Microbial metabolites affect tumor progression, immunity and therapy prediction by reshaping the tumor microenvironment (Review)

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Abstract. Several studies have indicated that the gut microbiome and tumor microbiota may affect tumors. Emerging metabolomics research illustrates the need to examine the variations in microbial metabolite composition between patients with cancer and healthy individuals. Microbial metabolites can impact the progression of tumors and the immune response by influencing a number of mechanisms, including modulation of the immune system, cancer or immune-related signaling pathways, epigenetic modification of proteins and DNA damage. Microbial metabolites can also alleviate side effects and drug resistance during chemotherapy and immunotherapy, while effectively activating the immune system to exert tumor immunotherapy. Nevertheless, the impact of microbial metabolites on tumor immunity can be both beneficial and harmful, potentially influenced by the concentration of the metabolites or the specific cancer type. The present review summarizes the roles of various microbial metabolites in different solid tumors, alongside their influence on tumor immunity and treatment. Additionally, clinical trials evaluating the therapeutic effects of microbial metabolites or related microbes on patients with cancer have been listed. In summary, studying microbial metabolites, which play a crucial role in the interaction between the microbiota and tumors, could lead to the identification of new supplementary treatments for cancer. This has the potential to improve the effectiveness of cancer treatment and enhance patient prognosis.

Contents

1. Introduction

A recent statistical survey indicated that there were almost 20 million new cases of cancer worldwide in 2022, with 9.7 million deaths attributed to cancer (1). Cancer has therefore emerged as a prominent factor contributing to human mortality. In recent decades, novel approaches for the prevention and treatment of cancer, including antibody-drug conjugates and immunotherapy (2-4), have been discovered. Although these therapeutic techniques have provided new opportunities for tumor treatment, their effectiveness is hindered by the resistance of tumor cells to drugs and the intricate structure of the tumor microenvironment (TME), which provides challenges in treating tumors (5,6). The irregularity of vascular networks within the TME can impede the transport of chemotherapeutic agents. Additionally, immunosuppressive cells within the TME have the capability to dampen immune responses, thereby attenuating the efficacy of immunotherapy. Exploring novel adjuvant therapy drugs is intended to improve the effectiveness of current treatments, ease patient distress and even achieve a cancer cure.

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A recent study found that a lack of microbiota within the TME inhibits the production of type I interferon (IFN-I) by monocytes, thereby inducing M2 polarization of macrophages (7). This results in the formation of an immunosuppressive TME, which enables tumor cells to avoid being detected and destroyed by the immune system. Disruption of the microbiota has an impact on the advancement of tumors, but the restoration of imbalances in gut microbial composition through fecal microbiota transplantation (FMT) has been proposed as a promising approach for tumor treatment (8). The microbiota also promotes cancer by inducing chronic inflammation. When *Ackermannia mucinophila* is lost in the gut, the intestinal barrier function is disrupted, resulting in liver inflammation and fibrosis (9). Prolonged inflammation and fibrosis can gradually lead to aberrant hepatocyte proliferation and injury, potentially culminating in the development of hepatocellular carcinoma. Tumor progression and the microbiome are strongly interconnected through a number of pathways. For instance methylobacterium contributes to the development of gastric cancer by decreasing the production of TGF-β and $CD8^+$ tissue-resident memory T-cells (10). *Candida albicans* promotes the secretion of interleukin (IL)-7, which promotes the release of IL-22 from RORγt+ (group 3) innate lymphoid cells (ILC3s) by activating the aryl hydrocarbon receptor (AHR) and STAT3 (11). IL-22 can promote tumor cell metastasis and the formation of intra-tumoral blood vessels (12,13). In summary, there have been an increasing number of studies that specifically investigating the relationship between the microbiome and cancer.

Microbes colonize numerous parts of the body (including tumors) and influence host tumorigenesis and tumor progression (14-17). Microbial metabolites, which are compounds produced during the growth and metabolic processes of microorganisms, have also been associated with the development of cancer (18). Gut bacteria convert primary bile acids into secondary bile acids, and elevated concentrations of secondary bile acids facilitate the proliferation of tumors by impairing the function of natural killer T-cells (19). In addition, some microbial metabolites are directly carcinogenic. For instance, cytotoxin-associated gene A produced by *Helicobacter pylori* induces BRCAness (the tumor exhibits characteristics associated with mutations in the BRCA1 or BRCA2 genes), promotes DNA double-strand breaks and induces bacteria-associated gastric cancer (20). In addition to causing cancer, some microbial metabolites may have anticancer effects. Reuterin, which is produced by *Lactobacillus reuteri*, selectively oxidizes proteins and inhibits ribosomal biogenesis and protein translation to restrict the proliferation and survival of colon cancer cells (21). In summary, microbial metabolites play a role in the development and advancement of tumors through several processes. Targeting these metabolites may therefore offer additional advantages in treating patients, such as enhanced therapeutic efficacy, reduced adverse effects and overcoming drug resistance.

Microbial metabolites can potentially serve as supplementary therapeutic agents to enhance current clinical techniques. Gut microbial metabolism produces butyric acid, which regulates the T-cell receptor signaling pathway to stimulate the generation of cytokines that possess antitumor effects (22). Butyric acid notably improves the antitumor capacity of immune cells, leading to improved effectiveness of anti-programmed cell death protein 1 (PD-1) immunotherapy. Microbial metabolites have a reciprocal impact on clinical therapy. The metabolism of *Fusobacterium nucleatum* results in the production of succinic acid, which hampers the synthesis of IFN-β and restricts entry of $CD8^+$ T-cells into the TME. As a result, the immune response against the tumor is suppressed (23). Therefore, microbial metabolites may have a dual impact, exerting both beneficial and harmful impacts on tumor treatment. To fully understand the dual impact, it is crucial to not only clarify its exact mechanism of action but also to consider the specific environment in which it produces its effects. Varying amounts of short-chain fatty acids (SCFAs) yield diverse outcomes in the therapy of tumors. In non-alcoholic fatty liver disease, high levels of SCFAs (when the concentration exceeds the threshold of host tolerance) leads to the progression of hepatocellular carcinoma (24). However, when present in normal amounts, SCFAs markedly hinder the advancement of colorectal cancer (25). Thus, the effect of microbial metabolites on tumors is not absolute, and different microbial metabolites have different effects at different concentrations.

The present review explores the functions and mechanisms of various microbial metabolites in the development of tumors, the advancement of tumors and the immune response to tumors. The impact of microbial metabolites on chemotherapy and immunotherapy are also investigated, providing a detailed explanation of the underlying mechanisms. The present review also evaluates the potential of microbial metabolites as supplementary therapeutic agents for cancer and suggests future research areas for microbial metabolites in the field of oncology.

