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Review

The Role of Intestinal Flora in Anti-Tumor Antibiotic Therapy

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Abstract

Anti-tumor antibiotics are chemical substances produced by micro-organisms to control cancer development. Some of the currently used cancer treatment regimens are anti-tumor antibiotics. However, many studies have demonstrated that anti-tumor antibiotics may have adverse effects on normal cells. This calls for development of strategies to alleviate these negative effects and improve cancer treatment. Recent studies have suggested that the efficacy of anti-tumor antibiotics may be affected by intestinal microbiota. For instance, intestinal microbiota can alleviate the negative effects of antibiotic treatment and regulate the tumor immune micro-environment. In this way, anti-tumor antibiotics can improve tumor control. However, the specific mechanisms need to be further explored. This review discusses the effect of intestinal flora on anti-tumor antibiotic therapy and summarizes the specific mechanisms by which antibiotics inhibit harmful intestinal micro-organisms and promote efficacy of probiotics, which may improve the control of neoplasm development and growth.

Keywords: anti-tumor antibiotics; intestinal flora; anti-tumor; metabolism; tumor immune

1. Introduction

The incidence of cancer has been on the rise worldwide. For instance, the GLOBOCAN 2020 report by the International Agency for Research on Cancer estimated that about 19.3 million new cancer cases and 10.0 million cancer deaths occurred in 2020 [1]. Therefore, prevention, prompt diagnosis, and aggressive treatment for cancer are necessary [2]. Cancer treatment options mainly include surgery, radiotherapy (RT), and chemotherapy [3]. Although surgical resection is suitable for early localized tumors, it is not effective for patients with intermediate and advanced stages. Moreover, the resectability of advanced pancreatic cancer cannot be evaluated preoperatively [4]. It has also been reported that tumor recurrence in surgical patients which result in poor 5-year overall survival (OS) rate [5]. Compared with surgery, radiation therapy has a lower local control effect on tumors. However, radiation therapy can also kill or damage normal tissues [6]. Chemotherapy has fewer toxic side effects than RT. Chemotherapy can shrink tumors and slow down the growth rate of cancer cells. Therefore, chemotherapy can be an important adjuvant therapy for malignant tumors [7].

Anti-tumor antibiotics, a common class of drugs in chemotherapy, has been used in the clinical treatment of cancer for many years [8]. Antibiotics are exogenous microbial metabolites which are metabolized by environmental micro-organisms. These metabolites can kill tumor cells, hence are used for cancer treatment. However, prolonged antibiotic use may cause toxic side effects, which limits their overall therapeutic effect [9–19].

Studies have shown that intestinal flora can inhibit tumor occurrence and development, and alleviate the negative effects caused by chemotherapies, such as antibiotics [20].

The intestinal micro-environment is the largest and most complex micro-ecosystem in the human body, which harbors about 80% of the body's normal microbiota. Digestion occurs in the intestinal micro-environment, thus intestinal flora participates in the regulation of digestion and metabolism. Intestinal flora metabolites mainly contain short-chain fatty acids (SCFAs), branched-chain fatty acids, indoles, amino acids, vitamins, amines, phenols, cholic acid, and choline [21].

Moreover, intestinal microbiota affects numerous aspects of human health. Micro-organisms influence intestinal micro-ecology and therefore affect the development of cancer and other diseases. In addition, intestinal flora metabolites regulate the phenotype of tumor somatic cell mutations and efficacy of immune checkpoint inhibitors (ICIs) [22]. Therefore, dysbiosis of intestinal microbiota and bacteria with carcinogenic properties can cause cancers, such as colorectal carcinoma (CRC) [23]. This shows that intestinal microbiota plays a key role in the occurrence and development of tumors.

This paper describes the role of micro-organisms and metabolites in anti-tumor research. In addition, we discuss

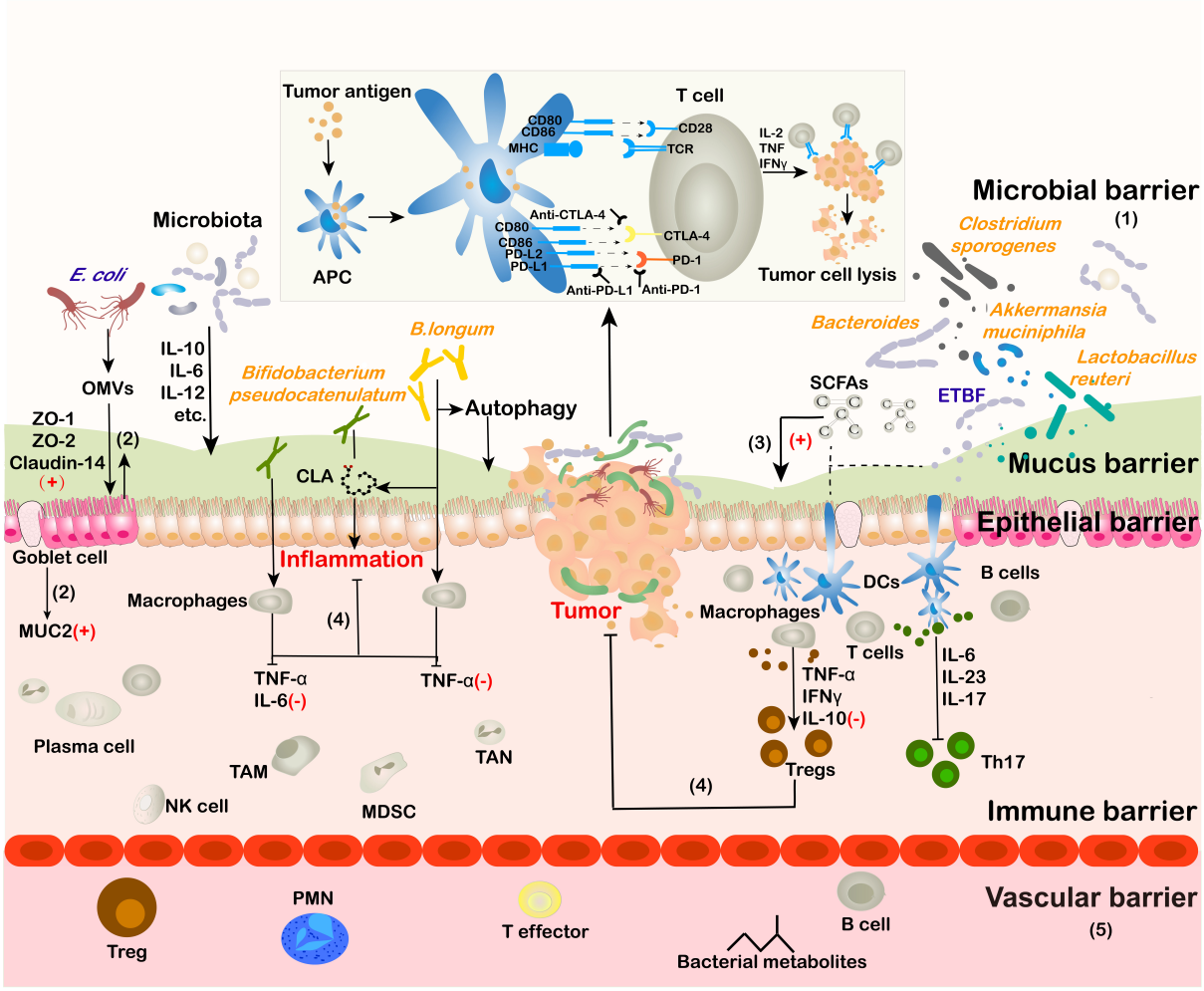

Fig. 1. Intestinal barriers and tumor. (1) Some normal bacteria in the microbial barrier can inhibit adhesion and colonization of epithelial cells by pathogenic bacteria [28]. In addition, they can secrete bactericidal and bacteriostatic substances to create a barrier effect against pathogenic bacteria [29]. (2) Intestinal probiotics increase the gene expression of mucus and protein expression of mucus 2 protein of goblet cell marker mucus to enhance the intestinal mucus layer [24]. (3) Intestinal flora protects the intestinal epithelial barrier by regulating TJ protein levels in epithelial cells and then inhibiting signaling pathways [24–26]. Meanwhile, intestinal metabolites such as SCFAs can enhance the epithelial barrier function [24,27]. (4) In the context of inflammation or tumor, intestinal bacteria and their metabolites not only activate anti-inflammatory factors [30] to regulate mucosal homeostasis, but also modulate immune responses to improve inflammation or fight tumor cells. (5) Imbalance of intestinal flora and inflammation can increase vascular barrier permeability [31], allowing some pathogenic bacteria to enter the bloodstream. This will also allow some immune cells and polymorphonuclear (PMN) [32] to enter the vascular barrier to regulate immune response.

whether anti-tumor antibiotics can modulate tumor immunity by influencing the intestinal microbiota. The relationships among intestinal bacteria, anti-tumor antibiotics, and tumors are also highlighted to provide ideas for controlling cancer development.

