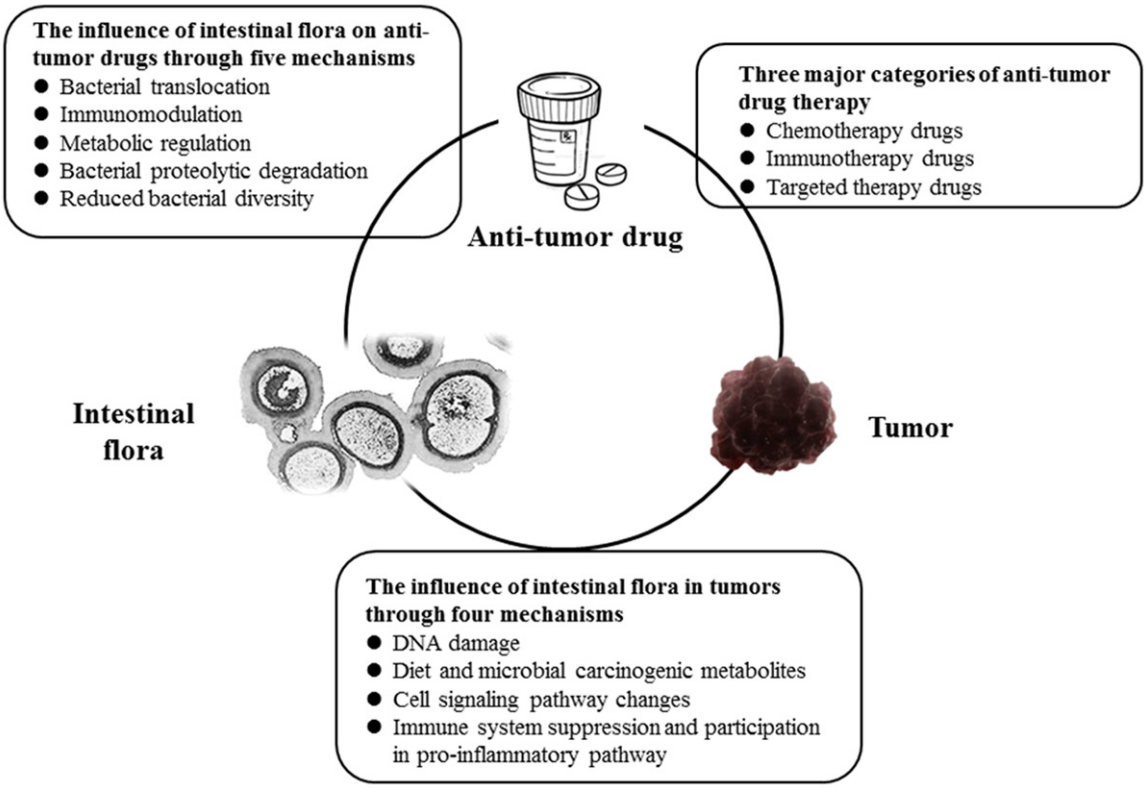

Figure 2. Diagram of the interaction of gut microbiome, tumors, and antitumor drugs. The gut microbiome affects the occurrence and development of tumors via four mechanisms, including DNA damage, diet and microbial carcinogenic metabolites, changes in cell signaling pathways, and immune system suppression and participation in pro-inflammatory pathways. The gut microbiome affects antitumor therapy drugs via bacterial translocation, metabolic regulation, bacterial protease degradation, and bacterial diversity reduction. Antitumor drug therapy is divided, based on the mechanism of action, into three categories: chemotherapy drugs, immunotherapy drugs, and targeted therapy drugs.

increase the mutation frequency of microsatellite instability(MSI) unstable sites [15]. The zinc-dependent *Bacteroides fragilis* toxin (BFT) secreted by *Bacteroides fragilis* (ETBF) binds to the receptors of tumor epithelial cells and induces the colonic epithelium by activating the H2A histone family member X, the promoter of DNA repair. By inducing the anti-apoptotic protein (cIAP2) and the polyamine catalyst spermine oxidase, which triggers ROS generation, DNA damage, and tumor cell proliferation [16]. *Helicobacter pylorus* is a typical bacterium that causes gastric cancer. It can induce DNA damage via oxidative stress and lead to gastric cancer [17].

These results support the hypothesis that *A/E E. coli* can promote colorectal carcinogenesis in humans by MMR. And the Clostridium clusters are the dominant regulators in the production of deoxycholic acid (DCA), which causes DNA damage and induces hepatic stellate cells to release proinflammatory cytokines and promote HCC development. co-colonization of the susceptible host with ETBF the potential for critical interactions in DNA mutations, cell signaling, and pro-carcinogenic inflammation known to be highly relevant to the promotion of human colon cancer.

Diet and the production of microbial carcinogenic metabolites

Diet influences the composition of the gut microbiota in the host. Moreover, daily diet and digested components can be metabolized by gastrointestinal microbes to produce various metabolites, which affect physical health to varying extents.

Dalmasso G et al. proved that in colorectal cancer, polyketide synthase-positive *E. coli* can

