Advances in the role of gut microbiota in the regulation of the tumor microenvironment (Review)

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Received March 16, 2023; Accepted August 1, 2023

DOI: 10.3892/or.2023.8618

Abstract. As a protector of human health, the gut microbiota plays an important role in the development of the immune system during childhood, and the regulation of dietary habits, metabolism and immune system during adulthood. Dysregulated gut flora is not pathogenic, but it can weaken the protective effect of the immune system and cause various diseases. The tumor microenvironment is a physiological environment formed during tumor growth, which provides nutrients and growth factors necessary for tumor growth. As an important factor affecting the tumor microenvironment, the intestinal microflora affects the development of tumors through the mechanisms of gut and microflora metabolites, gene toxins and signaling pathways. The present article aimed to review the components and mechanisms of action, clinical applications, and biological targets of gut microbiota in the regulation of the tumor microenvironment. The present review provides novel insights for the future use of intestinal flora, to regulate the tumor microenvironment, to intervene in the occurrence, development, treatment and prognosis of tumors.

Contents

1. Introduction

There are numerous microorganisms in the human intestinal tract, the number of which is >10-fold that of human cells, which can be divided into beneficial bacteria for human vitamin synthesis, food digestion and inhibition of the production of toxic substances; harmful bacteria that affect the function of the immune system and produce harmful substances; and neutral bacteria with dual roles, such as *Escherichia coli* (1). There is a dynamic balance between the intestinal flora and the host, which can maintain the normal physiological activities of the host. When the flora is imbalanced, it can cause inflammation and even diseases. The tumor microenvironment is the internal environment of tumor cells, which is not only limited to tumor cells but also includes various components of the microenvironment and nearby interstitial cells, blood vessels, cytokines and biomolecules (2). The present study conducted a computer search for articles related to the intestinal flora and the tumor microenvironment published in the Wan fang Data

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Key words: gut microbiota, tumor microenvironment, mechanism of action, biological target, clinical application

Knowledge Service Platform (https://www.wanfangdata.com.cn), CNKI (https://www.cnki.net), China Biomedical Literature Service System (http://www.sinomed.ac.cn/zh/), PubMed (https://pubmed.ncbi.nlm.nih.gov/advanced/) and Medline databases (https://ovidsp.ovid.com/autologin.cgi). The search time limit was from the establishment of each database until February 2023. The literature search revealed that recent studies have shifted their focus from the target of tumor treatment to the tumor microenvironment, and have revealed that the intestinal flora plays an important role in the regulation of the tumor microenvironment (3). The present review describes in detail the specific mechanisms of intestinal microflora affecting tumor microenvironment and introduces the application status and potential biological targets of intestinal microflora in tumor microenvironment intervention, aiming to provide a new direction for disease intervention and treatment.

2. Gut flora

There is a large number of symbiotic bacteria in the human gut, which dynamically changes under the influence of dietary habits, drug use and specific physiological conditions. The type and abundance of Gut microbiota are affected by genetic, environmental and economic factors as well as living habits, and cohabitation factors are more influential than genetic factors (4). With the continuous development and improvement of modern sequencing technology, genomic technology and *in vitro* culture technology of intestinal flora, the importance and mechanism of intestinal flora and various diseases have been gradually revealed. Intestinal flora can not only act as an intestinal barrier to resist the invasion of pathogens (5), but also play a role in the occurrence of various diseases such as solid tumors (colorectal, lung, and pancreatic cancer, etc.) and other diseases (leukemia, Alzheimer's disease, etc.), and their development and treatment are inextricably associated (Table I) (6-16).

3. Tumor microenvironment

The tumor microenvironment is a special biological environment formed by changes in the surrounding tissue structure during tumor growth and development. It was first described as 'seed and soil', with tumor cells as seeds, and the appropriate target organ and growth environment called the tumor microenvironment (17). In addition to 'seed' tumor cells, the tumor microenvironment also includes immune cells, adipocytes, stromal cells, extracellular matrix and acellular components (cytokines, signaling molecules and chemokines), which together provide nutrition, blood vessels, collagen and signaling molecules to form a complex and dynamic network system that provides support for the occurrence, proliferation, metastasis and immune escape of tumor cells (18). Since tumor cells have the characteristic of malignant proliferation, they consume large quantities of oxygen and nutrients in the soil, which is accompanied by the production of reducing substances (reactive oxygen species). Previous studies have revealed that a hypoxic microenvironment can promote tumor resistance (19), an acidic microenvironment is conducive to tumor cell metastasis (20) and highly reducing substances affect tumor treatment (21). The tumor microenvironment is an important condition to support tumor growth, and in-depth research and effective regulation of it will provide effective means for tumor treatment (Table II) (22-27).

4. Gut microbiota regulates the tumor microenvironment

In recent years, with the continuous development of technology and the increase in research, the concept of the tumor biological microenvironment has been proposed, which includes cell metabolites, the immune system, systemic metabolism, body circulation, and intestinal flora related to tumorigenesis, development and metastasis (28). Among these, the intestinal flora plays the most significant regulatory role on the tumor microenvironment, mainly through changes in the flora, brain-gut axis, hypothalamus-pituitary-adrenal axis, gut-liver axis and bacterial translocation, which affect the physiological state of target organs from a long distance. This, in turn, creates a favorable environment for tumor invasion (29-31).

Regulation of the components of the tumor microenvironment

Dendritic cells (DCs). DCs can be divided into conventional DCs and plasmacytoid DCs (pDCs), and the two phenotypes interact to maintain the morphology of DCs and the antigen expression capacity of $CD8^+$ T cells. A previous study has demonstrated that DC antitumor activity is activated under specific conditions, and, after maturation, T cells are stimulated to produce the cytokine IL-2 to convert macrophages in the tumor microenvironment to the M1 phenotype (32). It was revealed that the antitumor function of DCs was enhanced by injecting lipopolysaccharide (LPS) into antibiotic-treated mice *in vitro*; thus, it was speculated that the microflora may contact or migrate to the tumor site to form an antitumor microenvironment through the bacterial components similar to LPS (33) (Fig. 1).

Tumor-associated neutrophils (TANs). TANs can be divided into two phenotypes, tumor suppressor and tumorigenic, with notably high inhibitory and polarized properties. TANs are associated with tumorigenesis, proliferation and immune regulation, and they transform into a pro-angiogenic subtype under the synergistic effect of chemokines. TANs release neutrophil extracellular traps (NETs) to kill harmful microorganisms. NETs activate specific signaling pathways to stimulate dormant cancer cells, restore their proliferative activity, and promote tumor recurrence and metastasis (34). A previous study has shown that *Fusobacterium nucleatum* can change the composition and phenotype of tumor-associated macrophages (TAMs), TANs and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment, and can activate the E-cadherin/β-catenin signaling pathway to promote the malignant transformation of epithelial cells (35). *Helicobacter hepaticus* can stimulate the secretion of nitric oxide and TNF-α from neutrophils to promote the progression of colorectal cancer (CRC) (32) (Fig. 1).