2. Intestinal Flora and its Metabolites can Modulate Risk of Tumor Development

Intestinal flora and its metabolites are closely related to intestinal barriers (Fig. 1, Ref. [24–32]). Microbial barrier, mucus barrier [33], epithelial barrier [33], vascular barrier [34], and immune barrier [33] in the intestinal tract can resist the invasion of harmful substances from the external intestinal environment. These barriers also prevent the spread and development of intestinal cancer, such as CRC. It has been reported that intestinal flora improve the integrity and function of barriers. For instance, Bifidobacterium longum (B. longum), especially B. longum CCFM681 [35], can fortify the intestinal mucus layer by increasing mucin gene expression and goblet cell markers mucin 2 (MUC2) protein expression [25]. Probiotic Escherichia coli (E. coli) Nissle 1917 releases components, such as outer membrane vesicles (OMVs) to increase expression and redistribution of tight junction (TJ) proteins

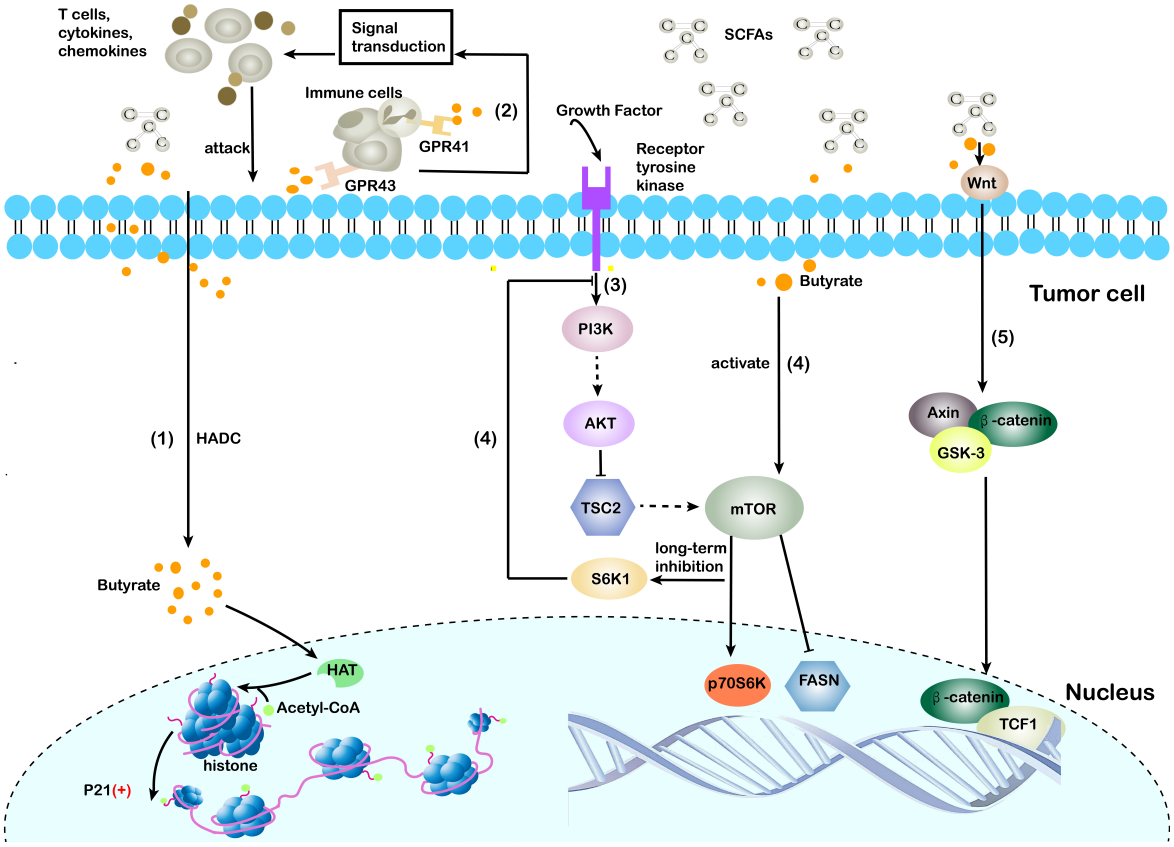

Fig. 2. Anti-tumor mechanisms of SCFAs. (1) DNA demethylation inhibits cancer cells proliferation [29]. (2) GPR41/GPR43 receptors exist on immune cells [29]. They interact with butyric acid. Through signal pathways, they regulate T cells, cytokines and chemokines to attack and inhibit cancer cells [77]. (3) Receptor tyrosine kinase stimulates PI3K under the activation of growth factors, which can change the AKT protein structure to activate tumor suppressor factors [78]. (4) mTOR, as a downstream target, can produce P70 ribosomal protein S6 kinase (S6K), which plays an important role in the apoptosis of cancer cell apoptosis. However, when mTOR is inhibited for a long time, the activity of S6K1 is reduced, and feedback inhibition loop of S6K1 to receptor tyrosine kinase is removed. This results are in promotion of tumor growth through more compensation circuits [79]. Butyric acid activates mTOR to inhibit the fatty acid synthase gene [29]. (5) Secretory glycoprotein regulates the activation through butyrate acid. Accumulated β-Catenin in the cytoplasm enters the nucleus and binds the TCF transcription factor family to initiate the transcription of downstream target genes and inhibit cancer cells [80].

ZO-1 and Claudin-14 [25]. It can also inhibit nuclear factor kappa-B (NF-κB)-mediated MLCK-P-MLC signaling pathway [26] to protect the intestinal epithelial barrier and reduce intestinal permeability. Meanwhile, intestinal microbiota, such as B. longum metabolites SCFAs (acetate and γ-aminobutyric acid), can modulate goblet cells, thereby release the stored mucin granules through autophagy and calcium signaling pathway to enhance mucus production [36]. It was reported that butyrate can up-regulate the expression and transcription of TJ protein Claudin-1 by inducing the association between SP1 and Claudin-1 promoter, thus enhancing intestinal epithelial barrier function [27]. Intestinal flora and its metabolites can directly or indirectly act on immune cells to improve the function of intestinal immune barrier [16–19,36–42]. Therefore, the intestinal microbiome and its metabolites protect the integrity of the gut.

Numerous studies have explored the role of intestinal flora on tumor immune micro-environment and tumor treatment. Intestinal flora can also inhibit tumor proliferation, differentiation, and migration by producing metabolites, such as SCFAs, amino acids, indoles, and polyamines [43–56]. These metabolites participate in various signaling pathways that regulate immune function including anti-tumor immunity [43,57–59]. Recent research has shown that intestinal flora can interact with antibiotics to stimulate immunity [60–63] and regulate tumor micro-environment [9,62,64–66].

2.1 Intestinal Flora Metabolites and Tumors

The anti-tumor effects of intestinal microbiota metabolites have attracted much attention in recent years (Table 1, Ref. [28,47–51,57,58,67–76]). Protein

metabolism occurs mainly in the intestine. Bacteria in the colon have relatively high efficiency in degrading endogenous and exogenous proteins [44]. Colonic microbiota has rich proteolytic activities. Bacterial peptidases, proteases, and endopeptidases from the microbiota hydrolyze dietary proteins, thus generating polypeptides and various amino acids, such as aromatic amino acids, methionine, cysteine, cysteine, and taurine [45]. Many bacterial commnunities in the intestine, such as Clostridioides, Bacillus, Lactobacillus, Streptococcus and Proteobacteria, can decompose and transform a small amount of undigested proteins, unabsorbed amino acids and other digestive products, a process known as "fermentation" [46]. Amino acid fermentation can produce several by-products, such as amines, phenols, indoles and its derivatives and other substances. SCFAs are the most abundant end-products of metabolism [43]. These intestinal flora metabolites, including SCFAs, indoles, amino acids, and polyamines can be used to prevent tumor development.

2.1.1 Short-Chain Fatty Acids (SCFAs)

Anaerobic bacteria produce short-chain fatty acids (SCFAs, volatile fatty acids) in colon fermented from undigested and absorbed carbohydrates in human body. Short-chain fatty acids mainly contain acetate, propionate, and butyrate. Concentrations of these components are highest in the cecum and proximal colon. Acetic acid and propionic acid are mainly produced by Bacteroidetes, whereas butyric acid is mainly produced by Firmicutes [30].

Short-chain fatty acids are key metabolites of intestinal micro-organisms which have diverse effects on the host. For instance, SCFAs participate in energy metabolism of body. Butyric acid significantly affects cells and is the main energy provider for colon epithelial cells [31]. However, it can inhibit the growth of cancer cells. Intestinal flora disorder is common in patients with CRC. Short-chain fatty acids can regulate intestinal flora [32]. Recent studies have found that SCFAs, such as butyric acid can also inhibit the proliferation of cancer cells or participate in immune regulation, hence achieve anti-tumor effects [44].

The acids can regulate the function of immune cells [45], such as monocytes, dendritic cells (DCs) , and macrophages. They can also regulate the differentiation of T and B cells and antigen-specific adaptive immunity [29,46], thus participating in tumor immunosuppression. Therefore, it is evident that, SCFAs can be used as intracellular agents [44] to inhibit the proliferation, differentiation, and migration of cancer cells by inhibiting histone deacetylation. It can also be used as extracellular regulators [57–59] to immunomodulate tumors through participation in various signaling pathways and thereby inhibiting tumor occurrence as well as development (Fig. 2, Ref. [29,77–80]).

2.1.1.1 SCFAs Mediate Histone Deacetylation Inhibition

According to the Warburg effect, most of the tumor cells produce the required energy in aerobic glycolysis. Butyrate cannot be metabolized in cancer cells because it is the energy source of colon epithelial cells. Consequently, there is increased accumulation of non-oxidized butyrate, inversely promoting the inhibition of histone deacetylation and thus increasing the expression of tumor apoptosis-related as well as cell cycle-related genes [81]. A study conducted by Eslami *et al.* [52] demonstrated that dietary fiber has tumor-suppressive effect using a mouse model colonized by butyrate-producing bacteria. They found that butyrate produced by a high dietary fiber diet can inhibit the proliferation of CRC cells and induce their apoptosis as histone deacetylation inhibitors.