Table 1. Recent study on the mechanism of gut microflora on tumor

Cancer type	Bacteria	Model system	Possible mechanisms	+/-	Ref
Colorectal cancer	Fusobacterium nucleatum	HCT116 human colon cancer cells	Binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration	+	[32]
		CRC tissue	suppress antitumor immune responses by decreasing CD4+ T-cell density and TOX expression in the progression of colorectal cancer	+	[28]
		mice (C57BL/6-Apc$^{Min/+}$, BALB/c Il-10$^{-/-}$, and BALB/c T-be$^{-/-}$ xRag2$^{-/-}$)	Modulates the Tumor-Immune Microenvironment (increase of DCs, CD103+, treg, th17, TAMs, and so on)	+	[33]
		CRC tissue	increasing the expression of inflammatory mediators through a possible miRNA-mediated activation of TLR2/TLR4	+	[26]
		CRC cell lines (HCT116, HT29, LoVo, SW480) APC$^{Min/+}$ Mouse	Activating Toll-Like Receptor 4 Signaling to Nuclear FactorLkB, and Up-regulating Expression of MicroRNA-21	+	[27]
		CRCcell lines (HCT116, DLD1, SW480, HT29, and RKO, HCT116 β-catenin$^{-/-}$ cell line); nude mice	modulating E-cadherin/β-catenin signaling via its FadA adhesin	+	[19]
		The human CRC cell lines SW480 and HCT116 and the mouse CRC cell line CT26; APC$^{Min/+}$, CARD3$^{-/-}$ and CARD3^{wt} C57BL mice	the Upregulation of CARD3 Expression	+	[23]
		CRC cell lines (HCT-116, LoVo)	upregulated KRT7-AS/KRT7 by activating NF-κB pathway	+	[24]
		U937 cells; human stool and CRC tissue	Autoinducer-2 induced macrophage M1 polarization by activating the TNFSF9/IL-1β pathway	+	[31]
		C57BL/6-Apc$^{Min/+}$ mice; The mouse macrophage cell line RAW 264.7	promoting M2 polarization of macrophages through a TLR4-dependent mechanism	+	[25]
	Bacteroides fragilis	CRC tissues; CRC cell lines (HCT116 and DLD-1)	the RHEB/mTOR pathway	+	[18]
	Bifidobacterium bifidum	C57BL/6 mice	increased the relative abundance of Akkermansia, Desulfovibrionaceae, Romboutsia, Turicibacter, V errucomicrobiaceae, Ruminococcaceae_UCG_013, Lachnospiraceae_UCG_004, and Lactobacillus. altered metabolites involved in the citrate cycle, glycolysis, butyrate metabolism, fatty acid biosynthesis, and galactose metabolism	-	[34]
	Clostridium butyricum	Apc$^{min/+}$ mice	inhibit intestinal tumor development by modulating Wnt signaling and gut microbiota	-	[20]
		C57BL/6 mice	regulate structure and composition of gut microbiota and reduces colitis associated colon cancer in mice, the mechanism may be inhibiting NF-κB pathway and promoting apoptosis		[21]
	E. faecalis	Young adult mouse colonic (YAMC) epithelial cells, murine macrophage RAW264.7 cells, and HCT116 human colon cancer cells; NOD/scid mouse	repetitive exposure of primary colonic epithelial cells to commensal-polarised macrophages, or the endogenous clastogen 4-HNE, induced CIN, caused transformation via BSE, increased expression of tumour stem cell and stem/progenitor-like markers, and led to the formation of poorly differentiated and invasive tumours in immunodeficient mice	-	[10]
	Gut microbiome	CLM mice	decreased mouse colon cancer CT26 cell liver, increases of Firmicutes and Proteobacteria, decreased T regulatory cells and increased natural killer T cells and T helper 17 cells, accordingly decreased IL-10 and increased IL17 secretion in CLM mice liver	+	[17]
	Enteropathogenic Escherichia col	CRCcell lines (HT29 and SW480)	Depletion of DNA Mismatch Repair Proteins	+	[6]

	Pks+E. coli		induces cellular senescence characterized by the production of growth factors that promote the proliferation of uninfected cells	+	[9]
Breast cancer	Gut microbiome	MCF7, SKBR-3, and 4T1 cells; Balb/c mice	Lithocholic acid depend on oxidative stress brought about by the downregulation of the NRF2/Keap1 system and the induction of iNOS, and nitrosative stress	-	[14]
			activates estrogen as a component of estrogen-like substances that activate estrogen	+	[13]
Gastric cancer	Helicobacter pylori		Oxidative stress results in DNA damage	+	[35]
Liver cancer	Gut microbiome	SPF C57BL/6 and BALB/c mice	uses bile acids as a messenger to regulate chemokine CXCL16 level on liver sinusoidal endothelial cells (LSEC) and thus controls the accumulation of CXCR6+ hepatic NKT cells	-	[15]
		C57/BL6 mice; Tlr2$^{-/-}$ mice	driven COX2 pathway produced the lipid mediator PGE2 in senescent HSCs in the tumor microenvironment	+	[22]
Colorectal cancer and erythroleukemia	F. nucleatum	the human EBV transformed 721.221 cells, the human colorectal line RKO, the human erythroleukemia line K562, the mouse thymoma BW cells and the NK tumor cell line YTS ECO	F. nucleatum bound tumors are protected from NK-mediated killing and immune cell attack due to an interaction between the fusobacterial protein Fap2 with the immune cells inhibitory receptor TIGIT	+	[29]

downregulate the expression of the SENP1 gene to cause the accumulation of cell senescence promoters and induce the senescence of intestinal epithelial cells, promoting the proliferation of uninfected cells. Growth factors subsequently promote tumor growth [18]. Wang X et al. repeatedly exposed primary colonic epithelial cells to symbiotic polarized macrophages or endogenous clastogen 4-HNE (4-human neutrophil elastase). Chromosomal instability (CIN) prompted to cause transformation and increasing the expression of tumor stem cells and stem cell-like markers. This occurrence led to immunodeficiency and poorly differentiated and aggressive tumor formation in mice. These findings confirmed that symbiosis induced endogenous CIN and cell transformation, leading to colorectal cancer [19]. Liver cancer is closely related to metabolites produced by the gut microbiome. In patients with liver cancer caused by alcohol, the abnormal metabolism of intestinal microbes triggers and mediates increased intestinal permeability. Gut bacteria can metabolize ethanol and produce acetaldehyde. Ethanol and the metabolic derivative acetaldehyde can disrupt the integrity of tight junctions in the intestine [20]. Metabolites such as deoxycholic acid and lipopolysaccharide produced by gut microbiome imbalance can promote liver inflammation and cause tumors [21]. *H. pylori* can cause gastric cancer by producing various virulence factors such as VacA (Vacuolating cytotoxin A) and CagA (cytotoxin-associated gene A) [17]. Intestinal microorganisms with *β*-glucuronidase (GUS) activity encoded by the GUS gene activate estrogen as a component of estrogen-like substances that activate estrogen, promoting the occurrence of breast cancer [22]. Patrik Kovács et al. showed that lithocholic acid, a bacterial metabolite, activates TGR5 (Takeda G-protein coupled receptor) and CAR (constitutive androstane receptor) to trigger a pair of oxidative stress and nitrosative stress that depends on NRF2/Keap1 system downregulation and iNOS induction to inhibit breast cancer cells [23]. Some intestinal bacteria can also use bile acid as a messenger to regulate the level of CXCL16, a hepatic sinusoidal endothelial cell (LSEC) chemokine. Consequently, the accumulation of CXCR6+ liver NKT cells is controlled, and the growth of a liver tumor is inhibited [24].