TAMs. TAMs are markedly adaptable, and with subtle changes in the tumor microenvironment, their phenotype would tranform from the antitumor M1 to the M2 one, which promotes tumor development and remodeling (32). TAMs are

Table I. Types and mechanisms of gut microbiota in different tumors.

Tumor type	Cancer type	Change in relevant flora	Mechanism of action	(Refs.)
Solid tumors	Colorectal cancer	*Bacteroides fragilis, Escherichia coli, Streptococcs bovis gallolyticus, Enteroccocus faecalis, Fusobacterium nucleatum* increase	Changes in flora promote the secretion of inflammatory mediators and produce reactive oxygen species	(6)
	Liver cancer	Microflora depletion	Produces bile acid and affects the liver immune function	(7)
	Pancreatic cancer	*Helicobacter pylori, Pseudomonas aeruginosa, Bifidobacterium*	Immune reaction, inflammation, anti-apoptosis	(8)
	Thyroid carcinoma	Increased number of bacteria causing cancer and inflammation	Impaired intestinal barrier and increased intestinal permeability make it easier for antigens to pass through and stimulate the immune system; microflora affects the supply of essential micronutrients	(9)
	Lung cancer	Firmicutes/Bacteroidetes reduction	Decreased circulating SCFAs, thus affecting host system immunity and inflammation	(10)
Other diseases	Leukemia	Change in flora abundance	Biological antagonism, immune regulation	(11)
	Chronic stress	Change in flora	Brain gut axis and ileum immune regulation	(12)
	Alzheimer's disease	*Helicobacter pylori* infection	Altered level of certain neurotransmitters, proteins and receptors involved in synaptic plasticity	(13)
	Diabetes	Significantly decreased number of *Bifidobacterium, Clostridium* and Firmicutes, and increased number of enterococcal feces	Low level of SCFAs leading to intestinal inflammation and insulin resistance	(14)
	Parkinson's disease	Chronic stress promotes inflammation in the intestinal environment and increases intestinal permeability	Brain-intestine axis	(15)
	Bipolar depression	Abundance of *Akkermania muciniphila* and *Citrobacter spp*.	Brain-intestine axis	(16)

SCFAs, short-chain fatty acids.

affected by the combined effects of various microbiota to regulate the progression of breast and colon cancer. Zhou *et al* (35) compared the fecal microbiota of patients with hepatocellular carcinoma (HCC) and healthy controls, and observed that the abundance of specific flora in patients with HCC was altered, and the authors predicted that tumor cells could alter the intestinal flora to produce TAMs, and reduce the level of antitumor immunity (Fig. 1).

MDSCs. Previous studies have revealed that, under the action of IL-17, MDSCs interact with *Bacteroides fragilis* (Bf) to indirectly induce ectopic colonic epithelial cells, and to induce the expression of IL-17 in intestinal epithelial tissue. Increased IL-17 expression and activated STAT3 signaling, as well as vascular growth factors and proangiogenic mediators, collectively promote colorectal tumor progression (32).

In addition, *F. nucleatum* promoted the regeneration of intestinal epithelial tissue by increasing the number of MDSCs in the tumor microenvironment. In the absence of microorganisms, the expression of the MDSC ligand C-X-C motif chemokine receptor 2 was enhanced, exhibiting immunosuppressive and tumor-promoting effects (32) (Fig. 1).

Cancer-associated fibroblasts (CAFs). CAFs induce chemoresistance in CRC through the synergistic action of hypoxia-inducible factor (HIF)-1α and TGF-β. It was revealed that CAFs can assist in tumor immune escape and resist the action of immunosuppressive drugs. They can induce an inhibitory T-cell microenvironment by recruiting chemokines and immune factors (CCL2, CXCL2, CXCL6, S100A9, IL6) (36) (Fig. 1).

Cytokines. The tumor microenvironment includes inflammatory, immune and hypoxia factors (Table III) (37-50). Numerous factors connect different components in the tumor microenvironment through specific signaling pathways, so that different tumor microenvironments are linked together to form a dynamic tumor-promoting or tumor-suppressing microenvironment (Fig. 1).

Table II. Tumor microenvironment components.

Tumor microenvironment components	Physiological function	Association with tumor	(Refs.)
CAFs	Stroma cell	Stimulation of tumor cell proliferation, invasion and metastasis; chemotherapy resistance; inhibition of T cells in tumors; regulation of the inflammatory response and immune system	(22)
TANs	Contain multiple lysosomes and havee strong chemotaxis and phagocytosis capacities	Recruitment of macrophages and regulation of T cells	(23)
TAMs	First line of defense against microbial infection	Promotion of cancer cell proliferation, angiogenesis, metastasis and immunosuppression	(24)
MDSCs	Myeloid suppressor cells have heterogeneity and differentiation potential, and usually play an immunosuppressive role in the tumor microenvironment	Immunosuppression promotes tumor cell proliferation and metastasis	(25)
DCs	As the main antigen-presenting cells, DCs are the bridge between adaptive and innate immunity	Immunosuppression	(26)
Hyaluronic acid	Extracellular matrix	Promotion of tumor cell proliferation, invasion, immune escape and drug resistance	(27)

CAFs, cancer-associated fibroblasts; TANs, tumor-associated neutrophils; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; DCs, dendritic cells.

Regulatory mechanism

Metabolites

Microbial metabolites. Short-chain fatty acids (SCFAs) are the fermentation products of dietary fiber. Ohtani Haraand Hara (51) identified that, in addition to maintaining intestinal homeostasis, intestinal microbiota metabolites could also transport SCFAs to the liver through the portal vein, and produce bile acids that induce DNA damage to remodel the tumor microenvironment and regulate liver function. Huang *et al* (52) collected feces from patients with liver cancer and healthy individuals for bioinformatics analysis, and observed that bile acids, a metabolite of the gut flora, can affect tumor treatment and prognosis by changing the immune microenvironment. In addition, butyrate and tryptophan metabolites produced by intestinal flora metabolism can affect the adaptive immunity of the body and promote antitumor therapeutic effects (53,54). Cholesterol is metabolized in the gut to produce three metabolites: Bile acids, steroids and vitamin D. Among them, bile acids can modulate the composition of the gut microbiota to affect peripheral and autoimmune immunity, while the metabolic reprogramming of cholesterol in the tumor microenvironment can cause tumor microbiota to change to an immunosuppressive type, thus providing an environment conducive to the proliferation of cancer cells (55) (Fig. 2).

Intestinal metabolites. Radiotherapy and chemotherapy have serious side effects during tumor treatment; thus, an increasing number of experts recommend a diet therapy. Due to their strong antioxidant function, natural polyphenols are often used as targeted regulators for colon cancer prevention and treatment (56). In addition, it was demonstrated that natural polyphenols can not only regulate oxidative stress, cell proliferation, apoptosis and inflammatory inhibition, but can also change the type of gut microbiota that stimulates the production of SCFAs to remodel the tumor microenvironment (56) (Fig. 2).