Studies have shown that SCFAs mediate histone deacetylase inhibition. SCFAs are histone deacetylase inhibitors that regulate the transcription of genes [47]. For instance, butyrate deacetylase has a significant antagonistic effect. It can non-specifically promote DNA methylation and histidine acetylation, affect DNA replication and transcription, increase the transcription of P21 gene, and inhibit the transformation of cells from G1 to S phase, thus inhibiting the proliferation of colon cancer cell [70]. Acetate-derived acetyl groups can enter T lymphocytes to form cellular acetyl-CoA pools, thus affecting the proliferation of cancer cells by influencing their histone acetylation and cytokine gene expression [43].

Recent studies have shown that SCFAs regulate cellular immune metabolism. Butyrate can intrinsically alter *Foxp3* gene in the T cells, thereby induce changes in the cells. It can inhibit histone deacetylase by enhancing histone H3 acetylation in the promoter and conserved non-coding sequence regions of the Foxp3 locus [82].

2.1.1.2 GPR41/GPR43 Signaling Pathway

GPR41/GPR43 is an orphan type of receptor in G protein-coupled receptors which is activated by SCFAs. GPR43 is highly expressed in immune cells [77]. Butyrate can diffuse to the intestinal epithelium and interact with the main SCFAs receptors in lamina propria (GPR41 and GPR43). Therefore butyrate can regulate gene expression in immune cells to control the production of T cells, cytokines, and chemokines, hence play a role in tumor immune regulation [43].

2.1.1.3 mTOR Signaling Pathway

Unlike the GPR42/GPR43 signaling pathway, mammalian target of rapamycin (mTOR) is an effector protein that functions by forming a complex with other proteins. The mTOR signaling pathway plays different roles in different diseases. It can modulate metabolic processes, apoptosis, and autophagy. Inhibition of fatty acid synthase can inhibit malignant phenotype of colorectal cancer by down-regulating energy metabolism and activating the mTOR cell

Table 1. Functions and effects of Metabolites of intestinal flora.

Metabolites		Source of metabolites	Effects
SCFAs	Butyric Acid [67]	*Coprococcuseutactus* *Coprococcus catus* *Eubacterium rectale* *Eubacterium hallii* *Faecalibacterium prausnitzii* *Roseburia*	
	Propionic acid [47]	*Bacteroides* *Phascolarctobacterium succinatutens* *Dialister* *Veillonella* *Megasphaera elsdenii* *Coprococcus catus* *Salmonella* *Ruminococcus obeum*	• Induce changes in genes, inhibit the proliferation cycle of cancer cells [70]. • Regulate the immune properties of immune cells, control the production of T cells, cytokines and chemokines [47]. • Activate mTOR pathway, regulate mTOR complex activity, modulate immune cells [47]. • Regulate Wnt activity in CRC, induce apoptosis and growth inhibition of CRC cells [57]. • Reduce PI3K/AKT signal transduction, change apoptosis-related protein expression, induce tumor cell apoptosis [58].
	Acetic Acid [47]	*Bacteroides* *Bifidobacterium* *Prevotella* *Ruminococcus* *Blautia hydrogenotrophica* *Clostridioides* *Streptococcus*	
	Amino acids [28]	*Clostridioides* *Bacillus* *Lactobacillus* *Streptococcus* *Morphic*	• Participate in various physiological functions of host health and disease, such as regulate the intestinal barrier and immune function [48]. • Reflect changes in cancer-related metabolism, be used as a marker of its pathology [49]. • Amino acids, their transporters and solute carriers can regulate tumor micro-environment [50].
	Polyamine [68]	*Campylobacter jejuni* *Clostridium saccharides* *Clostridium xylanolyticum* *Ruminococcus obeum*	• Regulate immune cells, stimulate anti-cancer immune, monitor, promote the emergence and maturation of immune cells, regulate systemic and mucosal adaptive immunity [71,72]. • Interfere with polyamine synthesis, damages the tolerance of tumor, micro-environment [51]. • As a drug delivery carrier in cancer, the future treatment of cancer Targets [68].
	Indoles [69]	*Clostridium sporogenes* *Ruminococcus gnavus* *Lactobacillus* *Bacteroides* *E. coli* *Proteus vulgaris* *Paracolobactrum coliforme* *Achromobacter liquefaciens*	• Modulates immune function, strengthen the intestinal barrier [73,74]. • Optimize the ICIs, limit the toxicity of ICIs in cancer immunotherapy [75]. • Have a variety of anti-cancer mechanisms, be used in the clinical anti-cancer drug development [76].

signaling pathway [43]. Besides butyric acid activating the mTOR path, valeric acid can also induce changes in T cells by regulating the activity of mTOR complexes and regulating their glucose metabolism, hence affecting proliferation of the cancer cells.

2.1.1.4 Wnt Signaling Pathway

The Wnt signaling pathway is a complex protein action network commonly used to regulate embryonic development and cancer [59]. It has been found that butyrate regulates Wnt activity in CRC cells [83]. Butyric acid affects apoptosis, cell cycle arrest, and differentiation of CRC cells by altering Wnt activity. In addition, it has been shown that butyric acid-induced apoptosis is directly related to the increased activity of Wnt which is induced by clonal growth inhibition in CRC cell lines of 10 individuals [84,85].

2.1.1.5 PI3K/AKT Signaling Pathway

The phosphatidyl inositol 3-kinase (PI3K)/AKT pathway regulates different biological processes. The PI3K/AKT signaling pathway can directly or indirectly regulate several key epigenetics. The carcinogenicity of the PI3K cascade involved in cancer is abnormally activated in human cancers [57]. Sitosterol can maintain the balance of intestinal flora and significantly increase acetic acid and propionic acid in intestinal flora metabolism. Sitosterol can also weaken the signal transduction of PI3K/AKT and change the expression level of several apoptotic-related proteins, eventually leading to tumor apoptosis [86]. Therefore, SCFAs can induce tumor cells apoptosis both *in vivo* and *in vitro*.

2.1.2 Amino Acids

Protein metabolism mediated by intestinal microbiota can influence immunity response of the host. Its metabolites (amino acids) can participate in various physiological functions related to host health and disease, such as regulating the intestinal barrier and immune functions [58]. Three aromatic amino acids (tryptophan, phenylalanine, and tyrosine) can produce 12 compounds in the metabolic pathway of the gut symbiont *Clostridium sporogenes*. It has been reported that nine compounds can accumulate in host serum, triggering changes in host immune activation and inducing widespread changes in bacterial-specific humoral immunity [53]. This suggests that gene manipulation of the metabolic pathway of aromatic amino acids in *Clostridium sporospora* can affect intestinal permeability and systemic immunity.

Amino acids are the primary metabolites of microorganisms and essential nutrients for living cells. Amino acids drive the proliferation of tumors. Metabolic changes in various amino acids, such as glutamine, sarcosine, and aspartic acid, affect tumor progression as well as cancer invasion [48].

Metabolism of amino acid is closely associated with cancer. Branched-chain amino acids (BCAAs), including leucine, valine, and isoleucine, are essential amino acids that cannot be synthesized in human body but are metabolized in the intestinal tract after ingestion of dietary protein. Intestinal microbiota of *Copri prevorella* can increase the circulating level of BCAAs [54]. BCAAs can affect various cancer phenotypes and also reflect systemic changes in the metabolism associated with certain cancers; and hence can be used as pathological markers [55]. A previous study showed that BCAAs inhibited tumorigenesis by controlling profibrotic signaling through inhibition of transforming growth factor-β1 signaling using atherosclerotic and high-fat diet-induced mouse models of nonalcoholic steatohepatitis-hepatocellular carcinoma [56]. Moreover, elevated levels of BCAAs in breast cancer, liver cancer, leukemia, and other types of cancers can adversely activate the mTOR signaling pathway which is associated with tumor growth. Furthermore, the regulation between BCAAs metabolism and α-KG-dependent gene expression can be applied in treatment of tumors in patients with acute myeloid leukemia [49]. The glutamine metabolism carried by the up-regulated amino acid transporters SLC1A5 and SLC6A14 may greatly affect tumor cells of breast cancer because of the changed amino acid metabolic pathway [87]. In addition, different amino acids with their transporters and solute carriers (SLCs) regulates the immune responses in the tumor micro-environment. Further, T cells activated in immunotherapy can reprogram metabolism of amino acids in the tumor cells, thus enhancing efficacy of immunotherapy [88]. These mechanisms of amino acid regulation provide insights into development of targeted tumor therapy.

However, there are only a few studies that have evaluated amino acids, their transporters, and metabolism in the human immune system. Most of their perceptions are based on *in vitro* experiments, such as test tube culture of immune cells and tumor cells [88].

2.1.3 Indoles

Intestinal flora breaks down tryptophan to produce indole metabolites, such as methyl indole, indoleacetic acid, and indole propionic acid [50]. Indoles are one of the most promising heterocyclic compounds for cancer treatment [89]. They are found from natural and synthetic sources. In addition, the derivatives of indoles have structural diversity and various therapeutic properties [90].

A healthy and diverse intestinal flora promotes the efficacy of tumor immunotherapy [91]. Indoles and amino acid metabolites of bacteria have immunomodulatory functions [92]. A previous study explored the role of *Lactobacillus reuteri* on intestinal intraepithelial $CD4^+$ $CD8\alpha\alpha^+$ T cells [93]. They found that L. *reuteri* produces an indole derivative of tryptophan (indole-3-lactic acid) by activating the ary-hydrocarbon receptor in $CD4^+$ T cells as well as reprogramming of the intraepithelial $CD4^+$ T cells into immunomodulatory T cells. The produced indole also maintain the integrity of the mucosal barrier and inhibits inflammation by activating the transcriptional regulator AhR, thus

controlling the function of T cells, DCs, and macrophages [73]. Changes in serum levels of indole propionic acid can also promote IL-22 transcription by activating the AhR signal pathway, modulating immune balance, strengthening the intestinal wall, and inhibiting inflammation hence positively affecting intestinal permeability and systemic immune function [73]. Indoles can maintain intestinal epithelial barrier function and immune homeostasis. Therefore, it is evident that indoles can be used to optimize the limitation of ICIs that are associated with toxicity and enhance efficacy of cancer immunotherapy [94]. Furthermore, indole-3-carboxaldehyde (3-IAld) protects mice with ICIs-induced colitis from intestinal injury through the dual effects of host and micro-organism [74]. Besides, 3-IAld does not impair the anti-tumor activity of ICIs when preventing intestinal injury [74].