In terms of diet, a large number of studies and investigations have confirmed that species of gut microbiota are affected by the products or byproducts of fresh red meat or processed meat, such as heme, nitrite, heterocyclic amines, and protein fermentation products, which are closely related to the occurrence of cancer. Heme promotes the proliferation of sulfide-producing bacteria, which causes mucosa damage and exposes epithelial cells to carcinogens, leading to carcinogenesis. In foods containing nitrates, the microbiota increases nitroreductase activity, which converts nitrates into carcinogenic N-nitroso compounds (NOC). Bacterial fermentation products of proteins in fresh red meat, such as hydrogen sulfide, ammonia, secondary bile acids, and phenolic compounds, increase the risk of colorectal cancer [25]. The intestinal microbiota ferments dietary fiber to produce short-chain fatty acids. Ma X et al. examined the regulation of sodium butyrate (NaB), the main product of intestinal microbial fermentation, on intestinal microbiota in mouse models of colorectal cancer liver metastasis (CLM). They also proved that NaB can effectively regulate the intestines of the mouse models of CLM, channel microbiota, and improve the host immune response to play a role in the treatment of CLM [26].

Thus, daily maintaining a healthy diet can prevent cancer and activate immune therapy for cancer by improving the composition of the gut microbiota.

Changes in tumor cell signaling pathways

Signal transduction between human cells can be achieved by direct contact between neighboring cells; however, the more commonly used technique is the secretion of various chemical substances by the cell to regulate their metabolism and functions and other cells. Changes in the gut microbiome of cell signaling pathways in cancer can lead to host cell growth disorders, stem cell-like characteristics, and loss of cell polarity [14].

Bao Y et al. indicated that *Bacteroides fragilis*-associated lncRNA (BFAL1) was identified. they search for lncRNAs associated with ETBF among eight candidates which filtrated in the GEO database, two colorectal cancer cell lines, DLD-1 and HCT116, Interestingly, significantly increased expressions of BFAL1 compared with

those in NTBF or simple medium-treated cells. This phenomenon indicated that ETBF increases the expression of BFAL1 in CRC cells. The expression profile of BFAL1 was validated and its function in ETBF-related carcinogenesis was investigated. BFAL1 mediates ETBF-induced tumor growth by activating the Ras homolog, which is the MTORC1 binding/mammalian target of the rapamycin (RHEB/mTOR) pathway. Further study showed that BFAL1 is competitively bound to miR-155-5p and miR-200a-3p to upregulate RHEB expression [27]. BFT secreted by ETBF binds to the receptors of tumor epithelial (**Figure 3A**), increasing the permeability of epithelial cells and stimulating the degradation of E-cadherin, a tumor suppressor protein. Wnt signaling is one regulator of cell proliferation, and, in the setting of mutant APC, This process then enhances β-catenin nuclear signal transduction results in dysregulated CEC proliferation causing an increase in c-MYC expression [28, 29], consequently promoting the proliferation of cancer cells [16]. However, Rubinstein MR proved that *Fusobacterium nucleatum* (*Fn*) adheres and invades epithelial cells via its distinct surface virulence factor, FadA. As an adhesion, FadA combines with E-cadherin to activate β-catenin signaling and promote carcinogenesis [30]. *Fn* can also form bacterial aggregates with non-invasive bacteria to invade cells. Chen D et al. found that *Clostridium butyricum* can inhibit intestinal tumor development in genetically modified models and its efficacy on the gut microbiota remain uncertain. *C. butyricum* inhibits intestinal tumor development in $Apc^{min/+}$ mice induced by high-fat diet. Moreover, the mechanisms involved in the protective effects of *C. butyricum* are related to suppressing the proliferation and promoting the apoptosis of tumorcells, modulating the gut microbiota, and inhibiting Wnt/β-catenin signaling. Importantly, *C. butyricum* treatment alters microbial-derived metabolites such as secondary bile acids and short-chain fatty acids and activates the Gprotein coupled receptors GPR43 and GPR109A, demonstrating that *C. butyricum* can potentially treat colorectal cancer [31]. Miao Liu et al. also suggested that *C. butyricum* can also regulate the structure and composition of the gut microbiome by inhibiting the NF-κB pathway and promoting cell apoptosis to reduce mouse colitis-related colon cancer (**Figure 3B**) [32].

It can be seen that the mechanisms of carcinogenesis induction by intestinal flora may include inflammation induction, altered cell signaling, and suppression of immune cell killing effects. However, the exact role of intra-tumoural bacteria in tumors is still not fully understood.

Immune system suppression and participation in pro-inflammatory pathways

The immune response is a physiological protection mechanism initiated by the body against foreign objects. The microbiota coexists with the animal body for a long time and participates in various processes of animal growth and development. The gut microbiota forms innate immunity and adaptive immunity in the body, as well as regulates the pathogenesis of intestinal and systemic diseases.

In colorectal cancer, *Fusobacterium nucleatum (Fn).* can activate the autophagy signal involved in cancer metastasis by specifically targeting the metastasis-promoting kinase CARD3 [33]. Moreover, *Fn*. increases the expression of KRT7-AS/KRT7 by activating the NF-κB pathway [34], improves the migratory ability of colorectal cancer cells *in vivo* and *in vitro*, and promotes the occurrence of cancer. Simultaneously, *Fn* infection can activate the IL-6/p-STAT3/c-MYC signaling pathway in a TLR4-dependent manner to encourage the growth of macrophages. M2 polarization [35] increases the expression of inflammatory mediators [36], promoting the growth of colorectal tumors (**Figure 3C**). Yang Y et al. confirmed that *Fn* can upregulate microRNA-21 expression by activating the TLR4/MYD88/NK-kb pathway and drive the proliferation of colorectal cancer cells and the occurrence of tumors [37]. Chen T et al. reported that *Fn* can inhibit the antitumor immune response by reducing the density of CD4+ T cells and TOX expression [38]. Gur C et al. determined a bacteria-dependent tumor escape mechanism-that is, the Fap2 protein of *Fn* can interact with TIGIT, the human immune cell inhibitory receptor. Tumors bound to *Fn* are thus protected from immune cells attacking and promote tumor occurrence and development [39]. *Fn* can also block the G1 phase of lymphocytes to inhibit T cell activation and suppress the immune system [40]. Wu J et al. showed that *Fn* auto-inducer 2 promotes the polarization of M1 macrophages