Non-hematopoietic components of the intestinal membrane. A previous study has shown that the lack of the ubiquitin ligase ring finger protein 5 in intestinal epithelial cells can lead to decreased secretion of intestinal antimicrobial peptides and cell death, which in turn changes the intestinal flora, regulates the activity of lymphoid organs and affects tumor cell invasion (57) (Fig. 2).

Genotoxins. The intestinal flora mediates cancer through genotoxins, such as colicin produced by *Escherichia coli*, which acts as a DNA alkylating agent to damage host DNA (58) and induce cell senescence. Bf toxin is activated by IL-17 in colonic epithelial cells. NF-kB signal transduction produces a series of inflammatory responses and accelerates the transformation of colitis to colon cancer (59). It has been revealed that genotoxin expression is exacerbated when the gut microbiota is altered (60) (Fig. 2).

Metabolic reprogramming. The tumor microenvironment supports the malignant proliferation of tumor cells by providing nutrients and redox requirements for tumor cell proliferation through aerobic glycolysis, and metabolic reprogramming of fibroblasts, T cells, TAMs and adipocytes (61). A previous study has demonstrated that tumor metabolic reprogramming

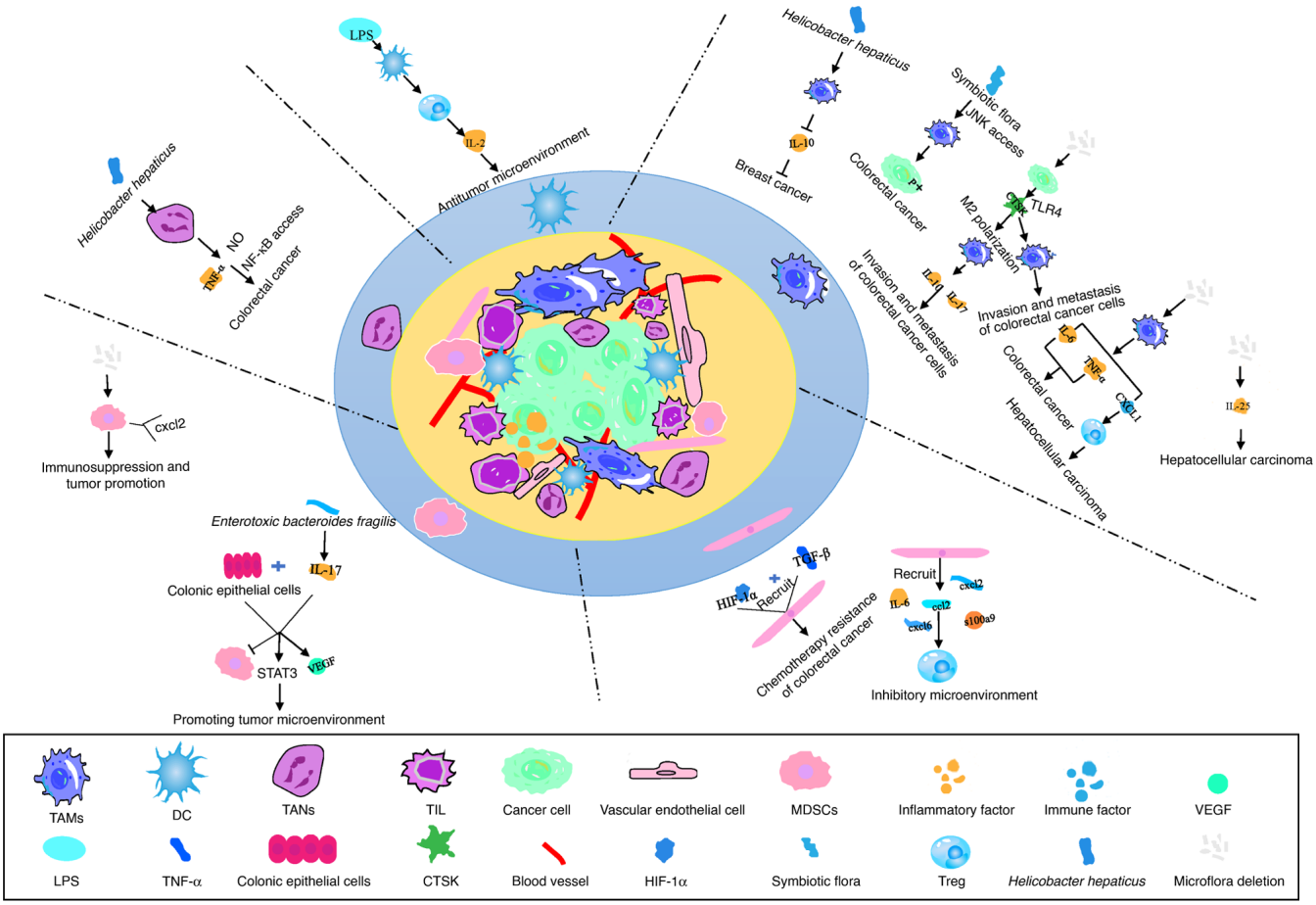

Figure 1. Intestinal flora regulates tumor microenvironment components. TAMs: *Helicobacter hepaticus* can activate TAMs and inhibit the production of IL-10, thus inhibiting the development of breast cancer. The imbalance of gut microbiota directly activates macrophages, macrophages release IL-6, TNF-α and CXCL10. IL-6 and TNF-α accelerate the development of CRC by promoting EMT, while CXCL10 induces T-cell infiltration in the tumor microenvironment and promotes the development of HCC. Intestinal microbiota bacterial diseases induce tumor cells to secrete CTSK, thereby activating macrophages through mTOR-dependent pathways. CTSK stimulates the macrophage secretion of IL-10 and IL-17, thus promoting the invasion and metastasis of CRC cells. Some symbiotic microbiota stimulate macrophages to increase c-Jun phosphorylation in CRC cells through the JNK signaling pathway, thus accelerating CRC cell proliferation. Intestinal microbiota bacterial diseases also induce the production of IL-25 from cluster cells, which promotes EMT and the migration of HCC cells. CAFs: CAFs influence the tumor immune microenvironment by recruiting chemokines and immune factors. MDSCs: IL-17 recruits bone MDSCs into the colon tumor microenvironment of mice colonized with enterotoxin bacteria, which indirectly induce the ectopic production of chemokines and growth factors through direct interaction with IL-17 receptors in CECs, and the expression of IL-17 in submucosa. IL-17 and transformed CECs jointly promote tumor development with angiogenic mediators, namely MMP-9 and VEGF, by inhibiting immune effector cells and activating the STAT3 signaling pathway. Early lack of microbiota in mice enhances the expression of C-X-C motif receptor 2 ligands. A number of gut pathogenic microorganisms or gut microbiota and their synergistic interactions with cytokines activate and proliferate MDSCs in the tumor microenvironment, thus mediating the immune escape of tumor cells. TANs: *Helicobacter hepaticus* can induce the generation of neutrophils, thereby inducing nitric oxide and TNF-α increased content, which activates the NF-κB signaling pathway and promotes tumor generation. DCs: Lipopolysaccharide and TNF-α stimulate DCs to mature and activate, and subsequently activate T cells to produce IL-2 to form an antitumor microenvironment. TAMs, tumor-associated macrophages; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; CTSK, carnosine K; CAFs, cancer-associated fibroblasts; MDSCs, myeloid-derived suppressor cells; CECs, colon epithelial cells; DCs, dendritic cells; TANs, tumor-associated neutrophils; CXCL, C-X-C motif ligand.

can mediate tumor immune escape. Lactic acid produced by glycolysis can stimulate tumor cell metastasis, and oxidized compounds highly expressed by tumor cells can accelerate the metabolism of tryptophan to kynurenine by T cells. The lack of tryptophan and the increase in kynurenine alter the function of T cells, rendering them unable to be activated by antigens, thus forming an immunosuppressive microenvironment (62) (Fig. 2).