Therefore, indoles may be crucial in anti-tumor therapies. For instance, indoles have many mechanisms of action with anti-cancer potential, providing safer and more effective anti-breast cancer drugs for breast cancer chemotherapy [75]. First, indole can be used as histone deacetylase inhibitors to inhibit tumor growth. For example, Panobinostat Lactate, a histone deacetylase inhibitor and a member of indoles. The inhibitor has been approved for marketing by the Food and Drug Administration in the United States. Resistance to anti-cancer drugs significantly limits cancer treatment. Several indole-containing compounds have also been developed to treat clinically resistant cancers [95].

2.1.4 Polyamines

Undigested amino acids act on intestinal bacteria to produce amines, such as polyamines, which contain spermidine, spermidine, cadaverine, and putrescine. Members of phylum pachylophylococcus that inhabit intestines can synthesize polyamines. Carboxyspermidine dehydrogenase/decarboxylase is the dominant polyamine biosynthesis pathway in the human intestinal microbiota [76].

Polyamines can exert a regulatory effect on immune cells. Spermidine found in natural polyamines has significant cardiac and neuroprotective effects. It has been found that spermidine stimulates anti-cancer immune monitoring in experimental rodent models [68,96]. Polyamines can also promote the emergence and maturation of immune cells and regulate systemic and mucosal adaptive immunity [71]. For instance, a previous study has shown that accelerated maturation of intraepithelial $CD8^+$ T cells and lamina propria $CD4^+$ T cells and early enhancement of B cells in the spleen occur in puppies receiving polyamine-rich breast milk [71].

Several studies have demonstrated that polyamine transport inhibitors can enhance the anti-tumor immune effect. The inhibition of polyamine synthesis disrupts the tolerant tumor micro-environment and hence reduces tumor growth rates [97]. Therefore, it is evident that tumor growth is related to polyamine biosynthesis. Inhibition of enzymes in the polyamine synthesis system can cause tumor regression [98]. Polyamine metabolism is dysregulated in different tumor states, often with elevated levels of polyamine and crosstalk between their metabolism and cancer-causing pathways, such as mTOR and RAS pathways [72]. Results of a therapeutic effect experiment showed that polyamine blocking therapy stimulates anti-tumor immune effects that depend on T cells and inhibits polyamine synthesis as well as exogenous polyamine uptake and thereby inhibiting tumor growth and development [99]. In previous studied [100], it was demonstrated that polyamines can be used as drug delivery carriers. Polyamines are elevated in cancer cells and can bind to DNA. Consequently, a series of polyamine analogues and polyamine-like structural substances have been synthesized to target epigenetic regulators. Therefore, the polyamine pathway should be considered as a target for treatment and prevention of different cancers.

2.2 The Anti-Tumor Role of Intestinal Flora in Tumor Immunity

Inflammation and immune imbalance are key factors that cause tumors. Chronic inflammation promotes tumorigenesis and development of cancer. Inhibition of inflammation *in vivo* can prevent the occurrence and further development of tumors, enhance normal immune functions in the body, thus eliminating the tumors. The function of immune system is important for tumor removal and self-defense. Therefore, it is necessary to control the tumor-related inflammatory environment and promote the development of immune function for maximum efficacy of the tumor therapy.

Intestinal flora can be crucial in regulation tumor-associated inflammation. The gut microbiome exists in a dynamic equilibrium with the human immune system. Changes in the number, type, proportion, and biological function of intestinal flora causes inflammatory response, immune system dysfunction, and cancer development [101].

Intestinal microbiota can regulate inflammatory responses by reducing the expression of inflammatory cytokines and chemokines in intestine. Previous studies have shown that B. *longum* alleviates colorectal colitis in mice by improving the level of interleukin-10 (IL-10), down-regulating IL-12, IL-17, and IL-23 in the serum, and regulating regulatory T cells (Tregs) [102]. In addition, B. *longum* KACC 91563 can reduce the IL-2, IFN-γ, IL-4, IL-6, IL-10, and TNF-α production in cells hence promoting inflammation [36]. Besides, the transcription factor NF-κB is a key mediator of the inflammatory response [103]. Dextran Sulfate Sodium Salt-induced colitis is effectively alleviated by B. *longum* through regulation of the NF-κB signal pathway. Similarly, Pseudotreptavirus-pseudo stretched *Bifidobacterium* reduces the levels of TNF-α and IL-6 in mice with colitis, while increasing the levels of IL-

10 as well as peroxisome proliferator-activated receptors. However, *Bifidobacterium* significantly inhibits the activation of TLR4/NF-κB pathway [35] .

The concentration of colonic metabolites, conjugated linoleic acid (CLA) produced by different intestinal strains, such as B. *longum* and *Bifidobacterium pseudocatenulatum*, are positively correlated with the effectiveness of the strains in alleviating colitis [35]. CLA improves colitis by down-regulating the concentrations of interferon-gamma (IFN-γ), IL-1β, and IL-12 in the colon [104]. The exposure of antigen-presenting cells to CLA can modulate the response of subsequent Th cells, thus improving the intestinal immune barriers.

Moreover, the effective exercise of tumor immunity is crucial for anti-tumor process. Intestinal flora can promote the anti-tumor effect of immune cells hence affecting the intestinal barrier and the efficient development of the immune function.

Intestinal flora is closely related to immune cells. Intestinal colonization of specific microbiota promotes the maturation of intestinal mucosa-associated lymphoid tissues [105]. Over 80% of plasma cells secrete IgAs in the lamina propria of the intestine. IgA can promote the homeostasis of intestinal and colon flora [38]. Human intestine has abundant memory IgM B cells. These cells are associated with abundant IgM plasma cells [39]. Moreover, intestinal microbes positively regulate adaptive immune cells, promote the differentiation of B lymphocytes, Th0, Th1, Th17, Treg cells, and other important immune cells, thus promoting the initiation of anti-tumor adaptive immunity as well as immune checkpoint blockade therapies [17]. The systemic immune functions can be boosted by B. *longum* KACC 91563, thus enhancing IgE production and regulation of Th1 (IL-2, IFN-γ)/Th2 (IL-4, and IL-10) balance [36]. In addition, intestinal flora can also participate in the regulation of immune cells by producing metabolic substances [9,10,16–19,36,38,39,41,42,103,106,107].

Recent studies have also shown that intestinal flora can play a positive role in tumor immunotherapy by activating specific tumor immune responses. Cancer cells develop various defense mechanisms to evade immune responses [40] through three stages (elimination, equilibrium, and escape) based on the immune editing theory [108]. Tumor cell proliferation and cancer development occur in presence of weak immune system [40,109]. Therefore, immunotherapy should be used to stimulate the immune functions of patients to attack tumor cells until they are eliminated [106]. ICIs are one of the most promising and effective tumor immunotherapies [9,10]. They mainly activate specific tumor immune responses by targeting specific molecules. Reactivating cytotoxic T lymphocytes to attack tumor cells [11] can prevent tumor cell escape and reconstruct the anti-tumor immune response.

In recent years, key immune checkpoint molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein-1/programmed cell death protein ligand-1 (PD-1/PD-L1) pathways have been found to be key targets for the treatment of different cancer immunotherapies [12,13]. Some clinical studies have shown that intestinal flora, such as symbiotic *Bifidobacteria*, can also potentiate the anti-tumor immunotherapy effects of PD-1 blockade [14,106] whereas Bacteroides can promote anti-tumor immunotherapy for CTLA-4 blockade [9].

For instance, DCs, as specialized antigen presenting cells, activates T cells in anti-tumor immunity [10]. The immune system can then recognize this exogenous antigen by interacting with its T cell receptor (TCR) and the peptide epitopes presented by MHC-I molecules on tumor cells [106]. The long-term interaction between CTLA-4 on the surface of effector T cells and CD80/CD86 expressed by DCs may be depleted [15]. *In vitro* experiments have demonstrated that *Lactobacillus* from intestinal tract can increase the expression of mature CD80 and CD86 in DCs. *Bifidobacterium* or other symbiotic bacteria can stimulate the maturation of DCs [16]. Therefore, specific bacterial species in ICIs can enhance DC activation, increase the infiltration of CTLs, and reduce the number of Tregs in TME thereby increase the sensitivity of ICIs to tumor cells [17].

Intestinal microbiota plays a key role in tumor immunotherapy. It promotes development, differentiation, and functions of immune cells through the intestinal microbiome as well as its metabolites. Intestinal microbiome, as the signal center of the body, can also combine environmental input, such as drugs and diet with immune signals to affect the normal immune function of the host [18]. Recent evidence has indicated that intestinal microbiome can modulate toxic side effects, drug resistance, and therapeutic effect in tumor immunotherapy [19,41]. Intestinal flora has an indirect bidirectional effect on immunotherapy by influencing the immune system of the host [20,42]. Therefore, studying the role of intestinal micro-organisms in blocking immunomodulatory effects, such as PD-1 and CTLA-4 is important towards the development of tumor immune checkpoint blockers.

2.3 Adverse Impact of Intestinal Microbiota on Cancerogenesis

Studies have suggested that adverse intestinal microbiota may also play a role in promoting the occurrence and development of tumors. How to overcome these factors remains to be further explored.