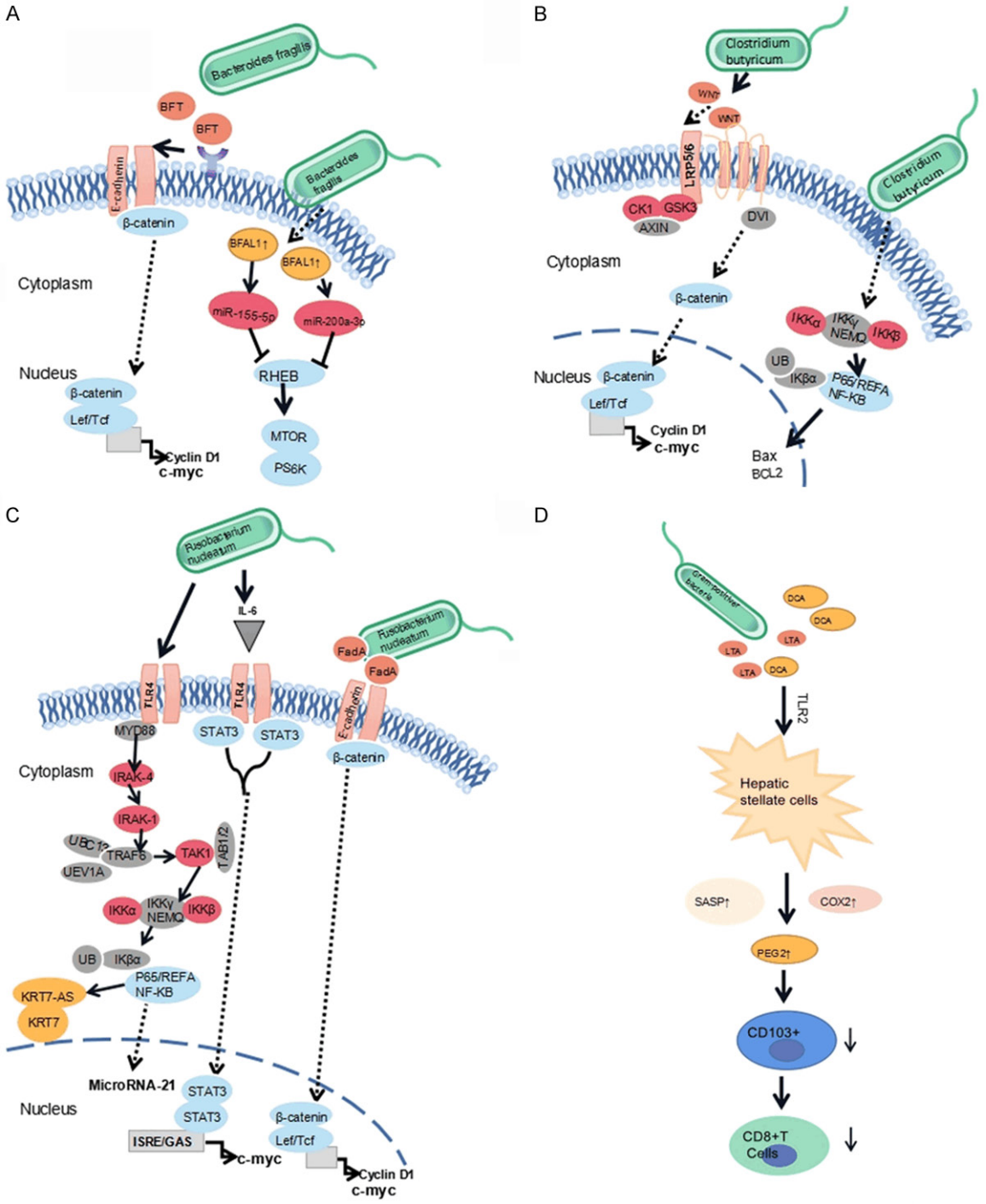

Figure 3. Effect of the gut microbiome on tumor cell pathways. A. ETBF can stimulate the overexpression of BFAL1, BFAL1, and miR-155-5p, moreover, miR -200a-3p competitively binds to activate the RHEB/mTOR pathway and promote tumor growth. BFT secreted by ETBF binds to the receptors of tumor epithelial cells to increase the permeability of epithelial cells and stimulate the degradation of the tumor suppressor protein E-cadherin, enhances β-catenin nuclear signal transduction, increases the expression of oncogene c-Myc, and promote the proliferation of cancer cells. B. *Clostridium butyricum* can be regulated by Wnt signaling, and intestinal microbiota inhibits the development of intestinal tumors. It may also regulate colon cancer by inhibiting the NF-κB pathway and promoting apoptosis. C. *Fusobacterium nuclei* increase the expression of KRT7-AS/KRT7 by activating the NF-κB pathway. It activates the IL-6/p-STAT3/c-MYC signaling pathway in a TLR4-dependent manner. Activating the TLR4/MYD88/NK-κB pathway upregulates MicroRNA-21 expression. D. In aging hepatic stellate cells in the tumor microenvironment, the COX2 pathway driven by intestinal microbes produces the lipid mediator PGE2, thereby inhibiting tumor immunity.

via the TNFSF9/IL-1β signaling pathway [41]. The binding and invasion of *Fn* with host cells induce the secretion of IL-8 and CXCL1, driving the migration of colorectal cancer cells [42]. Tze Mun Loo et al. demonstrated that the COX2 pathway driven by gut microbes produces the lipid mediator PGE2 in senescent hepatic stellate cells in the tumor microenvironment, inhibiting tumor immunity (**Figure 3D**) [43].

The gut microbiome increases the efficacy of chemotherapy and immunotherapy participating in the regulation of T-cell immunity, increasing effector T-cell responses, and participating in metabolism, increasing the efficacy of chemotherapy and immunotherapy, and reducing chemotherapy and immunotherapy-induced diarrhea. Most of the gut microbiome involved in cancer regulation can be found to belong to the normal genus, therefore, a stable gut microbiome is essential in anti-cancer therapy.

Gut microbiome interacts with antitumor drug treatment

The use of drugs to treat tumors is currently the most widely used non-surgical treatment. Since the development of modern antitumor drugs in the 1940s, antitumor drug therapy has undergone three changes: chemotherapy, immunotherapy, and targeted therapy. Studies have shown that drugs are mainly used to change the intestinal microenvironment and transfer the microbiome of different parts to induce microbial imbalance in the body. Proton pump inhibitors used to treat gastric acid-related diseases can increase the permeability of the gastric acid barrier, aiding the passage of oral microorganisms via the stomach to the intestine, leading to microbial imbalance [44]. The influence of the gut microbiome on antitumor drug therapy primarily occurs via five mechanisms: bacterial translocation, immune regulation, metabolic regulation, enzymatic degradation, and diversity reduction [45]. We previously described gut microbes as having the ability to influence the occurrence and development of tumors via different mechanisms. Thus, the interaction between the gut microbiome and antitumor drug treatment is discussed in this review.