2. Microbial metabolites remodel the TME to promote tumor progression

Tumors are not only composed of a simple set of tumor cells but also infiltrate and host a diverse set of host cells, cytokines and extracellular matrices (26-28). Consequently, throughout the process of tumor formation, tumor cells frequently utilize various tactics to influence both themselves and the neighboring cells. This fosters a favorable environment for the proliferation and metastasis of tumor cells. Research has indicated that tumor cells increase the concentration of lactate at the tumor location by employing glycolysis. The buildup of lactate is frequently linked to a reduction in the immune response against the tumor within the TME (29). Meanwhile, these lactates also serve as signaling molecules in both autocrine and paracrine mechanisms within the tumor, activating G protein-coupled receptor (GPR) 81 (30). Activation of GPR81 promotes angiogenesis and immune evasion within the TME. In pancreatic cancer, CD73 mediates activation of the p38/STAT1 axis by inducing extracellular adenosine accumulation, leading to the upregulation of C-C motif chemokine ligand (CCL) 5 transcription, which attracts regulatory T cells into the TME (31). Therefore, tumor cells exert an influence on the advancement of tumors by altering the programming of the TME. As the tumor advances, microbial metabolites are generated by microorganisms in the tumor and stored in the TME. These microbial metabolites will function as ligands

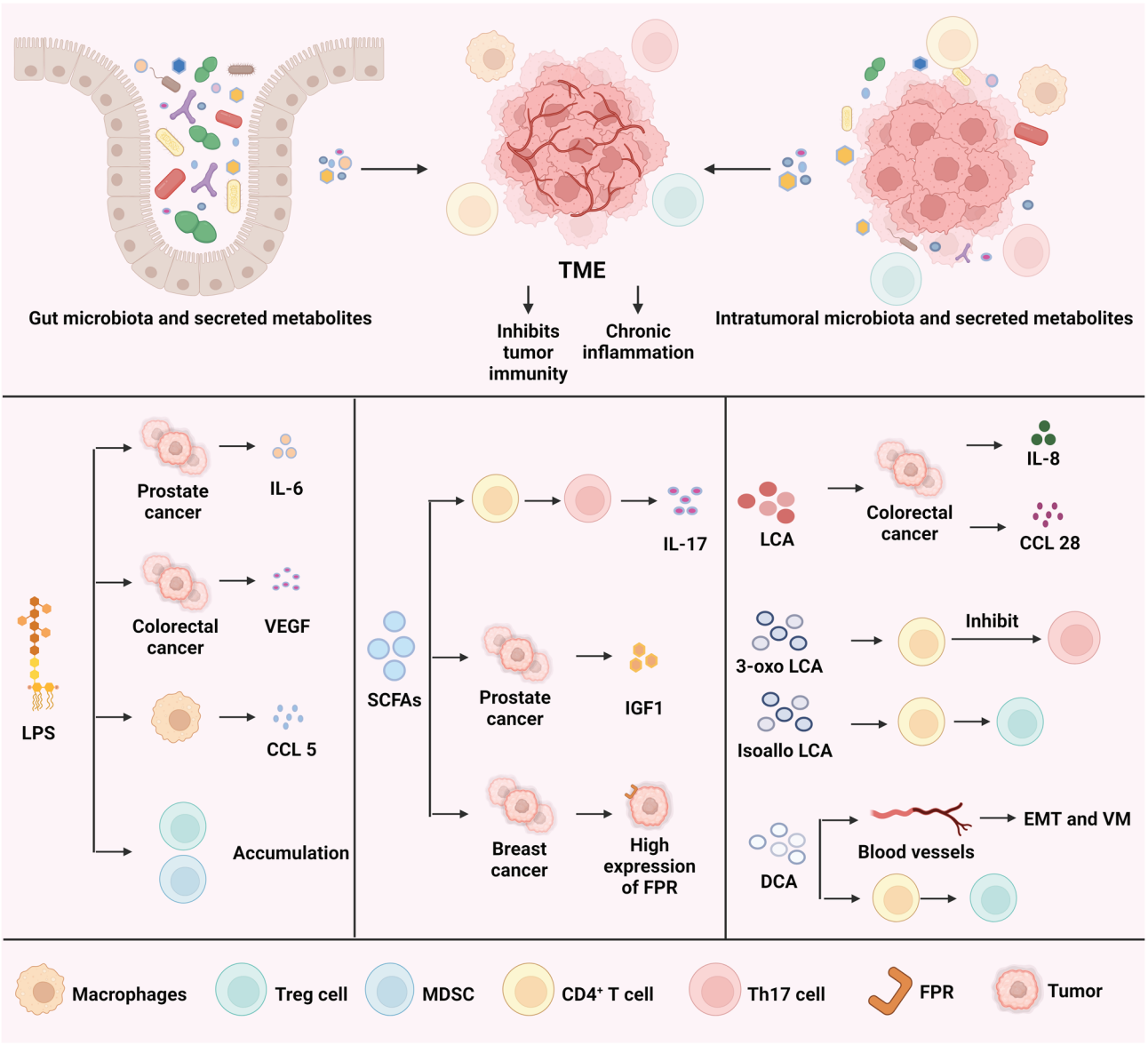

Figure 1. Mechanisms by which various microbial metabolites cause tumor progression and chronic inflammation. The TME is a complex system composed of immune cells, tumor cells, cytokines and blood vessels. Various metabolites enter the TME, affecting the activities of various internal cells and regulating the release of cytokines, thereby reshaping the TME to promote tumor progression. LPS activates the NF-κB signaling pathway in prostate cancer, promoting the release of IL-6. The binding of LPS and TLR4 on colorectal cancer cells promotes VEGF secretion. LPS activation of TLR4 induces macrophages to upregulate CCL5 expression. LPS can cause chronic inflammation, leading to the accumulation of MDSCs and Tregs. SCFAs promote the differentiation of $CD4^+$ T cells into Th17 cells and the release of IL-17. SCFAs stimulate prostate cancer cells to secrete IGF-1. The accumulation of SCFAs promotes high expression of FPR on the surface of breast cancer cells. The accumulation of LCA upregulates CCL 28 and IL-8 by activating the GPR and Erk1/2 MAPK signaling pathways. 3-oxo LCA and isoallo LCA respectively inhibit the differentiation of Th17 cells and promote the differentiation of Treg cells. DCA binds to VEGFR2 to promote EMT and VM, while also promoting the differentiation of $CD4^+$ T cells into Tregs. The figure was created using BioRender.com. TME, tumor microenvironment; LPS, lipopolysaccharide; IL, interleukin; TLR, toll-like receptor; VEGF, vascular endothelial growth factor; CCL,C-C motif chemokine ligand; MDSCs, myeloid-derived suppressor cells; Treg, regulatory T cell; SCFAs, short-chain fatty acids; Th, T helper; IGF, insulin-like growth factor; FPR, formyl peptide receptor; LCA, lithocholic Acid; GPR, G-protein coupled receptor; DCA, deoxycholic acid; VEGFR, VEGF receptor; EMT, epithelial-mesenchymal transition; VM, vasculogenic mimicry.