Immune reprogramming

Immune escape. Gut microbes influence tumor immunotherapy in multiple ways. Some bacteria achieve antitumor efficacy by activating immunity, while some help cancer cells to escape the immune system by mediating immunosuppression (63). Thus, increasing evidence has shown that the clinical treatment effect can be improved by regulating or supplementing microorganisms *in vitro* (64).

Bf can induce forkhead box $P3^+$ (a potent inducer of gastrointestinal immunity and peripheral tolerance) to induce regulatory T-cell (Treg) generation, while commensal microorganisms can promote the efflux of pDCs. pDCs and Tregs work together to mediate immune escape (65).

Reprogramming of immune cells. Mononuclear phagocytes are highly plastic, and the gut flora interferes with the reprogramming of mononuclear phagocytes in the tumor microenvironment into immunostimulatory monocytes and DCs, making the tumor microenvironment shift to a tumor

Table III. Cytokines in the tumor microenvironment.

Classification	Name	Role	(Refs.)
Inflammatory factors	IL-1β	Low concentration of IL-1β induces local inflammatory and protective immune responses, while high concentrations can lead to inflammation-related cancer tissue damage	(37)
	TNF-α	TNF-α can continuously activate NF-κB, which regulates inflammation	(38)
	IL-6	Participates in the inititation of the inflammatory pathway	(39)
	IL-10	Inhibits the inflammatory response	(40)
Immune factors	IL-17	Pro-inflammatory	(41)
	IL-22	Pro-inflammatory	(42)
	IL-35	Antitumor activity	(43)
	TGF-β	Suppresses the immune response	(44)
Chemokines	IL-8	Cancer-promoting factors promote tumor immune escape	(45)
	Recombinant chemokine CXCR6	Increases immune cell infiltration in tumor tissue	(46)
	Recombinant human CCL4	Achieves antitumor effects by recruiting regulatory T cells and promoting tumor macrophages	(47)
	Recombinant human CCL3	Participates in immune monitoring and tolerance	(48)
	Recombinant human CXCL5/CXCR2	By blocking the bridge between tumor and host cells in the tumor microenvironment, it can improve immune efficacy	(49)
	Recombinant human CXCL12	Antitumor activity	(50)

CXCR, C-X-C-motif receptor; CXCL, C-X-C-motif ligand; CCL, C-C-motif ligand.

suppressor environment (66,67). The mechanism is a microbiota-derived IFN-stimulating factor agonist that modulates macrophage polarization and natural killer (NK) cell-DC interactions through monocyte-induced IFN-1. Subsequent *in vitro* experiments confirmed that IFN-1 increased in mice under a high-fiber diet, and mononuclear phagocytes in the tumor microenvironment were remodeled, the number of DCs increased, and the efficacy of immune blocking agents was improved (68) (Fig. 2).

Signaling pathways and cytokines. The tumor microenvironment mainly includes inflammatory cytokines, immune cytokines and hypoxia cytokines. Research has revealed that, in colon cancer and other diseases, the intestinal flora, and the inflammatory, immune and hypoxic microenvironments cross-talk, are closely related and interact with each other. When the intestinal flora is imbalanced, it leads to the inflammation of epithelial cells, which leads to hypoxia. Increased HIF levels induce an increase in inflammatory (NF-κB) and immune (Th17, IL-17) factors, which aggravates inflammation and leads to cancer. The intestinal flora stimulates the release of TNF-α and VEGF, promotes angiogenesis in the tumor microenvironment, aggravates the hypoxia of the tumor microenvironment, increases the content of HIF, and further aggravates the hypoxia and inflammation of the microenvironment (69-72) (Fig. 3).

Other mechanisms. Phosphatase and tensin homolog (PTEN), as a tumor suppressor gene, can antagonize PI3K-Akt signaling to suppress tumorigenesis (73). Although PTEN deficiency is not sufficient to induce tumorigenesis, it can accelerate tumor progression. Howe *et al* (73) revealed that the pro-inflammatory *Acinetobacter acidophilus* was greatly reduced in the microenvironment of PTEN gene-knockout mice. Therefore, it was considered that *Adenobacter acidophilus* could help to prevent the protumor microenvironment caused by PTEN deficiency and form a preventive tumor microenvironment. The aforementioned study linked genetic changes to the gut microbiota and tumor microenvironment, thus providing new insights for subsequent studies on the role of gut microbiota in shaping the tumor microenvironment.

Cathepsin K (CTSK) mainly acts on bone remodeling and resorption. As the only upregulated metastasis-related signal in colon cancer cells, it has been revealed that intestinal flora dysbiosis leads to increased LPS content, which in turn promotes the expression of the CTSK gene and changes the tumor stromal microenvironment to promote colon cancer cell migration and invasion into the bone (74). As transcriptional regulators, microRNAs (miRNAs) play a significant role in various physiological activities such as immunity and metabolism. Through genomic analysis, it was identified that gut microbiota may reshape the tumor microenvironment by affecting miRNAs, thereby affecting the metastasis and prognosis of CRC (75,76).

In the treatment of diarrhea in piglets, it was identified that diarrhea was caused after weaning. Concurrently, the deletion of specific miRNAs would change the abundance of specific bacteria in the intestinal flora, resulting in increased expression of specific enzymes. Succinic acid is enriched in