Gut microbiome and chemotherapy drugs

Chemotherapy is a systemic treatment that uses chemical drugs to kill tumor cells and inhibit the growth and reproduction of tumor cells. Most chemotherapeutic drugs spread throughout the body, along with blood circulation, affecting normal cells in the body to varying degrees. The use of chemotherapy is often accompanied by serious side effects. Long-term use of chemotherapeutics leads to drug resistance in cancer cells. Most research on chemotherapeutics currently focuses on improving the defects of traditional drugs, such as using different dosage forms to enhance drug targeting and combining different drugs or small molecules with traditional drugs to improve and reduce the efficacy of traditional drugs. Gene therapy is combined with traditional medicine to improve the defects of traditional medicine.

Chemotherapy drugs affect the gut microbiome to a certain extent. For instance, chemotherapy can disrupt the normal functioning of the gastrointestinal tract, causing diarrhea, and the composition of the gut microbiota [46]. The gut microbiome can also, directly and indirectly, regulate the metabolism of chemotherapeutic drugs and host response to chemotherapy via different channels, affecting the efficacy of chemotherapeutic drugs and the sensitivity of the host to related toxic effects [14].

Cyclophosphamide (CTX), an anti-cancer metagenomic, is a significant alkylating agent whose therapeutic efficacy is due in part to its ability to stimulate antitumor immune responses. Studying mouse models, we demonstrate that cyclophosphamide alters the composition of microbiota in the small intestine and induces the translocation of selected species of Gram-positive bacteria into secondary lymphoid organs. There, these bacteria stimulate the generation of a specific subset of “pathogenic” T helper 17 (pTH17) cells and memory TH1 immune responses. Tumor-bearing mice that were germ-free or that had been treated with antibiotics to kill Gram-positive bacteria showed a reduction in pTH17 responses, and their tumors were resistant to cyclophosphamide. Adoptive transfer of pTH17 cells partially restored the antitumor efficacy of cyclophosphamide. These results suggest that the gut microbiota help shape the anticancer immune response [47]. Germ-free mouse models of cancer that have been treated with antibiotics to kill Gram-positive bacteria show a reduction of Th17 responses and resistance to cyclo-

phosphamide CTX is currently used in many solid cancers and hematological cancers [14]. The efficacy of CTX depends on intestinal bacteria, including the *Enterococcus* plaque and *Pasteurella enterica* identified in the study by Daillère R et al. *E. coli* metastasizes from the small intestine to the secondary lymphoid organs and increases the CD4+/Treg ratio in the tumor, and *Campylobacter* in the small intestine accumulates in the colon and promotes the infiltration of T cells that can produce IFN-γ in a cancer lesion. The immunosensor NOD2 limits CTX-induced cancer immune monitoring and the biological activity of these microorganisms [48]. Using mouse models, Sophie Viaud et al. proved that cyclophosphamide indirectly caused the accumulation of monocytes in the lamina propria and mesenteric lymph nodes and spleen by inducing abnormal biological metabolism in the small intestine and destroying mucosal integrity [49]. Zhu H et al. showed that ginsenosides have the dual effect of promoting the anti-tumor effect of CTX, that is, improving intestinal mucositis by regulating the gut microbiome and regulating Nrf2 and NFB pathways, indirectly improving antitumor immunity [50]. Other reports also indicated that various traditional Chinese medicine extracts, including wild *morel* polysaccharide [51], *jujube* polysaccharide [52], *camellia* extract [53], *cordyceps* polysaccharide [54], among others, can be used anti-tumor. This approach regulates the gut microbiome to improve the side effects and anticancer effects of CTX.

Cisplatin, a non-specific drug of the cell cycle exhibits a certain degree of cytotoxicity. It can inhibit the DNA replication of tumor cells and damage the structure of the cell membrane. It exerts a strong broad-spectrum antitumor effect and is mostly used to treat ovarian cancer, prostate cancer, testicular cancer, and other malignant tumors of the genitourinary system. The damage caused by cisplatin on the DNA replication of rapidly proliferating epithelial cells may destroy the mucosal barrier, leading to infection. Wu CH et al. reported that with its antioxidant and anti-oxidant effects, D-methionine could enhance the growth of probiotics (pine plants and *lactobacilli*), reduce gut microbiome imbalance caused by cisplatin, and maintain intestinal homeostasis [55]. Zhao et al. found that Lactobacillus supplementation significantly increased body weight, restored heart function, and reduced the expression of inflammatory genes, as well as improved the toxic effects of cisplatin [56] Zhou P et al. indicated that cephalosporin hydrochloride improved the intestinal microbial imbalance caused by the therapeutic effect of cisplatin chemotherapy by manipulating the gut microbiome by the allele analysis of microbial communities [57].

Gemcitabine (2', 2'-difluorodeoxycytidine) is a cytosine nucleoside derivative, and pyrimidine competes with the physiological nucleotide deoxycytidine during DNA synthesis. Exerting the effect of antimetabolites, gemcitabine can competitively antagonize pyrimidine. Moreover, gemcitabine is commonly used to treat pancreatic ductal adenocarcinoma (PDAC). The study by Geller LT et al. revealed that of the 113 human PDACs tested, 86 (76%) of the bacteria, mainly γ-proteobacteria, were positive. Bacteria can metabolize gemcitabine into the inactive form of 2', 2'-difluorodeoxyuridine. The metabolic process depends on the expression of the long isoform of the bacterial enzyme cytidine deaminase (CDDL) mainly present in γ-proteobacteria. In a mouse model of colon cancer, gemcitabine resistance is caused by γ-proteobacteria within the tumor, relies on CDDL expression, and can be disrupted by co-treatment with the antibiotic ciprofloxacin [58].