for specific receptors or as cytokines to regulate the activity of proteins and modify the TME. Research has shown that in mice with colon cancer, microbial metabolism leads to high levels of intestinal ammonia, which induces metabolic reprogramming of T cells, increasing T cell exhaustion and decreasing its proliferation (32). Administering streptomycin to animals with breast cancer results in a reduction in the abundance of lactobacilli in the intestinal tract. The proportion of $CD4^+$ and $CD8^+$ T cells that produce IFN-γ is decreased in the TME. Nevertheless, following the administration of lactobacilli, there is an augmentation in the lactic acid content at the location of the tumor, resulting in the disappearance of this phenomenon (33).

Therefore, microbial metabolites can facilitate the advancement of tumors by altering the TME. Byproducts of the microbial community in the gut and the microorganisms associated with tumors have a role in the advancement of tumors and long-lasting inflammation. Fig. 1 illustrates how gut microbiota, as well as intratumoral microbiota, and their metabolites collectively reprogram the TME. Additionally,

Fig. 1 outlines the mechanisms by which lipopolysaccharides (LPSs), SCFAs and secondary bile acids inhibit tumor immunity and induce chronic inflammation.

LPS. LPS is an essential component of the cell wall in Gram-negative bacteria (GNB). An examination conducted in 2020 on bacterial populations present in pan-cancerous tumors demonstrated that LPS has a crucial role in promoting inflammation in different types of cancer (34). Using polymyxin B to clear GNB from the intestines or using TAK-242 to block LPS activation of Toll-like receptor 4 (TLR4) can both alleviate the immunosuppressive microenvironment of colorectal cancer and facilitate T-cell infiltration into the tumor (35). Thus, LPS has the potential to trigger long-term inflammation, leading to the advancement of cancer. Long-term inflammation caused by LPS results in T-cell exhaustion, an increase in the expression of the PD-1/programmed death-ligand 1 (PD-L1) axis and the buildup of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). This leads to the development of a microenvironment that suppresses the immune system and promotes the proliferation and advancement of tumors (36).

Furthermore, LPS promotes the secretion of various cytokines that aid in tumor cell proliferation and metastasis. Activation of the NF-κB signaling pathway by LPS results in the secretion of IL-6, which activates STAT3 in an autocrine manner., promoting prostate cancer progression in mice (37). LPS also stimulates TLR4 to induce the expression of vascular endothelial growth factor (VEGF) C, which promotes tumor cell metastasis and lymphangiogenesis (38). Macrophages, which are integral components of the TME, exert a marked influence on the evasion of the immune system by tumors. Research has shown that stimulation of the TLR4 signaling pathway by LPS leads to an increase in the production of CCL5 by macrophages. Consequently, this obstructs the ability of T cells to destroy colorectal cancer cells and enables the cancer cells to avoid detection by the immune system. In addition, CCL5 regulates the process of removing ubiquitin molecules from PD-L1 and maintaining its stability (39).

SCFAs. SCFAs have been shown to possess antitumor capabilities (40). However, SCFAs may also promote tumor progression and metastasis via immunomodulatory effects, signal transduction regulation and inflammation modulation, all of which can remodel the TME. In the intestine of gnotobiotic mice colonized with the *F. nucleatum* Fn7-1 strain, Fn7-1 metabolism produces SCFAs that combine with GPR43 to increase colonic T helper 17 (Th17) cell frequency and promote IL-17A and IL-17F expression, which leads to chronic inflammation and increases the risk of colorectal cancer (41). Furthermore, SCFAs enhance the activation of the MAPK and PI3K signaling pathways in the neighboring prostate region by upregulating the production of insulin-like growth factor-1, hence facilitating the proliferation and multiplication of prostate cancer cells (42). The most prevalent SCFAs in the human body include acetic acid, propionic acid and butyric acid. Although the majority of studies concentrate on these three molecules, it is crucial not to disregard the potential influence of formate on the advancement of tumors. Genetic interference has been found to effectively decrease tumor cell invasion by inhibiting the synthesis of formate (43). Additionally, the accumulation of formate has been shown to increase the expression of the formyl peptide receptor, which enhances the invasive ability of cancer cells (44). Formate also plays a role in promoting colorectal cancer tumor invasion and enhancing the population of tumor stem cells through the activation of AHR signaling (45). Formate treatment induces a rise in Th17 levels (45), which are inflammatory regulatory cells that promote chronic inflammation. Therefore, formate may enhance the progression of colorectal cancer by promoting chronic inflammation.

Secondary bile acids. When considering the relationship between secondary bile acids and different tumor types, including colorectal cancer and liver cancer, it is important to investigate therapeutic approaches involving secondary bile acids to advance the prevention and treatment of these tumors (46,47). The gut microbiome produces bile salt hydrolases (BSHs) to deoxygenate primary bile acids into secondary bile acids, primarily deoxycholic acid (DCA) and lithocholic acid (LCA). These compounds can contribute to tumor progression by reshaping the TME (48). Unconjugated DCA and LCA buildup in the intestine and stimulate GPRs in regions where BSH is highly expressed. As a result of this activation, there is an elevated production of CCL28, which is regulated by β-catenin, in the tumor. Activation of the β-catenin/CCL28 axis leads to increased amounts of Tregs in the TME, which in turn creates an immunosuppressive microenvironment (49). In $Apc^{min/+}$ mice (a commonly used mouse model for colon cancer), the accumulation of DCA activates VEGF receptor 2, promoting vasculogenic mimicry and epithelial-mesenchymal transition (EMT) (50).

Additionally, secondary bile acids also induce the expression of cytokines that influence tumor progression. LCA activates Erk1/2 MAPK and inhibits STAT3 phosphorylation to promote IL-8 expression in colorectal cancer cells (51). LCA induces the progression and metastasis of colorectal cancer via promoting IL-8 expression (52). Furthermore, DCA activates $CD4^+$ T cells and induces IL-10 secretion to induce Treg cell differentiation, causing an immunosuppressive microenvironment (53). Furthermore, the release of IL-10 stimulates the polarization of tumor-associated macrophages (TAMs) towards the M2 phenotype, hence facilitating the proliferation and metastasis of colorectal cancer (54). The two derivatives of LCA are 3-oxo LCA and isoallo LCA. 3-oxo LCA hinders Th17 cell differentiation by binding to retinoid-related orphan receptor-γt, whereas isoallo LCA encourages the formation of Tregs by producing mitochondrial reactive oxygen species (ROS) (55).