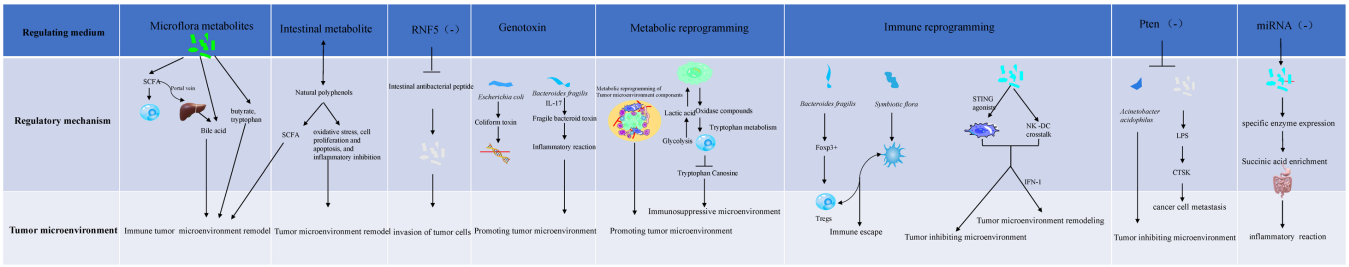

Figure 2. Mechanisms of intestinal flora-mediated regulation of the tumor microenvironment. Metabolites: i) Metabolites of flora: SCFAs can be transmitted to the liver through the portal vein to produce bile acid and change the tumor microenvironment. Butyrate and tryptophan affect the development of tumors by affecting their immune response. ii) Intestinal metabolites: Intestinal metabolism produces polyphenol analogues, changes the type of gut microbiota, stimulates the production of SCFAs and reshape the tumor microenvironment. Non-hematopoietic components of the intestinal membrane: When intestinal epithelial cells lack ubiquitin ligase, the secretion of intestinal cathelicidin decreases, and epithelial cells die, which causes changes in the gut microbiota and regulates the tumor immune microenvironment. Genotoxins: PKS gene-positive *Escherichia coli* can destroy the single-stranded DNA of intestinal cells, playing an indirect role in the development of CRC, and colon epithelial cells can cause DNA damage and activate Wnt and NF under the action of fragile bacteroid toxins-κB. STAT3 and other colon epithelial signal transduction pathways affect the self-renewal of colon mucosal epithelial cells and promote tumor formation. Metabolic reprogramming: The tumor microenvironment provides nutrients for malignant proliferation and metastasis of tumor cells by changing the metabolism of different components of the tumor microenvironment. Anaerobic glycolysis of tumor cells produces lactic acid, which can stimulate the production of hyaluronic acid and the expression of CD44, and is conducive to tumor metastasis. The hypoxic acidic tumor microenvironment caused by aerobic glycolysis inhibits the normal metabolism of immune cells and T cell function. Tumor cells mediate the metabolism of tryptophan in T cells by overexpressing indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase in order to transform tryptophan into caninurenine and its metabolites. Lack of tryptophan and accumulation of caninurenine metabolites would inhibit the function of effector T cells. Immune reprogramming: i) Immune escape: *Bacteroides fragilis*, as an inducer of forkhead box $P3^+$ (a powerful inducer that mediates gastrointestinal immunity and peripheral tolerance), can induce the production of IL-10-mediated mucosal surface tolerance, which can induce the generation of Tregs, while symbiotic microorganisms can promote the escape of pDCs. Both pDCs and Tregs work together to mediate immune escape; ii) reprogramming of immune cells: STING agonists derived from microbiota induce the production of IFN-I through mononuclear phagocytes in tumors, thus forming an antitumor microenvironment. By regulating the natural killer cell-DC crosstalk, the content of IFN-I is regulated, reshaping the tumor microenvironment, and facilitating the response to immune checkpoint blockade. In the absence of PTEN (gene of phosphate and tension homology deleted on chromosome ten) expression, miRNA expression and the proinflammatory bacteria *Akkermania muciniphila* in the gut microbiota decrease, forming a microenvironment that inhibits tumor growth. When the gut microbiota is altered, the lipopolysaccharide content, the expression of the cathepsin K gene and the risk of colon cancer cell metastasis increase. Due to the loss of miRNA, succinate produced by the microbiota accumulates in the colon, leading to diarrhea in weaned piglets. SCFAs, short-chain fatty acids; CRC, colorectal cancer; STING, stimulator of interefferon genes; Tregs, regulatory T cells; pDCs, plasmacytoid dendritic cells; miRNA, microRNA.

the intestine and promotes intestinal epithelial tissue fluid. The secretion of fluid causes an inflammatory response leading to diarrhea (77).

In summary, further studies are required to investigate whether the deletion of a certain miRNA can also cause changes in the homeostasis of a target organ (such as inflammatory response, pathway stimulation or immune response) and can help to regulate tumors through interacting with their microenvironment for the treatment and diagnosis of tumors (78).

Clinical application

Probiotics. A reasonable use of probiotics (as a common mean of regulating intestinal flora imbalances) in the treatment of colon cancer can not only change the composition of the flora but also regulate the immune response of the intestinal tract, thereby preventing and treating colon cancer (79). Galunisertib, a TGF-β blocker, was revealed to relieve immunosuppression by enhancing the infiltration of specific effector T cells and promoting DC maturation in the tumor microenvironment, when combined with *Bifidobacterium* probiotics (80).

Fecal microbiota transplantation (FMT). As a new therapy, FMT mainly transplants healthy human gut microbiota into patients to remodel and partly restore intestinal homeostasis. In 2013, it was used in the treatment of *Clostridium difficile* infection. Icreasing evidence has clarified the therapeutic effect of fecal transplantation for other diseases (18). For example, in 2021, allogeneic fecal bacterial transplantation was applied in phase I clinical trials in patients with anti-programmed cell death 1 refractory metastatic melanoma, and it was revealed that it could alter the infiltration and gene expression characteristics of immune cells in the tumor microenvironment (82). In addition, when using trastuzumab to treat a HER2-positive breast cancer mouse model, the researchers observed that allogeneic fecal bacterial transplantation enhanced the efficacy of trastuzumab in blocking cancer cell proliferation and improving immune cell infiltration in the tumor microenvironment (83). In recent years, the concept of autologous fecal transplantation has emerged, which is similar in concept to the preservation of neonatal umbilical cord blood, and implies the rejuvenation of intestinal flora. Although this concept has certain feasibility, its efficacy and safety have yet to be verified (84).

Natural extracts. Numerous studies have shown that natural plant extracts [triterpenoid saponins (85), safflower (86), *Astragalus* polysaccharides (87), puerarin (88)] and traditional Chinese medicine formulas [SWY (89), Wu Mei Wan (90), and parthenolide (91)] alter the tumor microenvironment by modulating the gut microbiota *in vitro*. However, their research is currently limited to animal experiments, and have yet to be used in clinical practice (92) (Table IV).

Diet. Diet is the most direct and important factor affecting the intestinal flora. It has been demonstrated that a high-fat diet can change the intestinal flora to accelerate intestinal inflammation through direct or extraintestinal effects, and change the metabolism and tumor immune microenvironment (93).