Fluorouracil (5-FU), a thymidylate synthase inhibitor, is widely used in the treatment of gastrointestinal tumors and is the first-choice treatment for colon cancer. However, its clinical application may cause severe colonic mucositis, the pathogenesis of which has not been fully explained by current preclinical studies [14]. Evidence of the involvement of intestinal microbiota has accumulated. Other studies found that 5-FU leads to intestinal microbe imbalance, which then triggers inflammation, worsens intestinal mucositis, and potentially leads to bacteremia and sepsis. Meanwhile, several preclinical studies have reported that the body undergoes a rapid transformation from symbiotic bacteria to *E. coli*, *Clostridium* spp., and *Enterococcus* after treatment with 5-FU via intraperitoneal injection [59]. Hong-Li Li showed that the gut microbiome actively participates in the pathological process of 5-Fu-induced intestinal mucositis. 5-Fu signifi-

cantly changed the profiles of inflammatory cytokines/chemokines in serum and colon. Adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and VE-Cadherin were increased. While tight junction protein occludin was reduced, however, zonula occludens-1 and junctional adhesion molecule-A were increased in colonic tissues of 5-Fu treated mice. Meanwhile, inflammation-related signaling pathways including NF-κB and mitogen-activated protein kinase in the colon were activated. The further study disclosed that 5-Fu diminished bacterial community richness and diversity, leading to the relative lower abundance of *Firmicutes* and decreased *Firmicutes/Bacteroidetes* ratio in feces and cecum contents, suggesting that 5-Fu-induced intestinal mucositis can potentially regulate the homeostasis of the gut microbiome [60]. Different drugs have been used to reduce this side effect and promote the antitumor effect of 5-Fu by regulating the gut microbiome and some cell signaling pathways. An J et al. proved that the symbiotic bacteria *Lactobacillus Plantarum* (LP) supernatant inhibited the expression of CD44, 133, 166, and ALDH1, which are specific markers for the colorectal cancer cell. The combination therapy consisting of LP and 5-FU can inhibit the survival of CRC and lead to cell death by inducing caspase-3 activity. The combination therapy of LP SN and 5-FU can induce the anticancer mechanism of the body by inactivating the Wnt/β-catenin signaling pathway of chemoresistant CRC cells and reducing the formation and size of the colon sphere [61].

Irinotecan (CPT-11) is a topoisomerase I inhibitor that inhibits DNA replication. It is used to treat advanced colorectal cancer, gastric cancer, pancreatic cancer, and small-cell lung cancer [14]. As a prodrug with a carbamate-linked piperidinyl group, CPT-11 increases solubility and bioavailability. The CPT-11 is removed in the body to produce SN-38, an active metabolite. However, once SN-38 enters the intestinal tract, SN-38 acts as a substrate of bacterial β-glucuronidase in the symbiotic microbiota, which removes the glucuronic acid group as a carbon source, produces reactivated SN-38 *in situ,* and reactivates the drug in the intestine. Consequently, several adverse reactions, such as diarrhea, occur. Wallace et al. reported that inhibiting the β-glucuronidase present in the bacterial symbiont can prevent the gastrointestinal toxicity of CPT-11 metabolites [62]. Yang W et al. evaluated the efficacy of amoxapine, a *β*-glucuronidase inhibitor, in reducing CPT-11-induced toxicity [63].

In conclusion, further studies have confirmed the changes in the gut microbiome after the application of chemotherapy drugs in malignant tumors. Supplementation of probiotics to reduce the toxic and side effects of chemotherapeutic drugs has also been increasingly regarded. At present, with the deepening of the research on the gut microbiome of patients undergoing chemotherapy for malignant tumors and the progress of research technologies (such as sequencing technology and single strain culture, etc.), the gut microbiome has potential in the field of cancer prevention and treatment.

Gut microbiome and immunotherapy drugs

Immunotherapy is a biological treatment method that restores the normal antitumor immune response of the body by regulating the balance between immune-promoting factors and immunosuppressive factors, thereby suppressing and eliminating tumors. Immunotherapy mainly includes immune checkpoint blocking, cytokine therapy, cell therapy, and therapeutic vaccines. However, this treatment remains immature and is in the clinical trial stage, and its specific treatment plan requires improvement. Immunotherapy drugs are mainly immune checkpoint inhibitors (ICIS). The immune access point destroys T cell activation via the inhibitory motif of the intracellular immune receptor tyrosine (ITIM), thereby counteracting TCR/CD3 or CD28-mediated tyrosine phosphorylation. ICIS can reduce the immune tolerance of tumor cells to tumor antigens and restore the antitumor response of the body by suppressing immune access points. The effect of the gut microbiome on immunotherapy is mainly indicated through the effect of cell therapy and ICIS. As early as 2015, Sivan et al. noticed that the abundance of some special commensal bacteria was related to the anti-PD-1 treatment effect in a mouse model [64]. Researchers compared the efficacy of anti-PD-1 treatment in genetically similar mice (C57BL/6) from 2 different facilities (JAX and TAC) that harbored significantly different

gut microbiota. The results showed that tumors grew more slowly and were more sensitive to anti-PD-1 therapy in JAX populations [64]. Cell therapy is a method of injecting tumor-specific immune cells in a microenvironment without detecting immunity for some tumors with poor immunogenicity; it is mostly used in the treatment of solid tumors. The efficacy of PD-1/PD-L1 and CTLA-4 inhibitors in ICIS has been fully proven and successfully applied to treat various tumors [65, 66].

When the apoptosis factor PD-1 recognizes its ligand PD-L1, the phosphorylation of ITSM tyrosine residues is induced, recruiting the tyrosine phosphatase SHP2, which induces the dephosphorylation and loss of Zap70 in T cells. PD-1 downregulates the activity of T cells and negatively affects the immune response, preventing T lymphocytes from targeting tumor cells, which is conducive to tumor immune escape [67]. This interaction between PD-1 and PD-L1 is blocked by some monoclonal antibodies, such as nivolumab, pembrolizumab, and atezolizumab. CTLA-4 is a membrane receptor on effector T cells, which binds to CD80/CD86 on antigen-presenting cells, thereby inhibiting T cells. Ipilimumab is a monoclonal antibody (ab) against CTLA4, which is mainly used to improve the overall survival rate of patients with metastatic melanoma (MM).

Many studies have shown that gut microbes significantly influence the efficacy of ICIS. Krista Dubin et al. conducted a prospective study on patients with MM treated with ipilimumab and correlated the fecal microbiota and its composition before and during the occurrence of colitis. The increase in the number of bacteria in Bacteroides is associated with the development of resistance to ICIS-induced colitis [68]. Marie Vétizou et al. found that the effectiveness of ICIS to block CTLA-4 is affected by the microbiota (*B. fragilis*, *Bacillus polymorpha*, and *Burkholderia*). *B. fragilis* can induce Th1 immune response, and DC matures to enhance CTLA-4 blockade [69]. Chaput et al. verified the regulatory effect of gut microbiota on CTLA-4 blockade in patients with MM. *Enterococcus faecalis* promotes Treg development, upregulates T cell ICOS expression, and enhances CTLA-4 blockade. *Bacteroides* can trigger baseline systemic inflammation [70]. Sivan A et al. found that the symbiotic signal of *Bifidobacterium* commensalism can regulate the activation of DCs at a steady-state, promoting the effector function of tumor-specific CD8+ T cells, boosting antitumor immunity, and enhancing the anti-PD-L1 effect [71]. Gopalakrishnan et al. proved that faecalis can activate CD4+ and CD8+ T cells in the circulation and tumors, as well as enhances the PD-1 blocking effect. By contrast, *Bacteroides* can upregulate MDSC and Treg in the system and hinder PD-1 blocking [72]. Matson et al. determined that bacterial groups containing *Bifidobacterium, Bifidobacterium longum*, among others, can upregulate the secretion of IFN-γ, increase CD8+ tumor-infiltrating T cells, and enhance the effect of blocking PD-1 [73]. Routy et al. found that *Akkermansia muciniphila* enhanced the ability of DC and promoted IL12 production by increasing CXCR3+CCR9+CD4+ T cells, enhancing the effect of blocking PD-1 [74].