3. Microbiota modulates tumor immunity by producing relevant metabolites

Studies suggest that the microbiome can improve disease control in individuals with tumors (56-58). A study found that FMT improved the effectiveness of anti-PD-1 therapy in mice with colorectal cancer (59). Another study demonstrated that FMT altered the cellular constitution within the TME of patients with melanoma, helping to surmount resistance to anti-PD-1 therapy (60). The TME is colonized by a diverse range of microbes, but its complex composition restricts the

manipulation of the microbiota. Microbial metabolites can be utilized to provide a more accurate control of the immune response in the TME, offering novel approaches for tumor research and treatment. For instance, a recent study aimed to examine the effects of the bacterial-derived metabolite, desaminotyrosine (DAT), on C57BL/6J mice. The results demonstrated that the group treated with a combination of DAT and anti-CTLA-4 had a higher immunotherapy response compared with the group that received only anti-CTLA-4 (61).

The success of immune checkpoint inhibitors (ICIs) in tumor therapy significantly relies on reactivating specific T cells and promoting the apoptosis of Tregs present within the TME (62,63). Therefore, it is highly probable that microbial metabolites can alter tumor immunity by reprogramming the TME. Alleviating the persistent inflammatory response in the TME could potentially facilitate the development of a beneficial immune microenvironment, and hence enhance the response of the immune system to the tumor. Moreover, activation of the immune system is essential for enhancing tumor immunity. Fig. 2 illustrates how trimethylamine N-oxide (TMAO), SCFAs and Trp-related metabolites promote antitumor immunity by reprogramming the TME and outlines the mechanisms through which they exert their effects.

TMAO. TMAO has been linked to a range of diseases, such as cardiovascular disease and liver, pancreatic and colorectal cancer (64-67). While the exact method by which TMAO contributes to tumor progression remains unclear, it is known that elevated levels of amines, as a metabolite, lead to oxidative stress (68). Oxidative stress can lead to an increase in intracellular DNA mutations and genomic instability, which in turn promotes cancer incidence and tumor progression. Recently, several investigations have established a connection between TMAO and different cancer types. For instance, TMAO produced by the gut microbiota during the breakdown of food has been found to stimulate macrophages, enhance the response of T cells and decrease the number of tumor cells in pancreatic ductal adenocarcinoma (PDAC) by increasing the production of IFN-I (66). Due to the connection between the pancreatic duct and the duodenum, microbial metabolites from the intestines can reach the pancreatic duct and surrounding tissues. This could potentially have a role in the development and treatment of PDAC. Immunotherapy has had little effectiveness in treating triple-negative breast cancer (TNBC) (69). A study that conducted a multi-omics analysis of patients with TNBC discovered that TMAO was linked to a cohort that received immunotherapy and exhibited an improved immune response. TMAO also triggers tumor cell pyroptosis by activating the endoplasmic reticulum stress kinase, PERK, while also boosting $CD8^+$ T cell-driven antitumor immunity in the host (70). Meanwhile, a study revealed a correlation between elevated blood levels of TMAO and colorectal cancer (71). However, the precise pathophysiology remains uncertain, but it is likely associated with the stimulation of persistent gastrointestinal inflammation. Hence, it is crucial to regulate the concentration of TMAO when employing TAMO for research or cancer therapy. Several strategies, including the suppression of crucial metabolic enzymes, dietary regulation and the use of antibiotics, have been suggested to manipulate the gut microbiome to produce TMAO (72-74).

SCFAs. SCFAs are important metabolites generated by the intestinal microbiota during the digestive process, mainly consisting of acetic acid, propionic acid and butyric acid. SCFAs promote the metabolism of intestinal epithelial cells and enhance the intestinal barrier function (75). Certain research suggests that increasing the levels of butyric acid in the stomach through pectin supplementation can promote the infiltration of T cells in the TME and improve the efficacy of ICIs in treating colorectal cancer (76). SCFAs have shown strong antitumor effects in multiple types of cancer, particularly colorectal cancer (77). The ability to act through different routes is made possible by the diversity of SCFAs and their derivatives. The antitumor actions of SCFAs are achieved through their binding to many GPRs, such as GPR41, GPR43 and GPR109a. Through the gut-hepatic axis, acetic acid binds to GPR43 in the liver, limiting IL-6 release and obstructing the JAK1/STAT3 signaling pathway to stop liver cancer from progressing (78). Moreover, a study found that the combination of propionic acid and GPR43 also inhibited the proliferation of liver cancer cells (79). In addition, propionic acid can inhibit the Hippo/Yap and MAPK signaling pathways by binding to GPR41 and GPR43, ultimately inhibiting the metastasis of breast cancer cells (80). Butyric acid acts on GPR109a in colon macrophages and dendritic cells, inducing the differentiation of Tregs and $CD4^+$ T cells and inhibiting the development of colitis and colorectal cancer (81). Moreover, a study has shown that GPR43 deletion accelerates the development of colorectal cancer by exhausting $CD8^+$ T cells and hyperactivating dendritic cells (82). In summary, SCFAs stimulate the proliferation and specialization of immune cells by attaching to GPRs. SCFAs also hinder the advancement and metastasis of tumors by attaching to GPRs on tumor cells. Additionally, SCFAs suppress long-term inflammation by activating GPR signaling, which prompts the development of Tregs.

Tumor progression has been closely linked to epigenetic reprogramming. Tumor cells frequently exhibit elevated levels of histone deacetylases (HDACs), which lead to increased histone deacetylation. This alteration affects the control of gene expression and facilitates the advancement and metastasis of tumors (83). Additionally, HDACs suppress both the immune response and inflammatory events in immune cells (84). HDAC inhibitors enhance the antitumor therapeutic efficacy of ICIs by modifying the immunosuppressive function of TAMs and impeding the ingress of MDSCs into tumors, thereby remodeling the immunosuppressive microenvironment (85). In a recent study, inhibition of HDAC by butyric acid caused an elevation in CD25 expression, INF-γ and tumor necrosis factor-α and greatly enhanced the antitumor function of cytotoxic T lymphocytes in pancreatic cancer and melanoma models (86). Propionic acid also inhibits IL-17 and IL-22 secretion by γδ T-cells via inhibition of HDAC, which could inhibit colitis-associated colorectal cancer development (87). A study has also demonstrated that butyric acid inhibits the growth and promotes the apoptosis of P815 mouse breast cancer cells by inhibiting HDAC, in addition to the effects of SCFAs on immune cells (88).