Clostridioides perfringens (*C. perfringens*) *enterotoxin* promoted the malignant progression of sessile serrated adenoma/polyp with dysplasia into colon cancer by activating the transcriptional co-activator yes-associated protein, suggesting that abnormal intestinal flora, such as *C. perfringens*, can increase the possibility of colon cancer [110]. Therefore, controlling adverse intestinal flora may prevent the occurrence of tumors. Besides, changes or

imbalance of intestinal flora may lead to changes in the micro-environment *in vivo*, such as inflammation or the decline of immune function, thus causing the occurrence and metastasis of tumors [102]. For example, enterotoxigenic *Bacteroides fragilis* (ETBF), a common human symbiotic bacterium, induces colitis, colonic hyperplasia, and tumor formation through the activator of transcription-3- and T-helper type 17 (Th17) - dependent pathway, showing a new mechanism for the occurrence of the human colon cancer. Intestinal flora is also involved in extra-intestinal cancer, causing inflammation originally present in the intestine to metastasize to other parts of the host body [111]. Consequently, it leads to the emergence of infection and inflammation on healthy tissues and organs, as well as carcinogenesis by affecting the occurrence, progression, and spread of cancer in epithelial barrier and sterile tissues [112,113]. Therefore, a well-balanced intestinal flora homeostasis is crucial for human health and improves the treatment of patients with tumors.

3. Anti-Tumor Antibiotics are Vital for Treatment of Malignant Tumors

3.1 Mechanisms of Action of Antibiotics as Cellular Inhibitors

Antibiotics are widely used to treat cancer. Anti-tumor is the function of antibiotics found in the process of fighting infections. Antibiotics are natural or derived chemicals produced by environmental microorganisms, including bacteria, fungi, and actinomycetes. For instance, Doxorubicin (DOXO, ADM), produced by *Streptomyces caesius* subspecies, is a traditional and common anthracycline antibiotic that has a broad anti-tumor spectrum and a decades-long history of clinical treatment of cancer [114].

Based on different targets of anti-tumor drugs on each phase of the cell proliferation cycle, the drugs can be divided into two categories: cell cycle specific and cell cycle non-specific drugs. The former only acts on a specific phase of the cell proliferation cycle. Their effects are weak and slow and takes a limited period of time to exert their killing effects. Pingyangmycin, which acts on the G2 phase belongs to this category. The latter directly acts on various phases of the cell proliferation cycle, without selection. Their effects are strong and fast, and can quickly kill tumor cells. Most anti-tumor antibiotics belong to this category.

Antibiotics are produced by many microorganisms and are known to exert anti-tumor effects through different mechanisms. Anthracycline antibiotics, such as Daunorubicin, DOXO, Epirubicin and Mitoxantrone, some of which are derived from *Streptomyces peucetius*, inhibit DNA replication and mRNA synthesis by forming stable complexes between base pairs embedded in DNA double-strands. Glycopeptide antibiotics, such as Bleomycin A5 (Pingyangmycin) and Bleomycin A6 (Boanmycin) are mainly produced by Streptomyces and Actinomyces. They inhibit DNA polymerase activities by breaking the single strand of DNA to interfere with the transcriptional process. The glycopeptide antibiotic (actinomycin D) and the anthracycline antibiotic (Aclacinomycin) inhibit RNA polymerase activities by embedding in the DNA double strand to bind guanine groups on DNA, thereby interfering with the transcriptional process. Some anti-tumor antibiotics derived from plant endophytic bacteria, marine fungi and soil bacteria, can inhibit the proteins associated with tumor cell division, proliferation, and migration. Midostaurin, which is derived from Actinomycetes and Rapamycin from Streptomyces inhibit important proteases in tumor cells. Antilekemic activities of anti-infectious antibiotic tigecycline are associated with inhibition of mitochondrial protein translation [115].

Therefore, anti-tumor antibiotics have a wide range of microbial sources and important tumor suppressive properties, thus, they are an important option for malignant tumor treatment.

3.2 Potential Risks of Anti-Tumor Antibiotics and Countermeasures

Various antibiotics, including Pingyangmycin, DOXO, Daunorubicin and Mitoxantrone among others are important in cancer treatment, however, they are associated with various side effects. They have been shown to lead to imbalanced intestinal flora and decreased microbial diversity. Suppressed microbial diversity correlates with reduced abundances of SCFAs (important metabolic compounds from intestinal flora) and may also induce damage to the TJ barrier of the intestinal epithelium [115]. They also affect the efficacies of ICIs *via* dysbacteriosis. In addition, they have a risk for cancer induction. In a previous meta-analysis [116], antibiotics were established to be an independent risk factor for cancer development (OR 1.18, 95% CI 1.12–1.24, $p < 0.001$), and excess long-term use of antibiotics was associated with slightly increased risks of various cancers, such as lung cancer, lymphoma, pancreatic cancer, renal cell carcinoma and multiple myeloma among others.

Toxic side effects limit the applications of anti-tumor antibiotics. The current clinical cytotoxic anti-tumor antibiotics do not exhibit ideal selective effects on tumor cells and normal cells. Since the drug kills malignant tumor cells, there is a certain degree of damage to some normal tissues, resulting in various adverse reactions. Common toxic reactions include bone marrow suppression and gastrointestinal reactions among others. Long-term and excess use of Bleomycin is associated with specific toxic side effects, such as interstitial pneumonia, pulmonary fibrosis and tumor resistance [117]. DOXO can induce acute cardiotoxicity, resulting in multifocal vacuole degeneration of myocardial cells, myoblast lysis, myocardial fibrosis and myocardial interstitial edema [118]. Actinomycin-D causes acute injury to human hepatic sinusoidal endothelial cells, hepatic sinusoidal obstruction and acute toxic damage to hepa-

tocytes [119]. Most of the non-absorbable antibiotics, like DOXO, may cause central nervous system diseases, such as brain dysfunction through the microbiome-gut-brain axis [120,121].

Reduction or elimination of potential risks of antibiotic drugs, such as cytotoxicity is a challenge in drug research. Various protective mechanisms have been explored. Bleomycin-associated lung toxicity can be controlled by deleting the sugar residue (d-mannosyl-l-glucose disaccharide) [122], or *via* combinations with traditional Chinese medicine antibiotics, Scutellarin [123] and Aucubin [124]. Combination with β-caryophyllene protected mice heart from DOXO-induced acute cardiotoxicity [125]. By overexpressing several specific drug transporters, the significance of pharmacokinetics of actinomycin-D were determined [64]. Chimeric molecules were formed by connecting two different pharmacophores with spacers [126], which helped in eliminating the toxic effects of anthracycline antibiotics. With advances in chemical and biosynthetic engineering, some natural active substances, such as patamycin, which have significant biological activities, but are not applied as therapeutic agents due to their strong cytotoxicity, have potential for clinical applications [127]. Toxicity reduction and efficacy enhancement in antibiotic treatment of tumors can be achieved through molecular structural modification [64,122,126,127] and drug combination therapy [123–125].

Although they have certain negative effects, antitumor antibiotics are important for treatment of malignant tumors. Degradation of anti-tumor antibiotics and toxicity changes are worthy of attention.

4. Intestinal Flora Influences the Efficacy of Antibiotic Cancer Regimens

Gut microbiota influences the efficacy of antineoplastic drugs [128]. Due to the antimicrobial activities of some cytostatics, during digestion and absorption, they can disrupt the diversity of intestinal flora. In addition, intestinal flora can directly or indirectly affect antibiotic breakdown and metabolism, thereby affecting the efficacy of antitumor antibiotics. Elucidation of these interactions may provide novel ideas for cancer treatment.

4.1 Intestinal Flora has an Influence on the Absorption and Metabolism of Antibiotics

Many drugs, especially natural products, are not directly absorbed by the body, but interact with intestinal microorganisms when they enter the intestines. This affects the ability of the intestinal flora to produce biologically active, inert or toxic metabolically active products, which are absorbed into the bloodstream to produce therapeutic or other effects [129]. Most of the existing anti-tumor antibiotic drugs are intravenously administered. These injected drugs are first metabolized in the liver after which they are partially excreted into the intestines with bile, where they are exposed to intestinal microbiota for further metabolism and reabsorption [130]. Therefore, intestinal flora are involved in internalization of anti-tumor antibiotics.

Some bacterial species of gut microbiome, especially enterobacteriaceae, affect the metabolism and efficacy of certain drugs [131]. Intestinal microbiota affects drug metabolism *via* various ways, including acetylation/deacylation decarboxylation, dehydroxylation, demethylation, dehalogenation and conjugate hydrolysis reactions on some drug-related toxicity [132]. Currently, studies on the mechanisms of intestinal bacteria on antitumor antibiotics are limited. DOXO can be metabolized and decomposed by *Raoultela planticola*, an intestinal bacterium of the enterobacteriaceae family. In anaerobic conditions, it decomposes DOXO into 7-deoxydoxorubicinol and 7-deoxydoxorubicinolone through reductive deglycosylation [133], confirming the catabolic effects of enterobacteria on anti-tumor antibiotics.

Metronidazole reduced *Fusobacterium* load and inhibited cancer cell proliferation as well as overall tumor growth in colon cancer xenograft mice models, implying that antibacterial intervention is a potential treatment option for patients with *Fusobacterium*-related colorectal cancer [134]. The metronidazole oral reagent and intestinal flora were incubated in anaerobic environments. The intestinal flora reduced metronidazole to N- (2-hydroxyethyl) oxalic acid and acetamide. The reduction degree was positively proportional to the residence time of sustained release in the intestines, while bioavailability was inversely proportional to its residence time [135]. These results imply that intestinal flora affect the metabolic outcomes of antibiotic drugs.