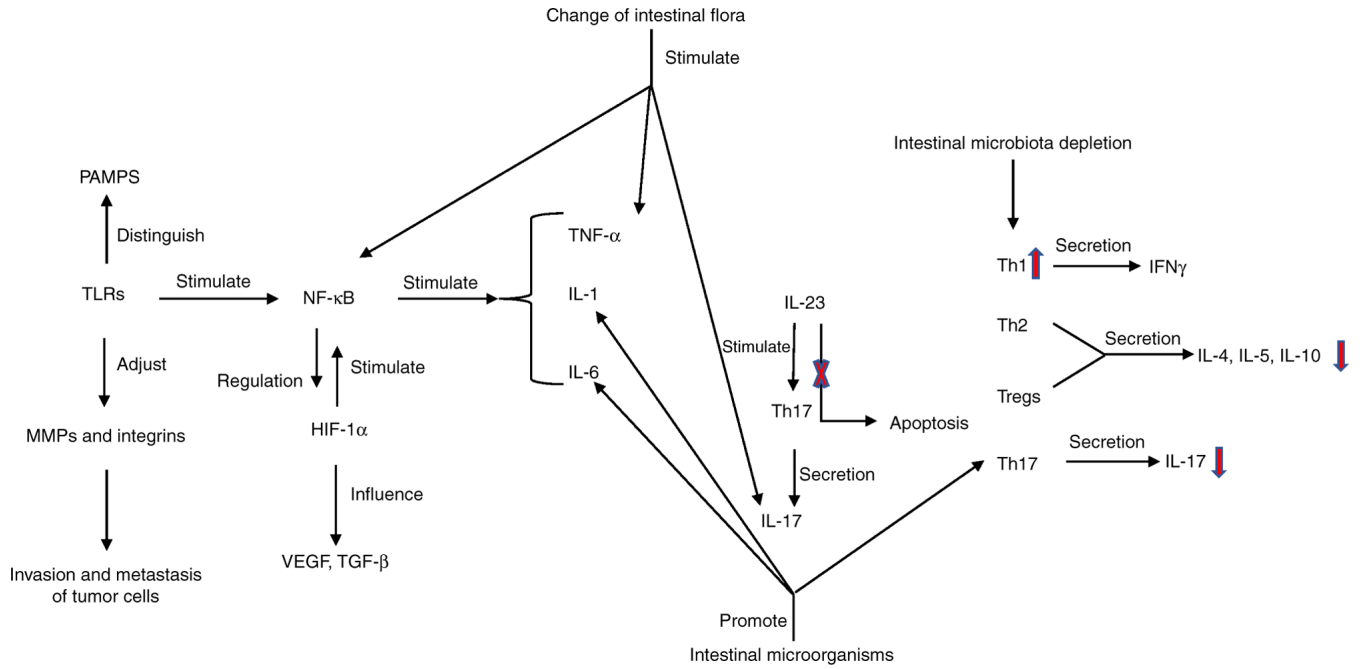

Figure 3. Signaling pathways and cytokines. The signal transmission of innate immunity in the intestine is mainly achieved through the recognition of NOD like receptors and TLRs to generate perception. Pathogen related molecular patterns of different microorganisms are recognized by TLRs, TLRs activate NF-κB and stimulate the production of inflammatory factors and chemokines. When the gut microbiota changes abnormally, TLRs will be abnormally activated, producing a series of inflammatory and tumor-promoting reactions. At the same time, they can regulate the invasion and metastasis of cancer cells via MMPs and integrins. Th17 cells can secrete IL-17 and IL-23, which can regulate Th17 cells. Blocking IL-23 secretion can alleviate inflammation. The content of HIF-1α in a hypoxic tumor environment increases, which activates NF-κB. NF-κB can increase macrophage HIF-1α expression in the tumor microenvironment. HIF-1α and TGF-β have synergistic effects. HIF-1α is positively associated with the angiogenic factor VEGF. Th cells mature into Th1, Th2, Treg and Th17 cells. Th1 cells secrete IFN-γ, while Th2 cells and Tregs secrete IL-4, IL-5 and IL-10 for antitumor effects, and Th17 cells secrete IL-17. After gut microbiota depletion, the content of IFN-γ increases and the IL-17 content decreases. PAMPs, pathogen-associated molecular pattern molecules; MMPs, matrix metalloproteinases; TLRs, toll-like receptors; Th, helper T cell; HIF, hypoxia-inducible factor; Treg, regulatory T cell.

A previous study has also revealed that a high-fat diet increases the sensitivity of the gut to carcinogens (94). Therefore, scientists suggest that a ketogenic and high-fiber diet can be used to regulate intestinal flora metabolism and tumor microenvironment (95). Dietary carrageenan, as a food additive, alters the gut microbiota resulting in SCFA reduction, mucosal thinning and changes in intestinal homeostasis to form a proinflammatory microenvironment. Therefore, it was speculated that this inflammatory response can be reversed by supplementation with probiotics (96). In addition to the direct factor of diet, the intestinal flora of the human body also includes the host environment. Since the growth of intestinal flora requires the body to provide ATP to support its growth and form colonies, factors such as a poor diet, antibiotics and intestinal diseases weaken the control of the body over the flora, thus resulting in changes in flora homeostasis. It is thus possible to quantify the conditions that control the growth of the microbiota, thereby defining the homeostasis and imbalances of the gut microbiota, and regulating microbiota imbalances (97).

5. Biological targets

The tumor microenvironment, as the place of tumor growth, regulates the occurrence, development and metastasis of tumors. As an important factor influencing the tumor microenvironment, intestinal microbiota has been demonstrated to interact with the tumor microenvironment. Based on extensive literature review, it has been revealed that the role of microorganisms in mediating the tumor microenvironment and then influencing tumor progression is played by a group of bacteria rather than a specific strain. The following is a summary of relevant biological targets, providing potential insights for their clinical applications (Table V).

Prevention. It has been identified that the induction of SCFA is strain-specific, thus, its inductive ability can be inferred from the abundance of gut flora to predict changes in the tumor microenvironment (98).

Quantitative analysis of the composition of bile acid, the metabolite of gut microbiota, and bile salts in feces can be used to identify the risk index of HCC, and to further combine the composition and category of gut microbiota to grade the risk of HCC. This may be related to the inflammatory environment formed by the gut microbiota and the tumor microenvironment, which can stimulate the occurrence and development of tumors. Therefore, the observation and intervention of gut microbiota can be a good means for the prevention and treatment of HCC (99).

Diagnosis. The quantity of *Fusobacterium nucleatum* DNA in the intestinal flora has been revealed to be positively associated with tumor stage, metastasis and patient survival. In clinical practice, the level of *Fusobacterium nucleatum* DNA can be measured for colon cancer tumor staging, metastasis, chemotherapy resistance, sex and prognosis (100).

Table IV. Regulation of intestinal flora by natural extracts.

Plant	Extract	Flora change	Regulatory mechanism	Disease treatment	Subjects	(Refs.)
Carthamus tinctorius	Safflower yellow	*Barnesiella* and *Ersipelotrichaceae incertae sedis* return to normal levels	Improvement of the immune microenvironment	Hepatocellular carcinoma	*In vivo* test in mice	(86)
Astragalus membranaceus	*Astragalus* polysaccharides	Regulation of changes in *Bifidobacterium pseudolongum, Lactobacillus johnsonii* and *Lactobacillus* flora	Improvement of the metabolism of glutamate and creatine could control tumor growth	Melanoma	*In vivo* test in mice	(87)
Pueraria lobata	Puerarin	Restoring imbalance of firmicutes to acteroides	Regulation of the content of SCFAs and aminoacid metabolites by adjusting the gut/bone axis could improve the bone microenvironment	Osteoporosis	*In vivo* test in mice	(88)
Zingiber officinale Roscoe, *Allium tuberosum* Rottler ex Spreng., *Pyrus Bretschneider* Rehder, *Nelumbo nucifera* Gaertn.	Chinese herbal compound extract	The expression of the class Bacilli, the genus *Turicibacter*, the family Turicibacteae, and the order Turicibacterales return to normal levels	Regulation of metabolism, changes in the tumor microenvironment	Esophageal precancerous lesion	*In vivo* test in mice	(89)
Wumei, Huanglian, Xixin, Guizhi, Dangshen, Fuzi, Huajiao, Ganjiang, Huangbai, Danggui	Chinese herbal compound extract	Bacteroidetes and firmicutes imbalance restoration	Downregulation of the NF-κB/IL-6/STAT3 signaling pathway to regulate the inflammatory environment of the intestine	Colorectal cancer	*In vivo* test in mice	(90)
Feverfew	Parthenolide	*Alloprevotella* displayed high abundance	Improves the Treg/Th17 balance in intestinal mucosa mediated through increased microbiota-derived SCFA production	Inflammatory bowel disease	*In vivo* test in mice	(91)

Treg, regulatory T cell; Th, helper T cell; SCFA, short-chain fatty acid.