Trp metabolites. The presence of Trp metabolites in organisms is influenced, either directly or indirectly, by the gastrointestinal

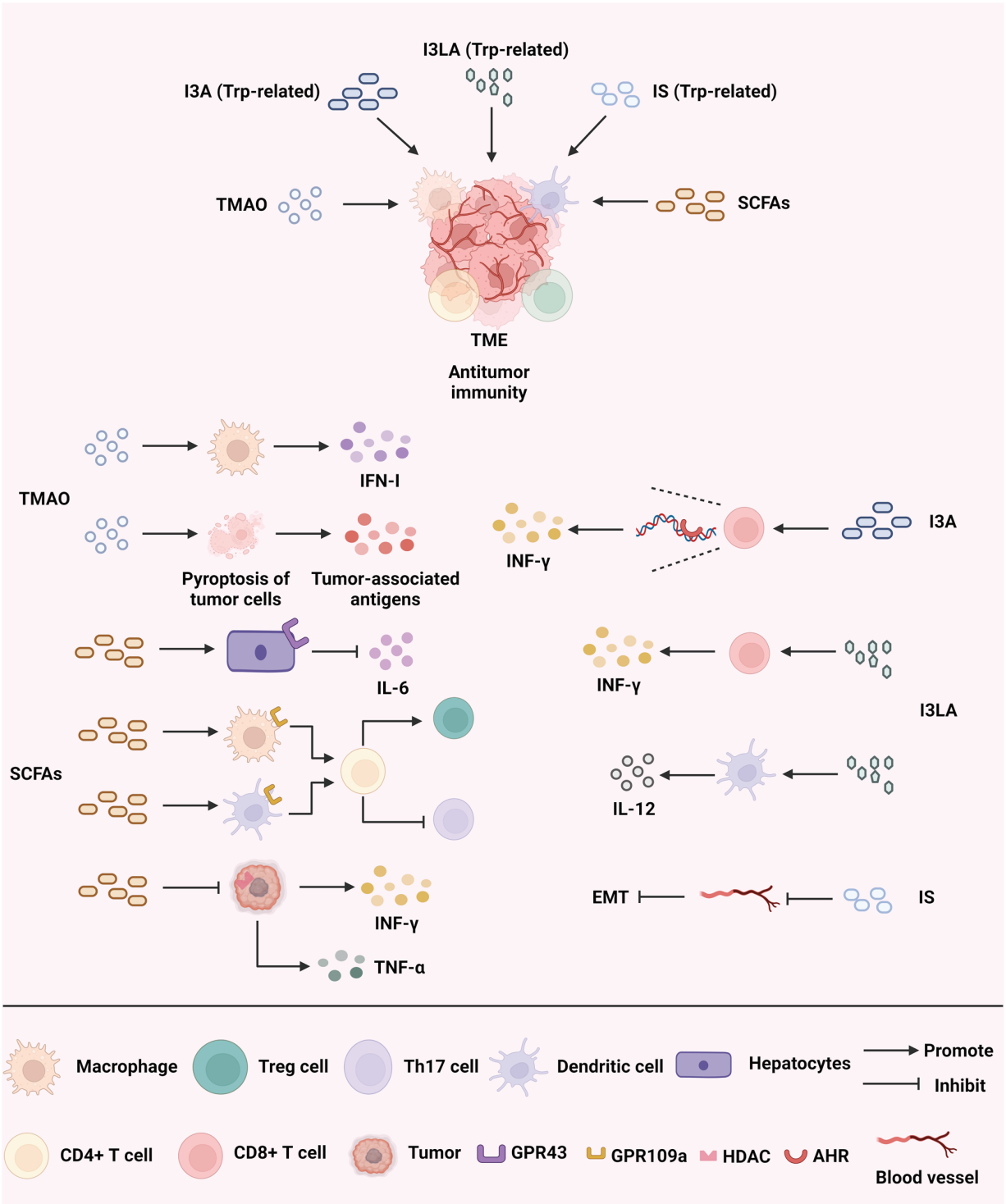

Figure 2. Various microbial metabolites reshape the TME to promote antitumor immunity. TMAO activates M1 macrophages to release IFN-I. TMAO induces triple-negative breast cancer cell pyroptosis, leading to the release of various tumor-associated antigens into the TME. SCFAs binding to GPR43 expressed on liver cells inhibit the secretion of IL-6. SCFAs binding to GPR109a on macrophages or dendritic cells promote the differentiation of $CD4^+$ T cells into Tregs and inhibit differentiation into Th17 cells. SCFAs inhibit the activity of HDACs in tumor cells, thereby promoting the release of INF-γ and TNF-α. I3A binds to the AHR of $CD8^+$ T cells, promoting the secretion of IFN-γ. I3LA alters chromatin accessibility, activating $CD8^+$ T cells to release IFN-γ. I3LA also binds to dendritic cells to promote the secretion of IL-12. IS induces oxidative stress and nitrosative stress to inhibit EMT. The figure was created using BioRender.com. TME, tumor microenvironment; TMAO, trimethylamine N-oxide; IFN, interferon; SCFAs, short-chain fatty acids; GPR, G-protein coupled receptor; IL, interleukin; Treg, regulatory T cell; Th, T Helper; HDAC, histone deacetylases; TNF, tumor necrosis factor; I3A, indole-3-aldehyde; AHR, aromatic hydrocarbon receptor; I3LA, indole-3-lactic acid; IS, indoxyl-sulfate; EMT, epithelial-mesenchymal transition.

microbiome. Metabolites and enzymes associated with Trp have been identified as prospective targets for pharmaceutical advancements in the treatment of various disorders, such as psoriasis, atopic dermatitis and hepatic fibrosis (89-91). Trp metabolites have been reported to act selectively on AHR (92). Indole-3-aldehyde (I3A) activates the AHR of $CD8^+$ T cells

in the melanoma TME, promoting $CD8^+$ T-cell differentiation and IFN-γ production (93). This enhances ICI-induced antitumor immunity. However, in PDAC, Trp metabolites bind to the AHR of TAMs and reduce the frequency of intratumoral $CD8^+$ T cells, creating an immunosuppressive microenvironment (94). This implies that the effects of Trp metabolite-mediated AHR activation may vary among tumor types or be influenced by heterogeneity in the TME.