As natural metabolites, polysaccharides are an important member of the natural antibiotic family with antitumor effects. After entering the intestinal tract, polysaccharides are catabolized by intestinal flora. About 20% of the genome of *Bacteroidetes* is used for ingesting and decomposing complex polysaccharides [135]. Priority carbon sources for most human intestinal microbes are glycosaminoglycans (GAGs), a polysaccharide. Utilization of GAGs is based on its carbohydrate structure [136,137]. The mechanisms underlying the preferential utilization of GAGs by intestinal microbiota were explored, and were shown to result in complete metabolism of diverse GAGs. Intestinal flora, especially Bacteroidetes, contain a large number of enzymes that can lyse polysaccharides. Comparisons of 25 *Firmicutes* and *Bacteroides* from different sources revealed that each Bacteroide genome contains a large number of genes involved in polysaccharide acquisition and metabolism. Bacteroides contain hundreds of glycosidolytic enzymes and polysaccharide lyases that allow them to up-regulate the expressions of polysaccharide utilization sites encoding multiple glycoside hydrolases [137,138]. In this study, *Pachychocetes* were found to have a small number of related genomes and glycan degrading enzymes.

Natural polysaccharides are fermented by intestinal flora to produce SCFAs. An Azomethane/Dextran sodium sulfate-induced inflammation in a tumor mice model demonstrated that *Ganoderma lucidum* polysaccharides modulated the intestinal microbiota, enhanced the production of SCFAs, improved intestinal barrier functions and inhibited TLR4/MyD88/NF-xB and MAPK signaling cascades, thereby suppressing tumorigenesis [139].

Through the mediating effects of intestinal microbiota on oral or injected anti-tumor antibiotics, microbiota are important for digestion, absorption and utilization of such drugs, and they may enhance the efficacy of antineoplastic treatment.

4.2 Intestinal Bacteria Reduce Anti-Tumor Antibiotic-Associated Toxicities through Drug Metabolism

In most advanced cancer patients, cytotoxic drugs, such as anti-tumor antibiotics are the mainstay for their treatment. However, these drugs are associated with various treatment-related diseases and unpredictable toxic side effects. Specific adverse reactions and high costs are the main challenges in targeted tumor therapies [128].

Intestinal microbiota can indirectly reduce the toxicity of drugs by regulating host metabolism and producing metabolites that compete with drug receptors. Intestinal microbiota modulate host responses to chemotherapeutic drugs to promote drug efficacy, impair and eliminate anticancer effects, as well as to modulate toxicity [138].

DOXO is a typical example of the attenuating effects of intestinal microbes on anti-tumor antibiotics. DOXO exhibits cardiotoxic properties and may induce jejunum crypt epithelial cell apoptosis and intestinal mucosal damage [140,141]. Intestinal microbiota are closely correlated with DOXO-induced mucosal damage [140]. Muramyldipeptide, a peptidoglycan motif that is common in all bacteria, has strong protective effects against oxidative stress-mediated cell death [142]. Intestinal bacteria are important in repair of DOXO-induced intestinal injury, and secretion of immunomodulatory chemokines associated with such injuries are correlated with intestinal bacteria [99]. Therefore, regulation and manipulation of intestinal microbiota to reduce damage to intestinal mucosa during DOXO therapy is associated with less damage during tumor therapy. A model of bacterial community dynamics under simulated chemotherapy pressure was developed to explore the effects of bacterial interactions on microbiome elasticity during drug detoxification. Bacteria with biotransformation resistance significantly reduced DOXO concentration in the medium, allowing drug-sensitive strains to grow in a single culture [143]. Moreover, *in vivo* metabolism of other antibiotics requires the regulatory effects of enterobacteria. These studies have clinical implications for development of probiotics with enteric-specific protective effects for patients treated with DOXO and other anthracycline drugs, as well as for understanding *in vivo* metabolism of antibiotic tumor drugs by gut microbiota.

The extent to which many oral oncology drugs are exposed and absorbed in the intestines before entering the circulatory system determines their absorption rate and bioavailability degree [129]. The microbiome regulates the body's responses to cancer treatment by influencing the absorption degree of oral drugs in the gut and their interactions with intestinal bacteria.

Intestinal microbes influence tumor treatment responses by modulating drug metabolism and regulating susceptibility to toxic side effects [99,129]. In addition, the loss of protective functions when the intestinal barrier interacts with the environment, such as increased intestinal permeability and changes in microbiota composition and quantity, is thought to be a mechanism that may explain the pathogenesis of immune-related toxicity [144]. Therefore, in the context of multiple therapeutics, selection of efficacious prediction markers for identifying reactions and toxicity is an important, challenging task in drug therapy.

There is a need to identify antibiotics and anti-tumor drugs that can achieve the best clinical therapeutic effects and minimize drug toxic effects.

5. Interactions and Synergy between Antibiotics and Intestinal Microbiome in Tumor Therapy

5.1 Co-Regulation of Tumor-Associated Inflammation and Effects on the Tumor Micro-Environment

About 15% of human cancers are due to infections and chronic inflammation [145]. Cancer is a systemic disease: inflammatory immune cells, cytokines and chemokines affect tumor growth, metastasis, and spread [144].

Inflammation is involved in almost all stages of tumorigenesis [145]. It promotes tumorigenesis by altering host physiology. Through high-throughput sequencing, Arthur *et al.* [46] found that colitis promotes tumorigenesis by altering the composition of the intestinal flora in mice, IL-10 deficient mice were highly susceptible to colitis and that colitis induces the expansion of genotoxic microorganisms. Chronic inflammation is involved in carcinogenesis through mutations, genomic instability and epigenetic modifications [37]. Inflammation stimulates pluripotent stem cells or progenitor cells in various tissues to produce cancer stem cells [37]. In addition, inflammatory bowel diseases have been shown to cause mutations in cancer-related genes, such as TP53, to accumulate in intestinal epithelial cells [146]. Inflammatory cells, such as neutrophils and $\gamma\delta$T cells, can further aid in tumor adhesion and metastasis [147].

Anti-microbial antibiotics can inhibit infection and inflammation [148] and play a regulatory role in intestinal flora. Inflammation is the body's defense response to exogenous injury stimuli. Viral and bacterial infections can directly or indirectly (e.g., through chronic inflammation) induce abnormal DNA methylation, leading to oncogenic mutations in host cells [149]. In cases of inflammation, an-

tibiotics do not have direct inhibitory roles. They play a preventive role by eliminating the pathogens responsible for inflammation. For instance, for inflammatory bowel disease caused by virulent *E. colistrains*, *Bacteroides* spp, and *Mycobacterium avium* subspecies paratuberculosis, the use of ciprofloxacin, metronidazole, rifaximin, clarithromycin and other antibiotics can improve the clinical symptoms [150]. For *Helicobacter pylori* infection that may lead to gastric muco-associated lymphoid tissue lymphoma and early gastric cancer, a combination of PPI, clarithromycin, and nitroimidazole is available as first-line treatment, with simultaneous or sequential administration ranging from 3 to 14 days [151].

Chemotherapeutic agents are associated with barrier damage and critical function deteriorations of tissues and organs [152]. Anti-tumor antibiotics cause tissue cell destruction and epithelial barrier damage [64,116], which may trigger inflammation. However, antibiotics are ineffective against this type of inflammation. Intestinal flora can play an important role in clearing inflammation and inhibit the formation of a micro-environment that is conducive for tumor growth.

Anti-microbials antibiotics play a certain role in regulating intestinal flora. A healthy and stable intestinal environment is of great significance in improving the inflammatory environment and in maintaining the homeostasis of the body's internal environment. Intestinal flora and their metabolites have a major role in this process. However, some intestinal flora have the potential to induce the occurrence and metastasis of inflammation-associated cancer [4,111,112]. Therefore, selection of appropriate intestinal microbiota is a major challenge in microbiome therapy. Symbiotic flora exerts different effects on the type of inflammation in different treatment regimens, which affects tumor treatment outcomes, highlighting the need to manipulate the human gut microbiota to promote cancer treatment [65,153]. After metronidazole treatment of fecal microbiota transplantation donor mice, their microbiota still retained the ability to control inflammation, accompanied by enrichment of *Lactobacillus* and iNKT cells [153]. Thus, antibiotics have the ability to maintain and promote normal defense functions.

Elucidation of the joint modes of action can provide new ideas for controlling inflammation. Normal and steady states of the intestinal microbiome are closely associated with chronic inflammation and tumor growth. Elucidation of the relationship between antibiotics, intestinal flora and inflammation, correct use of anti-microbial antibiotics for early prevention and maintenance of healthy bacterial homeostasis to achieve the synergistic effects of the two in inhibiting inflammation and tumor emergence is a direction for further studies.

5.2 Antibiotics Improve the Tumor Immune Environment through the Intestinal Flora

The combination of broad-spectrum antibiotics (ampicillin & colistin & streptomycin) and imipenem was associated with intestinal microecological disorders and weakened anti-tumor effects of anti-CTLA-4 [9]. Treatment of natal K/BxN mice with vancomycin or ampicillin strongly inhibited rheumatoid arthritis development [154]. However, targeted inhibitory effects of antibiotic therapy on microbiota, such as inhibition of Gram-negative bacteria by vancomycin, anaerobic bacteria and gram-negative bacteria by metronidazole and neomycin sulfate, and gram-positive bacteria by ampicillin, all reduced Th17 cell numbers by varying degrees. Recovery of Th17 cells was achieved after the recovery of microbiota [60]. Thus, intestinal microbiota can alleviate antibiotic-induced damage to immune functions. Proper regulation of intestinal flora can also alleviate and counter the effects of incidences as well as severity of intestinal lesions caused by antibiotic therapy to enhance drug efficacy. A recent study [155] evaluated the relationship between pATB, concurrent ATB and OS, progression-free survival, and objective response rates in 302 stage IV NSCLC patients. Contrary to previous reports that antibiotics weaken the efficacy of ICIs and affects prognosis, it was found that antibiotic exposures do not affect clinical outcomes of first-line immunization combined with chemotherapy in NSCLC patients. There are positive correlations between antibiotics and tumor immunity. Pingyangmycin, a bleomycin-type antineoplastic antibiotic with good clinical therapeutic effects enhances the therapeutic outcomes of anti-PD-1 antibodies associated with tumor-infiltrating $CD8^+$ T cell enlargement [156].