Table V. Mechanism of action and diseases of biological targets.

Target action	Target name	Mechanism of action	Disease	(Refs.)
Prevent	Anti-inflammatory characteristic bacteria with potential for producing butyric acid	Changes in microbiota result in changes in the content of butyric acid, a metabolite of the microbiota	Colon cancer	(98)
	Bile acid	Formation of an inflammatory microenvironment	Hepatocellular carcinoma risk prediction and grading	(99)
Diagnosis	Number of DNA fragments from *Fusobacterium nucleatum*	Microbiota dictates tolerogenic vs. immunogenic cell death of intestinal epithelial cells	Staging, metastasis, chemotherapy resistance, and prognosis of colon cancer	(100)
	Increased *Leptotrichia* and decreased *Porphyromonas* in saliva	Gut microbiota can be connected in series with related flora through the mesentery lymphatic pathway	Early diagnosis of pancreatic cancer	(101)
	Abundance of *Akkermansia*	Secretion of interferon by $CD8^+$ T cells causes tumor killing	Diagnostic and therapeutic targets of ovarian cancer	(102)
Treatment	Beneficial microbiota such as *Bifidobacterium, Bacteroides fragilis* and *Akkermansia muciniphia*	Regulation of the tumor immune microenvironment	May be used as a sensitive target for immunotherapy	(103, 105)
Prognosis	CTSK	CTSK secreted by tumors can bind to Toll-like receptor 4 and stimulate M2 polarization of tumor-associated macrophages through the mTOR-dependent pathway, thereby inhibiting the development and metastasis of colorectal cancer	Invasion and metastasis of colon cancer	(74)
	Pseudomonas, Saccharopolysaccharide, Streptomyces and *Clostridium*	Effects on tumor growth and immune infiltration	Prediction of long-term survival of patients with pancreatic cancer	(109)

CRC, colorectal cancer; CTSK, cathepsin K.

There are differences in the types and abundance of gut microbiota among different diseases, such as *Bacteroides*, *Lachnospiraceae incertae sedis*, and *Clostridium* XIV, which can be used to identify small liver cancer (52).

Pancreatic cancer, as the most lethal malignant tumor, can not be diagnosed by common detection methods in the early, or even in the mid or late stages (101). Yang *et al* (101) revealed that *Leptotrichia* increased and *Porphyromonas* decreased in the saliva of patients with pancreatic cancer, suggesting that it could be used as a marker for early diagnosis. Gut microbiota can enter the pancreas through the mesentery lymphatic pathway to connect different flora, and affect the occurrence and development of pancreatic cancer remotely.

Wang *et al* (102) revealed that *Akkermansia* in the intestines of patients with ovarian cancer was significantly reduced by analyzing the abundance of gut microbiota of patients. In addition, when the gut microbiota of these patients was inoculated into mice by fecal bacteria transplantation, the progression of ovarian cancer in mice was accelerated. The addition of *Akkermania* can significantly inhibit the progression of ovarian cancer in mice. This research has shown that *Akkermania* restores the integrity of the intestinal mucosa, activates T-cell immune response in the tumor microenvironment, and strengthens immune monitoring. This aforementioned study (102) provided a new direction for the relationship between gut microbiota and the immune microenvironment in ovarian cancer, and also suggests that *Akkermania* can be used as a new target for diagnosis and treatment of ovarian cancer.

Treatment. A previous study has demonstrated that the intestinal flora inhibits apoptosis, changes epigenetic transplantation, repairs damaged DNA and participates in other mechanisms to generate therapeutic resistance, but it can also be used as a target to manipulate and improve the therapeutic effect of treatments (103).

Traditional radiotherapy is the most effective method to treat tumors. As an important factor in regulating the tumor microenvironment, gut microbes are impacted from the effect of radiotherapy. It has been revealed that there are differences in the sensitivity of different gut microbiota to radiotherapy, but the specific mechanism remains unknown (104). Therefore, the sensitivity of patients to radiotherapy may be evaluated by

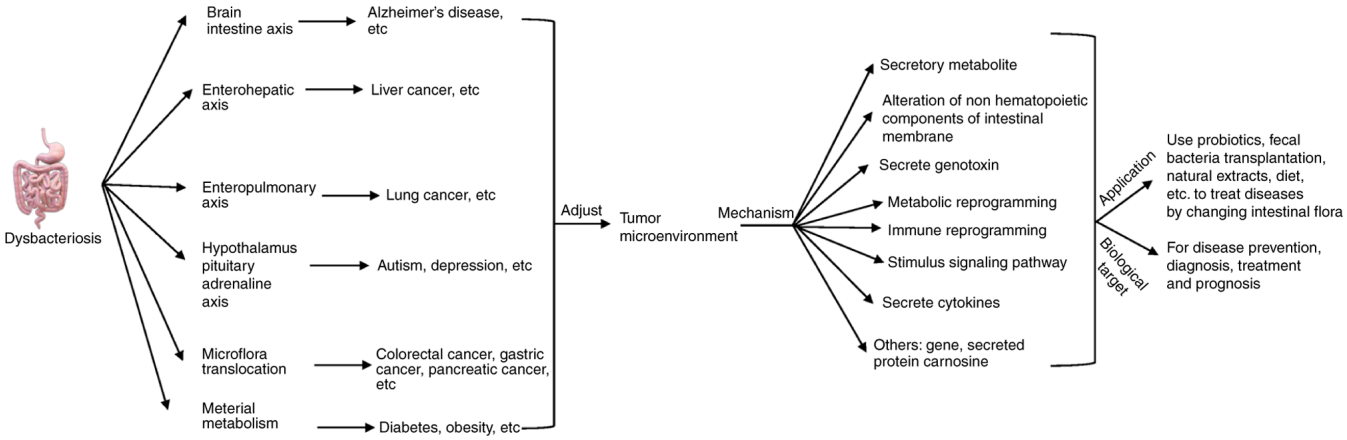

Figure 4. Intestinal flora, disease, tumor microenvironment, influence mechanism and application. Dysbiosis of intestinal flora can affect the tumor microenvironment through various pathways such as the intestinal-liver and intestinal-brain axes, which can cause various diseases such as Alzheimer's disease, liver cancer, lung cancer and Parkinson's disease. The mechanisms by which the intestinal flora regulates the tumor microenvironment mainly involve metabolites, non-hematopoietic components of the intestinal membrane, genotoxins, metabolic reprogramming, immune reprogramming and regulation of signaling pathways. Study of the association between intestinal flora, disease and tumor microenvironment revealed that probiotics, fecal transplants and natural extracts could be used to modify the intestinal flora to treat diseases, while the related regulatory mediators could be applied as biological targets for disease prevention, diagnosis, treatment and prognosis.

analyzing the types of intestinal flora, with the intent that the treatment plan can be timely adjusted.