Epigenetic modifications are of the utmost importance in the regulation of gene expression and are critical in the development, progression and treatment of numerous types of cancer. An examination of the effects that microbial metabolites have on epigenetic modifications will establish a solid theoretical basis for the advancement of novel approaches in the field of tumor immunotherapy. Tumor immunity can be regulated by Trp metabolites via epigenetic modifications. Indole-3-lactic acid alters chromatin accessibility to initiate the antitumor activity of $CD8^+$ T cells and directly enhances the secretion of IFN-γ and granzyme B by tumor-infiltrating $CD8^+$ T cells to kill tumor cells, and also promotes IL-12a secretion by binding to dendritic cells (95). IL-12a in turn further induces the proliferation of $CD8^+$ T cells and promotes tumor immunity (96).

A modest elevation in oxidative stress and suppression of EMT can greatly impede the growth and metastasis of tumor cells. Indoxyl-sulfate (IS) suppresses the activity of nuclear factor erythroid 2-related factor 2 and stimulates the production of inducible nitric oxide synthase, leading to the occurrence of oxidative and nitrosative stress. Additionally, IS hinders EMT, resulting in a notable decrease in the metastasis of breast cancer cells to adjacent tissues (97). The metabolism of Trp is not only regulated by the gut microbiome but also by tumor cells (98). Tumor cells often exhibit heightened activity in Trp metabolic pathways, such as indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase, which facilitate the conversion of Trp into kynurenine. This process increases the number of Tregs in the TME and boosts the expression of PD-1 on $CD8^+$ T cells, helping tumor cells avoid detection by the immune system (99). An extensive examination of the regulatory mechanisms of Trp metabolism will provide new targets and strategies for tumor therapy, given the intricate nature of the Trp metabolic pathway.

4. Impact of microbial metabolites on clinical cancer therapy

At present, a substantial percentage of individuals diagnosed with cancer undergo radiotherapy as part of their treatment. While a number of individuals have experienced positive outcomes from radiotherapy, it can nevertheless result in various negative effects. For instance, research has demonstrated that whole-brain radiotherapy administered to patients with lung cancer and brain metastases will ultimately result in memory impairment (100). A retrospective cohort study found that patients with nasopharyngeal carcinoma had a higher incidence of oral mucositis during radiotherapy (101). The detrimental consequences of these side effects might significantly impair the quality of life of the patient and perhaps result in treatment discontinuation or decreased patient tolerance. The critical clinical problem of mitigating harmful effects in patients following radiotherapy is increasingly recognized. Evidence indicates that microbial metabolites possess the ability to alleviate detrimental effects on the host following exposure to ionizing radiation. Increased concentrations of propionate and Trp metabolites, which show long-term radioprotection, were found in the intestines of mice that received high doses of radiation but maintained a normal lifespan (102). Meanwhile, DCA can be used to treat radioactive skin injuries, promote wound healing and reduce epidermal hyperplasia (103). As a result, microbial metabolites are important in cancer therapy, and an increasing number of studies are investigating the potential applications of microbial metabolites to enhance therapeutic outcomes or minimize side effects in patients with cancer (104-106). The role of microbial metabolites in immunotherapy and chemotherapy are the focus of this section. Table I presents clinical trials regarding LPS, SCFAs and urolithin A (UroA), aimed at investigating the role of microbial metabolites in cancer treatment. Table II presents experimental and observational clinical trials of gut microbiota to explore their impact and mechanisms in cancer treatment.

Chemotherapy. Chemotherapy is a popular cancer treatment that can halt cancer from progressing via several methods, but drug resistance and adverse effects remain a problem. As such, reducing the adverse effects and medication resistance linked to chemotherapy is a major task. As demonstrated in Fig. 3, the combined use of microbial metabolites and various chemotherapy drugs can regulate the TME through multiple mechanisms, promoting tumor cell apoptosis.

UroA is a product of gut microbial metabolism. UroA has been reported to downregulate the expression of breast cancer resistance protein (a drug efflux transporter protein), which would contribute to the sustained efficacy of mitoxantrone in cancer cells (107). Meanwhile, in a recent study, UroA and its structural analog, UAS03, were combined with the chemotherapeutic drug, 5-fluorouracil (5FU), and investigated for their anticancer effects. The results showed that UroA/UAS03 re-sensitized 5FU-resistant colorectal cancer to chemotherapy by modulating the FOXO3/FOXM1 axis (108). These findings indicate that the use of UroA in combination with low-dose chemotherapeutic drugs can provide similar antitumor effects as high-dose chemotherapeutic drugs, potentially minimizing the negative side effects associated with chemotherapy. Furthermore, UroA can suppress the growth of gastric cancer cells, hinder their capacity to invade and metastasize and stimulate their programmed cell death (109). This indicates that UroA may emerge as a novel adjuvant cancer therapy medication. However, further investigations are necessary to confirm the safety and effectiveness of UroA, as well as to identify the ideal therapeutic concentration and clinical protocol.

Butyrate is a SCFA produced by gut microbiota, typically generated as a byproduct during the fermentation of dietary fibers in the colon. Butyrate has demonstrated potential efficacy as an adjuvant treatment drug in chemotherapy by modulating cellular metabolism, reducing oxidative stress and preserving liver function through various mechanisms (110-112). The coadministration of butyrate and irinotecan induces programmed cell death in colorectal cancer cells by modulating the BAX/BCL-2 ratio,

Table I. Current list of clinical trials on microbial metabolites in various types of cancer, according to https://clinicaltrials.gov/.

Study ID	Disease	Purpose	No of patients	Inclusion criteria	Study state
NCT05751837	Cancer	The main objective is to activate the immune system by injecting LPS into abdominal tumors and evaluate its potential effects on tumor treatment.	6 adults	Participants must have at least two index non-visceral intra-abdominal tumors that are grossly visible, >1 cm^3 in volume and amenable to biopsy and injection of investigational drug or control solution at the time of laparoscopy.	Recruiting
NCT04700527	Cancer	To assess and compare GI toxicity from RT between subjects who receive therapeutic SCFA and those who receive placebo, identifying a safe, low-cost therapeutic to reduce GI toxicity from therapeutic or environmental radiation.	122 adults	Subjects with histological or cytological evidence/confirmation of GI, urologic or gynecologic malignancy.	Not yet recruiting
NCT06022822	Prostate cancer	This phase II randomized control trial assesses the effect of Uro-A supplementation compared to placebo in men with biopsy-confirmed prostate cancer undergoing RP progressive disease.	90 adults	Participants must have pathologically confirmed adenocarcinoma of the prostate with FFPE biopsy tissue available for analysis. Diagnosis can be any time in the 6 months prior to registration or randomization.	Not yet recruiting