Therefore, antibiotics can play a beneficial role in tumor immunotherapy, regulating bacterial balance by increasing the presence of anti-tumor beneficial microorganisms and inhibiting the abundance of tumor-associated flora.

Fusobacterium nucleatum is a common bacterial species in CRC tissues. Treatment of colon cancer xenografted mice with metronidazole reduced the Fusobacterium load in the tumor micro-environment and slowed down tumor cell proliferation [66]. Similarly, C4/butyrate produced by gut bacteria such as Clostridia impairs APC activities while reducing vancomycin-enhanced RT anti-tumor activities. Interestingly, vancomycin treatment targeted Gram-positive bacterial populations, including Clostridia and reduced SCFA and C4 concentrations in stool and tissue samples [66]. These results inform on antibiotic-targeted interventions in cancer-associated microbiota, providing a basis for potential treatment of cancer patients.

Antibiotic intervention of intestinal flora has a positive role in tumor immunity. Intestinal flora of some patients with pancreatic cancer promotes immunosuppression and tumor immune evasion by inducing $Foxp3^+$ Treg cell

proliferations [61]. Inhibition of relevant microbial growth by using appropriate antibiotics can control precancerous lesions and cancer progression. Butyrate induces T cell changes via epigenetic changes of the *Foxp3* gene [84], implying that antibiotics act on intestinal bacteria to regulate the effects of their metabolites. Antibiotic mixture (ABX) ablation of the microbiome can inhibit pancreatic duct adenocarcinoma (PDA) invasion [157]. Therefore, oral antibiotic induced immunogenic reprogramming of the tumor micro-environment after ablation, including increased differentiation of M1 macrophages, enhanced TH1 differentiation of $CD4^+$ T cells and activation of $CD8^+$ T cells, significantly up-regulates PD-1 expressions on effector T cells, and promotes checkpoint targeted immunotherapeutic outcomes. Thus, modulation of the microbiome by oral antibiotic orientation has great prospects for enhancing immunotherapy.

The use of antibiotics and probiotics to rebuild healthy intestinal micro-environments has a certain reference value. Refilling of mice fecal microbiome reversed intratumor immunogenicity changes attributed to antibiotic ablation bacteria, so that genes associated with T cell proliferation and immune activation were up-regulated in tumors of antibiotic-treated mice. These findings imply that the reconstructed microbiome better regulated the immunogenicity of PDA. In addition, antibiotics are beneficial for preventing the transfer of intestinal micro-organisms and maintaining a stable microbial distribution *in vivo*. Disruption of intestinal vascular barrier leads to systemic transmissions of intestinal bacteria and CRC liver colonization [34], while ABX treatment effectively reduces bacterial metastasis to the liver and intestinal lumen.

Therefore, interactions between antibiotics and intestinal flora can effectively alleviate immune function damage caused by antibiotic treatment, while targeting tumor or immune related intestinal flora components. Studies have evaluated the synergistic effects of intestinal microbiota and anti-tumor drugs in stimulating anti-tumor adaptive immune functions [17], although there are few studies on antibiotic drugs. Combination immunotherapy regimens are a key direction for future cancer treatment. The combination of antibiotics and ICIs is a potential approach for experimental treatment of cancer. Interactions between antibiotic therapy, intestinal microbial diversity, and anti-tumor immunotherapy are another scientific pathway that is worth of explorating.

5.3 Drug Combinations for better Tumor Suppression Effects

Common anti-tumor antibiotics, such as DOXO, are highly toxic with various side effects in patients. Studies have developed a lipid delivery system co-loaded with curcumin and DOXO, which makes use of their synergistic anti-tumor effects. It can initially achieve therapeutic effects of attenuation and efficiency enhancement [62]. Thus, antibiotics can synergistically work with other drugs to achieve better anti-tumor outcomes.

Double-hit lymphoma, a tumor with a higher degree of malignancy, involves the activation of both MYC and B-cell lymphoma-2 oncogenes. Experimentally, the combination of tigecycline, which is effective against MYC-driven lymphomas, with the B-cell lymphoma-2 inhibitor (Venetoclax), showed significant anti-tumor effects. Tigecycline has good prospects for combination with Rituximab, the current first-line treatment option for lymphoma [158].

Anti-tumor effects of antibiotic combinations have a certain relationship with intestinal flora. Intestinal homeostasis was shown to contribute to normal anti-tumor immune functions of mice [63,159]. A combination of antibiotics are conducive for regulating the effects of microflora imbalance caused by a single antibiotic. Intestinal tumors are often accompanied by dysregulated intestinal flora. Polysaccharides regulate the ratio of beneficial to harmful bacteria in the intestinal flora to maintain a healthy intestinal microbiota balance [160]. Jiyan Su *et al.* [161] performed 16S rRNA sequencing analysis on mice 4T1-breast cancer models and found that the combined action of paclitaxel (PTX) and Ganoderma spore powder polysaccharide (SGP) improved the PTX-induced intestinal microbiome dysregulation.

The combination of anti-bacterial agents and radiotherapy has improved therapeutic outcomes. Vancomycin combined with RT exhibited better anti-tumor effects than the use of a model drug alone [66]. Vancomycin in combination with RT can reshape the tumor micro-environment, but also be IFN-γ and CD8 dependent, enhancing local antigen presentation accompanied by cytotoxic T cell infiltrations in the tumor.

With regards to single use of antibiotics for anti-tumor treatment, efficacies should be improved while side effects should be minimized. Synergistic effects from the combination of antibiotics with other drugs can significantly improve intestinal flora abundance and species diversity. Enhanced anti-tumor effects of antibiotics directly inhibits tumor development. Regulating the occurrence and development of tumors that are caused by antibiotic-mediated dysbiosis can also indirectly inhibit tumor proliferation. Drug combinations can also improve tumor attenuation efficiencies of antibiotics while maintaining normal bacterial homeostasis. Thus, combinations of antibiotics with other anti-tumor drugs have better tumor control outcomes.

6. Discussion

Studies have reported on anti-tumor activity of intestinal microbiome. The intestinal flora produces metabolites, such as SCFAs, indoles, amino acids, and polyamines, which have cancer-suppressing effects. They inhibit cancer cell proliferation, differentiation as well as migration by suppressing histone deacetylation in tumor cells and immunomodulate tumors by participating in various signaling pathways, promoting immune cell functions for bet-

Table 2. Categories, names and functions of antibiotics.

Categories	Names	Functions
Anti-tumor antibiotics	DOXO	• DOXO inhibits macromolecular biosynthesis by intercalation with DNA. This further inhibits the progress of topoisomerase II and inhibits transcription in tumor cells [8].
	Pingyangmycin	• Anti-tumor effect of Pingyangmycin combined with anti-PD-1 antibody [156]. Pingyangmycin inhibits glycosaminoglycan acidification in cancer cells and tumor tissues [163].
	Daunorubicin (DNR)	• DNR reduces cell viability and promotes apoptosis by modifying NF-kB. DNR inhibits DNA synthesis in H35 HCC cells and SUP-T1 lymphoma T lymphoblasts [164].
	Mitoxantrone	• Mitoxantrone does not cause toxicity to non-malignant cells at doses coacted with apoptosis-inducing ligands on tumor cells. Mitoxantrone can up-regulate the expression of death receptors and change the expression patterns of pro-apoptotic and anti-apoptotic genes, which is beneficial to cell apoptosis [165].
	Bleomycin	• Bleomycin inhibits DNA synthesis and inhibits the growth of cancer cells [166].
	Actinomycin D (dactinomycin)	• Actinomycin D has high antibacterial and antitumor activities. Its cytotoxicity and antitumor effects are related to DNA function, inhibiting RNA transcription, and thus inhibiting protein synthesis [167].
Anti-bacterial antibiotics	Vancomycin	• Vancomycin is a glycopeptide antibiotic that works by inhibiting cells well and is used to treat drug-resistant Gram-positive bacteria [168].
	Azithromycin	• Azithromycin prevents bacterial growth by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thereby inhibiting mRNA translation.
	Rifaximin	• Rifaximin plays an antibacterial role by specifically binding to the β subunit of bacterial DNA dependent RNA polymerase to inhibit bacterial RNA synthesis.
	Tigecycline	• Tigecycline is a new type of glycyrrhizin antibacterial drug with antibacterial and antitumor activity. It mainly affects the proliferation, migration and invasion of tumor cells by inhibiting mitochondrial protein synthesis and inducing mitochondrial dysfunction.