In conclusion, the gut microbiome plays an important role in the regulation of host innate and adaptive immune systems, especially intestinal mucosal immunity. Moreover, it can not only induce the anti-tumor immune response but also promote the efficacy of immunotherapy.

Gut microbiome and targeted therapy drugs

Targeted therapy aims to design corresponding therapeutic drugs, based on their specific carcinogenic sites, allowing the selective targeting of drugs to specifically reduce or kill tumor cells. Common tumor-targeted therapy drugs include small molecule drugs, such as tyrosine kinase inhibitors, in addition to monoclonal antibody drugs involved in immunotherapy. However, the antitumor effect of targeted therapy is relatively weak, and combination with other drug treatments is generally necessary.

Vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs) are the standard first-line drug treatment for patients with metastatic renal cell carcinoma (mRCC). Common VEGF-TKIs include sunitinib, pazopanib, and rafinib. However, about 50% of mRCC patients treated with VEGF-TKIs experience diarrhea [75-77]. VEGF-TKIs often have to be stopped or reduced to relieve diarrhea during clinical treatment. Sumanta K et al. investigated and analyzed the fecal bacterial profile of mRCC

patients treated with VEGF-TKIs and found that *Bacteroides* was highly expressed, whereas *Prevotella* was poorly expressed in patients with diarrhea [78]. These results indicate the high correlation between the targeted drugs VEGF-TKIs and gut microbiome. Although the specific mechanism of action between the two has not been elucidated. A clinical study showed that fecal microbial transplantation (FMT) has apparent and statistical significance in improving VEGF-TKI-dependent diarrhea in mRCC patients [79]. This consistency not only provides the auxiliary role of FMT in cancer treatment but also further demonstrates the interaction between VEGF-TKIs and gut microbes.

These results prove that these targeted drugs may act not only via well-defined mechanisms but via the gut microbiome as well. Meanwhile, the influence of the gut microbiome during targeted drug therapy cannot be ignored. At present, despite findings on the correlation between targeted therapy drugs and intestinal microbes, studies have rarely reported on the interaction of gut microbiome and tumor-targeted therapy drugs. The specific relationship still needs further research.

The effect of the gut microbiome on tumors also confirms the complexity of the bacteria-immune-tumor axis. Most studies are limited to animal models. Due to differences in intestinal flora between humans and animals, the species, number, and proportion of bacteria are not completely consistent, and there are few tumor species and drugs to be studied. There is also a lack of clinical studies on the anti-tumor efficacy of bacteria on more types of targeted small-molecule drugs. Further research is still necessary to determine the correlation, but these issues will certainly be one of the hot spots in the frontier field of precision medicine research in cancer in the future.

Summary and outlook

In summary, the gut microbiome is mainly involved in the occurrence and development of tumors in four ways: inducing DNA damage, diet, and microbial carcinogenic metabolites; changing tumor cell signaling pathways; suppressing the immune system; and participating in proinflammatory pathways. The generation of different tumors also leads to changes in the microenvironment and types of the gut microbiome. The efficacy of antitumor drugs is also affected by many aspects of the gut microbiome. The influence of the gut microbiome on antitumor drug therapy is primarily exerted via five mechanisms: bacterial translocation, immune regulation, metabolic regulation, enzymatic degradation, and diversity reduction.

The gut microbiome is mainly applied in the clinical treatment of cancer via probiotics and prebiotics, antibiotics, and fecal microflora transplantation. Probiotics are defined as live microorganisms that are beneficial to the health of the host when used in moderation [80]. Bacterial genera considered as safe such as *Lactobacillus* or *Bifidobacterium* currently dominate the probiotic product market [81]. Prebiotics refer to a substrate selectively utilized by host microorganisms and provide health benefits. They include fructo-oligosaccharide and galactose, which can be preferentially metabolized by bifidobacteria [82]. Most clinical gastrointestinal indications can benefit from probiotics and prebiotic interventions. Probiotics are clinically indicated in noncancer conditions., including necrotizing enterocolitis [83], pediatric colitis [84], and neonatal scurvy [85]. The most common application of prebiotics is reflected in infant formula [86]. Probiotics and prebiotics are most commonly used to prevent colon cancer in the clinical treatment of cancer. For instance, oral administration of live *Lactobacillus casei* can inhibit tumor recurrence in patients who have undergone resection of colorectal tumors [87]. Probiotics and prebiotics have good clinical application prospects, but further research is needed to determine the potential probiotic strains and the options for the optimal dosage and time [88]. Antibiotics refer to a class of secondary metabolites produced by microorganisms or higher animals and plants during their lives that have anti-pathogen properties or other activities and can interfere with the development of other living cells. Antibiotics, which are currently among the best-selling drugs, can transform the gut microbiome into a temporary quasi-stable or alternative stable state so that it may resist external effects, as demonstrated by clindamycin, adriamycin, mitomycin, and so on. However, antibiotics are prone to develop drug resistance, in addition to their powerful antagonism toward diseases, and their effects on

other gut microbiomes in the body have yet to be elucidated. Moreover, studies have confirmed that using antibiotics before tumor immunotherapy can decrease the overall curative effect and survival prognosis [88]. All these indicate that antibiotic treatment is a double-edged sword, needs to pay extra caution when applying to clinical treatment [89], and exhibits significant duality [90]. FMT refers to the restoration of intestinal microbial diversity by transplanting the functional flora in the feces of a healthy person into the gastrointestinal tract of the patient to rebuild new gut microbiome [91]. FMT is an effective technique for the treatment of *Clostridium difficile* infection. The efficiency of FMT in preventing the recurrence of *C. difficile* infection has reached 90%. FMT manipulation of the intestinal microbiota shows potential as a treatment for inflammatory bowel disease and irritable bowel syndrome [92]. With regard to the clinical treatment of tumors, FMT has improved VEGF-TKIs-dependent diarrhea in mRCC patients. The clinical application of these gut microbiome provides a solid foundation for the application of gut microbiome in personalized tumor treatment.