LPS, lipopolysaccharide; GI, gastrointestinal; RT, radiation therapy; SCFA, short-chain fatty acid; UroA, urolithin A; RP, radical prostatectomy; FFPE, formalin-fixed paraffin embedded.

while also augmenting the responsiveness of cancer cells to irinotecan (113). Meanwhile, butyrate and oxaliplatin can synergistically inhibit the proliferation, invasion and metastasis of colorectal cancer cells and promote the apoptosis of these cells (114). Furthermore, the intestinal bacterium, *F. nucleatum,* promotes resistance to chemotherapy in colorectal cancer by modulating autophagy (115). Butyrate downregulates the expression of adhesion-associated outer membrane proteins and inhibits *F. nucleatum* growth, enrichment and adhesion in colorectal tissues, thereby reducing *F. nucleatum* colonization and mitigating *F. nucleatum*-induced chemoresistance (116). Gut microbiota can produce indole-3-acetic acid (3-IAA) by metabolizing tryptophan from the diet. Neutrophil-derived myeloperoxidase (MPO) is essential for the joint action of 3-IAA and chemotherapy. MPO catalyzes the oxidation of 3-IAA. When combined with chemotherapeutic drugs, the oxidative products of 3-IAA can reduce the production of enzymes that degrade ROS. This leads to an increase in ROS levels and a decrease in tumor cell autophagy, ultimately inhibiting the development of tumor cells (117). Therefore, appropriate intervention in the nutrition of patients with cancer during treatment may have a positive impact on chemotherapy.

Microbial metabolites can both increase and impair the efficacy of chemotherapy. A study has demonstrated that *Lactobacillus* residing in tumors can lead to resistance to radiotherapy and chemotherapy. This resistance is achieved by modifying the metabolism of the tumor and the signaling pathways related to lactate (118). Furthermore, the metabolites produced by microbes as they metabolize chemotherapy drugs can lead to undesirable responses. A randomized controlled trial conducted in 2021 revealed that bacterial glucuronidase can break down the inactive metabolite of irinotecan, SN-38G, into its active form, SN-38. This process subsequently leads to damage in the intestinal mucosa (119).

Immunotherapy. ICIs have been used with great success in cancer treatment, but many adverse effects (such as gastrointestinal reactions) that occur during treatment have limited their wider application (120). Nevertheless, the integration of ICIs with microbial metabolites could potentially resolve this issue. I3A was found to have a protective impact on enteritis generated by ICIs in mice. Additionally, I3A protected enteritis induced by ICIs in mice that received FMT from I3A-treated mice via modifying the composition and function of the gut microbiome (121). The TME

Table II. Current clinical trials on relevant microorganisms in various types of cancer, according to https://clinicaltrials.gov/.

Study ID	Disease	Purpose	No. of patients	Inclusion criteria	Study state
NCT06039644	Breast cancer	To explore after consumption of probiotics of lactobacillus composite strain powder sachets for 6 months in BC chemotherapy, and whether it assists patients in alleviating the side effects of chemotherapy.	100 adults	Stage I-III patients with BC receiving anthracycline-based and taxane-based chemotherapy (not limited to before or after chemotherapy/surgery).	Not yet recruiting
NCT05725720	Diffuse large B-Cell lymphoma	Investigate the potential impact of the GM on treatment response and prognosis in patients with DLBCL undergoing CAR-T cell therapy.	90 adults	Patients diagnosed with histologically confirmed DLBCL who are eligible for CAR-T cell therapy based on clinical approval for commercial products.	Recruiting
NCT05112614	Cancer	This study examines how GM can affect cancer therapy in patients with cancer undergoing cancer therapy or SCT. Information from this study may help doctors improve the way cancer treatment is delivered and increase its efficacy and success.	5,000 adults condition	Diagnosis of cancer and undergoing cancer therapy or scheduled to start cancer therapy or undergoing stem cell transplant for any hematological.	Recruiting

BC, breast cancer; GM, gut microbiome; DLBCL, diffuse large B-cell lymphoma; CAR-T, chimeric antigen receptor T cell; SCT, stem cell transplant.

consists of a complex network of various cytokines, immune cells and cancer cells. Fig. 4 illustrates that UroA, SCFAs, LPS and inosine act on components of the TME to activate the immune system and promote the transition from a 'cold' TME (TME lacking immune cell infiltration and activity) to a 'hot' TME, thereby enhancing the efficacy of immunotherapy.

At present, a considerable proportion of individuals with cancer do not demonstrate a strong reaction to ICI therapy due to cancer cells employing various strategies to avoid detection by the immune system (122-125). Therefore, activation of immune cells within the microenvironment has become a crucial research avenue to enhance the efficacy of ICIs. In a recent study, UroA alone led to a notable decrease in M2-like macrophages and an elevation in $CD4^+$ and $CD8^+$ T-cell infiltration within the TME, as well as downregulation of PD-1 expression and a rise in the overall survival rate of mice with cancer (126). Moreover, the reciprocal impacts of microbial metabolites can potentially lead to a reduction in the effectiveness of ICIs. Despite their anticancer properties, SCFAs hinder the effectiveness of anti-CTLA-4 antibodies in treating melanoma. This is due to their ability to decrease the presence of tumor-specific and memory T cells, while simultaneously boosting the proportion of Tregs (127).

Prior research has demonstrated that cytokines exert influence on the proliferation, progression and therapeutic interventions of cancer by regulating the function of both immune cells and tumor cells. Tumors with excessively active cytokine signaling pathways frequently experience increased tumor proliferation and invasion, significantly reducing the effectiveness of ICIs (128-130). Targeted binding against cytokines and their receptors may also leading to new strategies for tumor therapy (131-133). Microbial metabolites may indirectly influence the efficacy of ICIs by modulating cytokines. LPS upregulates IL-6 levels, which leads to tumor cell proliferation by activating JAK/STAT signaling (134). Furthermore, elevated levels of IL-6 in the TME not only diminishes the effectiveness of ICIs but also intensifies the negative side effects caused by ICI treatment (135). In addition, IL-12 can reprogram the TME, directly bind to the IL-12 receptor on $CD8^+$ T cells and activate these cells, while promoting the infiltration of $CD4^+$ T cells and downregulating the number of Tregs, which ultimately significantly improves the efficacy of ICIs (136,137). A variety of microbial metabolites modulate IL-12 secretion. Research has shown that LPS induces IL-12 secretion, which is inhibited by butyrate (138).