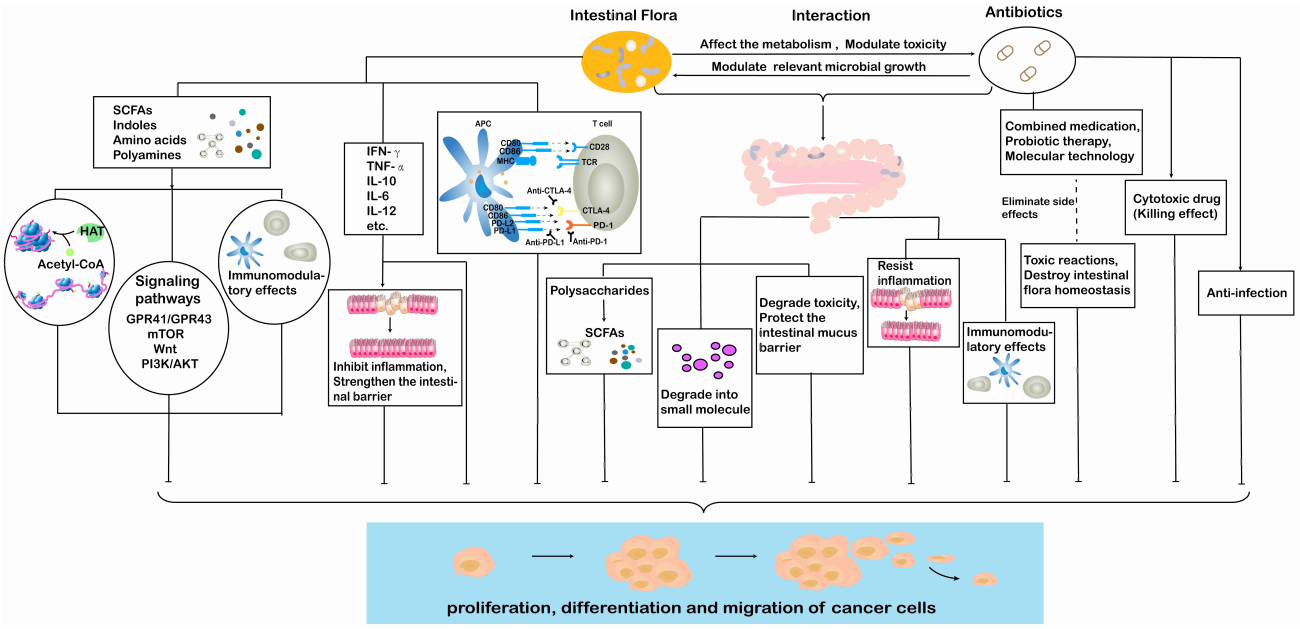

Fig. 3. Intestinal flora, antibiotics and tumors. Intestinal flora inhibits tumor development by secreting metabolites with anti-cancer effects, such as SCFAs, indoles, amino acids and polyamines, or adjusting the tumor-related inflammatory environment. They also regulate immune function. Intestinal flora can promote the digestion and absorption of antibiotics, degrade the toxicity of antibiotics and reduce the damage to normal cells of the body. Antibiotics help to preserve bacteria which are beneficial to homeostasis through specific selection. More importantly, the interaction between antibiotics and intestinal bacteria inhibits tumor progression.

ter anti-tumor outcomes. By secreting anti-inflammatory mediators, regulating inflammation-related signaling pathways and strengthening the intestinal barrier, intestinal microbiomes can directly or indirectly adjust the tumor-related inflammatory environment. Intestinal microbiome are also involved in regulation of the body's tumor immune environment by participating in PD-1, CTLA-4 and other pathways to block immune regulation and to promote immune system functions. Changes and imbalances in intestinal microbiota diversity can bring a series of changes in the tumor or anti-tumor effects, and lead to cancer occurrence, progression and metastasis [133]. Thus, significance of the roles of intestinal microbiota in tumor prevention and control should be elucidated. However, solely relying on self-regulation of intestinal microbiota cannot achieve significant cancer treatment outcomes.

Antibiotics, which are produced by natural microbial metabolism, have strong tumor suppressor abilities and can better exert their anti-tumor effects through interactions with intestinal flora. Upon entry into the body, anti-tumor antibiotics are digested and absorbed. Through the actions of intestinal flora, they are degraded into small molecule substances that are easily absorbed. Intestinal flora can regulate the degree of anti-tumor antibiotic absorption and utilization in the gut. They can also metabolize drugs to reduce the toxic effects of anti-tumor antibiotics on body parts such as the intestinal mucosa. Antibiotics with antibacterial activities can exert inhibitory effects on inflammation. Studies should evaluate the coexistence of favorable intestinal flora and how they work together in inflammatory and tumor immune environments. After the mushroom polysaccharide antibiotic enters the body, it is degraded into oligosaccharides or monosaccharides by the intestinal flora, and metabolized to produce acetic acid, propionic acid, and n-butyric acid. Thus, there is a positive link between antibiotics and enterobacterial metabolite SCFAs. Metabolites like butyric acids can also exert their regulatory effects on intestinal microbiota [162], thereby controlling tumors. Therefore, studies should design better approaches to achieve a balance between antibiotics and intestinal flora to enhance their effectiveness against tumors.

Antibiotics exert anti-bacterial and anti-tumor effects, both of which inhibit the occurrence and development of tumors (Table 2, Ref. [8,156,163–168]). Common anti-bacterial antibiotics such as penicillin, cephalosporins, amikacin, azithromycin, clindamycin, can inhibit inflammation and alleviate the conditions that contribute to tumor growth. Antibiotics such as, DOXO, Pingyangmycin, Mitoxantrone, Boanmycin, and actinomycin-D, exist as cytostatic agents and can inhibit tumor cells. Moreover, antibiotics with both anti-bacterial activity and anti-tumor effect, such as tigecycline, Metronidazole, have been reported. Studies have shown that the combination of anti-bacterial and anti-tumor antibiotics can produce better effects on tumor inhibition.

Applications of antibiotics has certain limitations, such as causing toxic reactions, and destroying intestinal flora homeostasis among others. But it is still an effective cancer treatment scheme widely used in clinical practice due to its strong anti-tumor effects. As cytotoxic drugs, antibiotics can directly act on all stages of tumor cell proliferation cycles. It can effectively and rapidly kill tumor cells. Moreover, its adverse effects can be optimized and improved through combined medications, probiotic therapy, molecular technology and so on. It can also interact with intestinal flora to enhance tumor inhibition. Therefore, we should have confidence in the efficacy of anti-tumor antibiotics. From an intestinal flora perspective, it is important to develop new strategies and optimization schemes for the treatment of tumors with anti-tumor antibiotics. The combination of antibiotics and intestinal flora plays an active role in cancer therapy (Fig. 3). Intestinal flora can minimize the side effects of anti-tumor antibiotics to promote tumor control.

As mentioned above, combined use of antibiotics and probiotics can protect the intestinal environment against the aggressive effects of chemotherapy. Studies have shown that probiotics can be used as a preventive microbial nutritional supplement to maintain intestinal balance. These probiotics regulate the excretion of intestinal acids, immune responses, competition for nutrients and intestinal receptor sites, and antimicrobial agents [169]. Other guidelines and recommendations suggest that probiotics can be used to regulate the gastrointestinal microbiome to control disease development [170]. In recent years, primary studies and meta-analyses have investigated the safety of probiotic treatments. It has been reported that probiotic treatment can cause adverse reactions. Therefore, the use of probiotics needs to be optimized to reduce the associated negative effects. Some of the adverse events are caused by a combination of probiotic and antibiotic, mixed dietary therapies, corticosteroids, immunosuppressants, or other potential confounding factors. Moreover, the long-term effects of probiotics need to be investigated [171]. Therefore, further systematic, retrospective, and meta-analyses should be conducted to determine the benefits and side effects of probiotics in the treatment of tumors.

Finally, most of the existing research has been conducted on human tumor graft models or diet-induced tumor animal models. Therefore, the interaction between intestinal microbiome and tumors in the human body and the specific pathways involved need to be investigated.

7. Conclusions

Analysis of the interaction between intestinal flora and anti-tumor antibiotics has shown that the body's immune function is important to the control of tumor development. Therefore, future studies should explore the effect of intestinal flora and anti-tumor antibiotics on tumor immune environment. This suggests that a combination of antibiotics

and intestinal flora is better modality to regulate the tumor micro-environment. Specifically, tumor immune functions, immune cell activation, immune system strengthening and tumor immune detection should be strengthened.

Antibiotics are potential treatments for tumors. The intestinal microbiome has great prospects in tumor treatment. It regulates the metabolism and degradation of antibiotics. The synergy between intestinal microbiome and antibiotics in the control of tumors need to be explored. Interactions between intestinal flora and antibiotics can eliminate the deficiencies of the either agent. It is important to balance the relationship between antibiotics and intestinal bacteria for better anti-tumor therapeutic effects. It is a market with great potential that cannot be ignored.

Abbreviations

RT, radiation therapy; SCFAs, short-chain fatty acids; ICIs, immune checkpoint inhibitors; CRC, colorectal carcinoma; B. *longum*, *Bifidobacterium longum*; EBTF, enterotoxigenic *bacteroides fragilis*; Th17, T helper type 17; *E. coli*, *Escherichia coli*; TJ, tight junction; ZO, Zona occludens protein; NF-κB, nuclear factor kappa-B; DCs, dendritic cells; mTOR, mammalian target of rapamycin; PI3K/AKT, phosphatidyl inositol 3-kinase/AKT; BCAAs, branchain-chain amino acids; 3-IAld, indole-3-formaldehyde; Treg, regulatory T cells; CLA, conjugated linoleic acid; IFN-γ, interferon-gamma; CTLA-4, cytotoxic T lymphocyte antigen 4; PD-1/PD-L1, programmed cell protein 1/death ligand 1; APC, antigen presenting cell; TCR, T cell receptor; MHC, major histocompatibility complex; DOXO, doxorubicin; GAGs, glycosaminoglycans; S6K, S6 kinase.

Author Contributions

XY, AW and WL designed and wrote the paper. YX designed the figures and tables. XD and YZ edited the paper. KT and XX provided advises. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare that the research was conducted without of any commercial or financial relationships that could be construed as a potential conflict of interest.

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