Inflammation and tumors are highly correlated. Surveys have determined that up to 20% of tumors are related to chronic infections and that many environmental causes and risk factors of tumors are related to some forms of chronic inflammation [93]. Chronic inflammation is linked to various processes leading to tumorigenesis, including cell transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [94]. Two molecular and cellular pathways related to inflammation and tumors have thus far been clarified: in the internal pathway, the genetic events that cause tumors initiate the expression of genes which related to inflammation, guiding the construction of the inflammatory microenvironment; in the external pathways, inflammatory conditions promote the development of cancer [95]. Inflammatory bowel disease (IBD-CRC) in colorectal cancer involves two main clinically defined subtypes: ulcerative colitis and Crohn's disease (CD). The total risk of CRC associated with ulcerative colitis is 1.4%, which increases with the disease duration [96]. The overall risk of CRC in patients with Crohn's disease is 2.5 times that of the general population [97]. A multicenter prospective study of CD patients with Crohn's disease activity index <150 indicated that gut bacterial DNA is a related factor leading to CD complications [98]. Arthur JC et al. reported that in $IL10^{-/-}$ mouse strains susceptible to colitis, chronic inflammation targets intestinal microbes and can induce the expansion of microbes, including *E. coli* with carcinogenic effects [99]. This finding suggests that intestinal microbes are among the causes of colon cancer related to IBD-CRC [100]. Ana et al. evaluated the effects of the COX-2 inhibitor lumiracoxib and the TNF antagonist etanercept on TNBS-induced colitis in Wistar rats. They found that COX-2 inhibitors and TNF antagonists can both improve the inflammatory response and protect against colon injury [101]. Maria K et al. conducted a stool study on patients with ulcerative colitis and found that the mucosal antimicrobial peptide expression and intestinal microbiota showed significantly different patterns before the treatment of TNF antagonist treatment responders and non-responders. This finding indicates that intestinal antibacterial drugs or microbial composition can affect the treatment of anti-TNF drugs [102]. These results prove the close connection between chronic inflammation and cancer, cancer-related inflammation, and the gut microbiome. However, the relationship between anti-inflammatory drugs, gut microbiome, and tumors needs to be clarified, and the direct relationship between anti-inflammatory drugs and tumors has to be examined. Therefore, the aforementioned anti-inflammatory drugs provide the possibility to prevent and treat cancer, and treat cancer effect may be bridged by the gut microbiome. The development of new antitumor drugs also provides new ideas.

At present, traditional antitumor drug treatment faces problems such as drug targeting, drug resistance, drug side effects, and individual differences. Reports on improving antitumor drugs in the past three years have mainly focused on the use of three methods: changing the dosage form of drugs, combining drugs with peptides or small molecule extracts, and drug therapy combined with gene therapy. Improving human health by regulating the microbiota is a continuous development strategy. However, a study of 13,355 prokaryotic RNA gene sequences detected in multiple

Table 2. Abbreviations

Abbreviation	Full name	Abbreviation	Full name
cIAP2	Anti-apoptotic protein 2	CPT-11	Irinotecan
MMR	mismatch repair	NaB	Sodium butyrate
ROS	reactive oxygen species	CLM	Liver metastasis of colorectal cancer
ETBF	enterotoxigenic *Bacteroides fragilis*	BFT	*Bacteroides fragilis* toxin
H2AX	H2A histone family member X	MM	Metastatic melanoma
CIN	chromosomal instability	CRC	colorectal cancer
4-HNE	trans-4-hydroxy-2-nonenal	COX2	cyclooxygenase-2
LCA	lithocholic acid	PGE2	prostaglandin E2
CD	Crohn's disease	TLR4	Toll-like receptor 4
IBD	inflammatory bowel disease	IL-6, IL-12	Interleukin-6, Interleukin-12
INOS	inducible nitric oxide synthase	CTX	Cyclophosphamide
LSEC	liver sinusoidal endothelial cell	IFN-γ	Interferon γ
CXCL16	CXC chemokine ligand *16*	CEH	Cefopurine hydrochloride
NKT cells	natural killer T *cells*	CDDL	a long isoform of the bacterial enzyme cytidine deaminase
Fn	*Fusobacterium nucleatum*	SN	supernate
NOD2	nucleotide-binding oligomerization domain 2	ICIS	Immunoretrieval point inhibitors
Nrf2	red derived nuclear factor 2 correlation factor	Zap70	Zeta-chain-associated protein kinase 70
PDAC	pancreatic ductal adenocarcinoma	MDSC	myeloid-derived suppressor cell
LP	*Lactobacillus Plantarum*	PD-1	programmed death 1
ITIM	immunoreceptor tyrosine-based inhibitory motif	TNBS	2,4,6-trinitrobenzene sulfonic acid
SHP2	Src homology 2 domain-containing tyrosine phosphatase	CDAI	Crohn's disease activity index
DC	dendritic cells	p-STAT3	Phosphorylated-signal transduction and activators of transcription 3
Treg	regulatory T cells	5-FU	5-fluorouracil
VEGF-TKIs	vascular endothelial growth factor-tyrosine kinase inhibitor	GUS	Gut microbial β-glucuronidase
TOX	thymocyte selection-associated high-mobility group box	BFAL1	*Bacteroides fragilis*-associated lncRNA1
FMT	transplantation of fecal microbiota	mRCC	metastatic renal cell carcinoma
VEGF-TKIs	vascular endothelial growth factor and tyrosine kinase inhibitor	IBD-CRC	inflammatory bowel disease colon cancer
MSI	microsatellite instability		

colon mucosa and feces of normal people showed that the biological diversity of the gut microbiome between different individuals is highly significant [103]; besides, diet can quickly change the intestinal microbiota in the body [104]. Simultaneously, different individual ages and geographic environments can produce large differences [105]. Therefore, different personalized programs have to be formulated based on different patients. Ann's approach to personalized tumor treatment is targeted intervention of key intestinal bacteria in the body to facilitate treatment with different antitumor drugs. However, to realize this method, it is necessary to identify a new method of classifying the specific bacterial flora involved in the pathological process of tumors and drug treatment. To achieve test biomarker based on the physiological and pathological state of the patient, specific flora has to be selected to aid in the treatment of a specific tumor with a specific drug in various ways, a large number of follow-up studies on the relationship between tumor, gut microbiome and drugs should also be conducted. The acronyms of this article are now attached at the end of the review (**Table 2**).

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Disclosure of conflict of interest

None.

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