Traditional radiotherapy and chemotherapy are aimed at the tumor cells themselves, using physical rays and chemical drugs to kill them, but drug resistance is prone to occur. It has been revealed that the combination of traditional therapy and immunotherapy can greatly reduce the drug resistance of tumor cells and improve the therapeutic effect. Research has shown that gut microbiota can affect the effectiveness of immunotherapy (105). PD-1/PD-L1 has good efficacy in the treatment of solid tumors, and has been demonstrated that, in *in vitro* experiments in mouse models, mice with oral microbiota have improved anti-PD-1 efficacy than untreated mice (32). Transplanting fecal bacteria from patients who have responded to anti-PD-1 antibodies into germ-free mice could significantly improve the control effect of T cells on tumors, and have a favorable effect on PD-1/PD-L1 immunotherapy. Immune checkpoint inhibitors (ICIs), as a new treatment method, exhibit favorable curative effects, but some patients are insensitive to them or develop resistance to their long-term use (106). It was shown that patients who responded well to ICIs had a high number of beneficial bacteria in the gut (*Bifidobacterium,* Bf*, Akkermansia muciniphia*), which could help to restore and enhance the therapeutic effect of ICI and immunotherapy in patients (79). As the latest targeted therapy, chimeric antigen receptor T-cell immunotherapy (CAR-T) is based on the principle of isolating the T lymphocytes of the patient, expanding them *in vitro* to make them carry tumor cell antigens, and then infusing them back into the body of the patient, in order to achieve rapid and precise tumor treatment. Through clinical stool sample observation and genome sequencing analysis, it was identified that, in patients with B-cell malignancies, there was a strong association between changes in gut microbiota and clinical treatment outcomes of CAR-T therapy (107).

In addition, studies have demonstrated that microorganisms in tumors, oral microbiota, and other factors can affect the tumor immune microenvironment, thereby affecting tumor immunotherapy. Therefore, understanding the relationship between microorganisms, the tumor microenvironment and diseases provides a new target for better use of microorganisms to treat diseases accurately (108).

Prognosis. Pancreatic cancer is a malignant tumor of the digestive tract with extremely high mortality, because its early diagnosis is difficult. Yang *et al* (101) revealed that the imbalance of intestinal microbiota is closely related to the incidence and prognosis of pancreatic cancer. In addition, Huang *et al* (52) revealed that high bile acid metabolism, low levels of *Bacteroides*, *Lachnospiracea incertae sedis*, and *Clostridium XIVa* and content of operational taxonomy unit markers related to bile acid metabolism could be used to predict the postoperative survival time of patients with liver cancer.

As a measure of gut microbiota imbalance and CRC metastasis, CTSK secreted by CRC could accelerate the phenotype transformation of TAMs to M2 by regulating the TLR4-mTOR signaling pathway, thereby accelerating the progression of CRC. Concurrently, it can secrete inflammatory factors to promote cancer cell invasion and metastasis. Therefore, it has been suggested that CTSK may serve as a new prognostic and therapeutic target for CRC (74). In other research, four characteristic microbes in the tumor microbiota (*Pseudomonas, Glycopolysaccharides, Streptomyces* and *Clostridium*), which could predict the long-term survival of patients with pancreatic cancer, were also identified. Using donor fecal microbiota transplantation, it was determined that the tumor microbiota may be regulated differently and affect tumor growth and immune infiltration (109).

6. Conclusions

Overall, the gut microbiota regulates intestinal and distant tumors through changes in the microbiota, brain-gut axis, hypothalamic pituitary adrenal axis, intestinal liver axis and

bacterial translocation. It is mainly manifested in the regulation of each component in the tumor microenvironment, to achieve the regulation of the tumor microenvironment. Its regulatory mechanisms include changes in gut and microbiota metabolites, gene toxins, metabolic reprogramming, immune reprogramming, signaling pathways and cytokines. The transplantation of probiotics and fecal microbiota methods in the treatment of tumors in the microenvironment of gut microbiota regulation have matured. However, other treatment methods are still at the theoretical stage and have not been clinically validated, and their adverse effects on the body remain unclear. In addition, the present review also summarized and compared the biological targets of gut microbiota regulating the tumor microenvironment, providing a theoretical basis for future applications in the prevention, diagnosis, treatment and prognosis of tumors (Fig. 4).

At present, most of the specific microbiota and pathway changes in the regulatory mechanism of disease-gut microbiota-tumor microenvironment lack *in vivo* and *in vitro* experiments. Numerous studies have demonstrated that substances such as vitamins (81) and lactic acid produced by glycolysis in the tumor microenvironment (110) can change the intestinal flora or tumor microenvironment, however whether these substances mediate the regulation of gut microbiota in the tumor microenvironment has not yet been elucidated, which will open up new directions for future research. As a key cell in tumor immune regulation, tumor-infiltrating myeloid cells, a component of the tumor microenvironment, require modification and activation by m6A methylation (111). Previous studies have revealed that the methylation of intestinal flora can interfere with the expression of the oncogenic gene p53 and activate it. SCFAs promote early onset and metastasis of tumors (112), and it has been shown that quantification of m6A methylation may serve as a potential biological target for pancreatic cancer prognosis (113). Thus, whether the methylation of gut microbiota also regulates tumors by affecting the function of tumor-infiltrating myeloid cells, provides a new objective for future research.

There are complex connections between the gut microbiota and the tumor microenvironment, and the gut microbiota-tumor microenvironment directly affects the prevention, diagnosis, treatment and prognosis of diseases. Therefore, an in-depth study of the association between the gut microbiota and the tumor microenvironment will provide new means for the targeted treatment of clinically common and difficult tumors by regulating the intestinal flora and tumor microenvironment in the future.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Inner Mongolia Autonomous Region Health Science and Technology Plan Project Assignment (grant no. 202201184), the Inner Mongolia Medical University Zhiyuan Talent Program (Good Learning Talent Program) (grant no. ZY0202031), the Program for Young Talents of Science and Technology in Universities of Inner Mongolia Autonomous Region (grant no. NJYT23050) and the Inner Mongolia Autonomous Region 'Grassland Talent' project youth innovation and entrepreneurship talent project (grant no. 2022073).

Availability of data and materials

Not applicable.

Authors' contributions

CH and GH conceived and designed this review. TX and YL wrote the first draft. SJ critically revised the review for important intellectual content. ZR, SR, ZY, ZJ and TC contributed in the writing of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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