In summary, microbial metabolites can modify the immunological status of the TME, converting it from a 'cold' to a 'hot' environment, and control the relative amounts of different cytokines, all of which will increase the effectiveness of ICIs. Microbial metabolites also have the potential to influence cytokine receptors in addition to immune cells and cytokines.

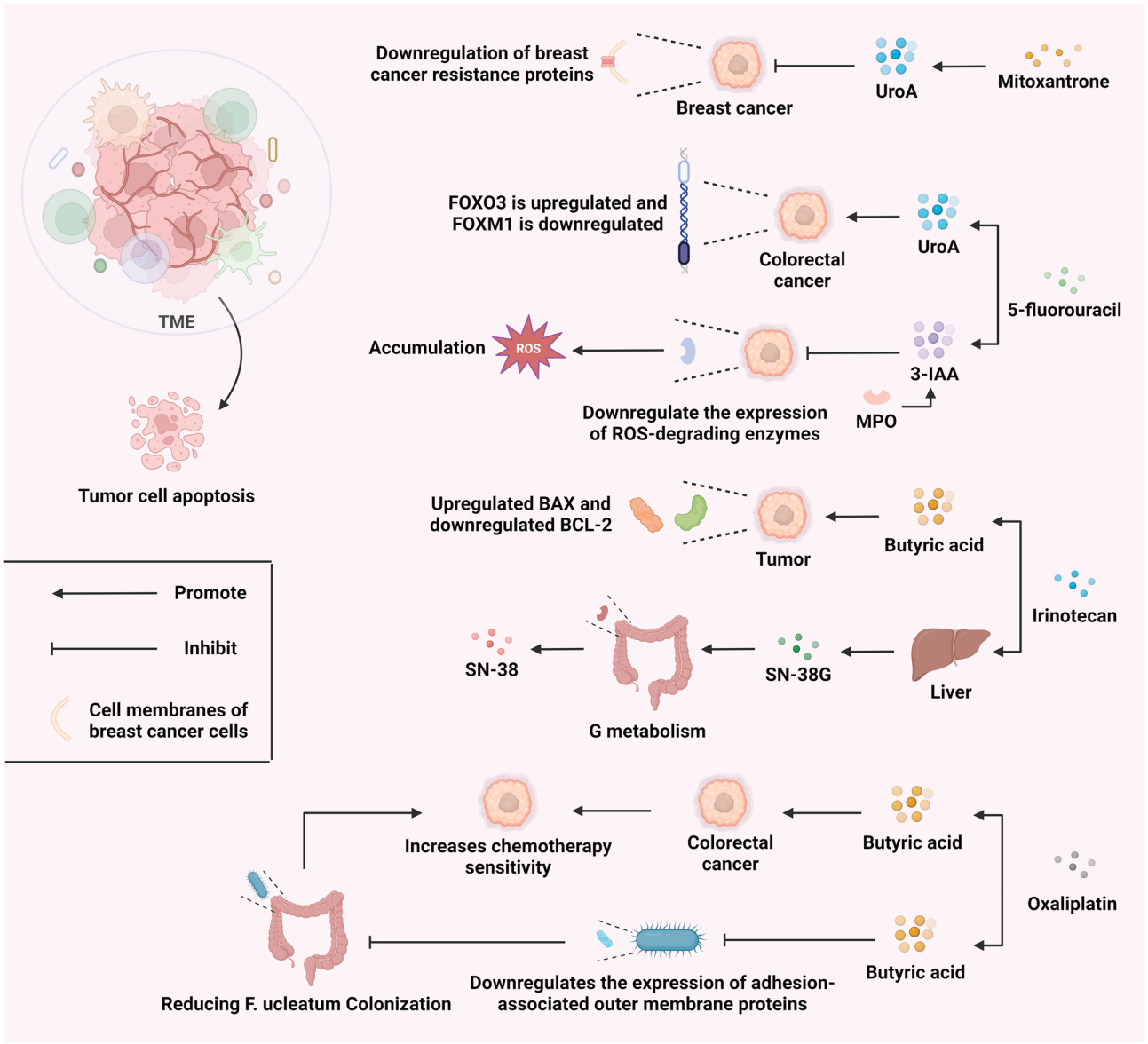

Figure 3. Outcome and underlying mechanism of the combined use of microbial metabolites and chemotherapeutic drugs. Microbial metabolites enhance the efficacy of chemotherapy drugs, promoting apoptosis of tumor cells. The combination of mitoxantrone and UroA downregulates the expression of drug-resistant proteins in breast cancer cells. The combination of 5-FU and UroA upregulates FOXO3 and inhibits FOXM1, promoting the apoptosis of tumor cells. The product of 3-IAA oxidized by MPO downregulates the synthesis of ROS-degrading enzymes, leading to ROS accumulation and enhancing the efficacy of 5-FU. Succinic acid increases the ratio of BAX/BCL-2 in tumor cells, promoting the antitumor ability of irinotecan. Irinotecan is metabolized by the liver into the inactive product SN-38G, which is hydrolyzed into the active product SN-38 by the G of intestinal bacteria. Although this enhances the side effects of irinotecan, it improves the efficacy against metastatic CRC. Succinic acid directly increases the chemosensitivity of CRC cells, enhancing the efficacy of oxaliplatin. Succinic acid also inhibits the expression of adhesion-related outer membrane proteins of *Fusobacterium nucleatum*, reducing its colonization in the intestine and enhancing the chemosensitivity of CRC cells. The figure was created using BioRender.com. UroA, urolithin A; 5-FU, 5-fluorouracil; 3-IAA, indole-3-acetic acid; MPO, myeloperoxidase; ROS, reactive oxygen species; TME, tumor microenvironment; G, glucuronidase; CRC, colorectal cancer.

It has been found that inosine binds to A_{2A} in the presence of exogenous IFN-γ to promote the differentiation of Th1 cells and significantly increase the expression of the IL-12 receptor and IFN-γ in Th1 cells, which may effectively improve the efficacy of ICIs (139).

5. Conclusions, limitations and future directions

The present review examined the relationship between microbial metabolites and cancer based on previous studies, specifically focusing on two aspects: Tumor therapy and tumor progression. Microbial metabolites exert dual impacts on tumors. Microbial metabolites impact tumor development by reprogramming the TME, which involves altering the makeup of immune cells and the expression of cytokines. Microbial metabolites also enhance tumor cell proliferation, invasion and metastasis by influencing a number of signaling pathways, resulting in increased tumor cell growth. The present review also summarized the impact of microbial metabolites on current cancer treatments and described the mechanisms by which microbial metabolites influence treatment efficacy. In this context, microbial metabolites again exhibit dual effects. Microbe-derived metabolic products have the potential to improve the outcomes of

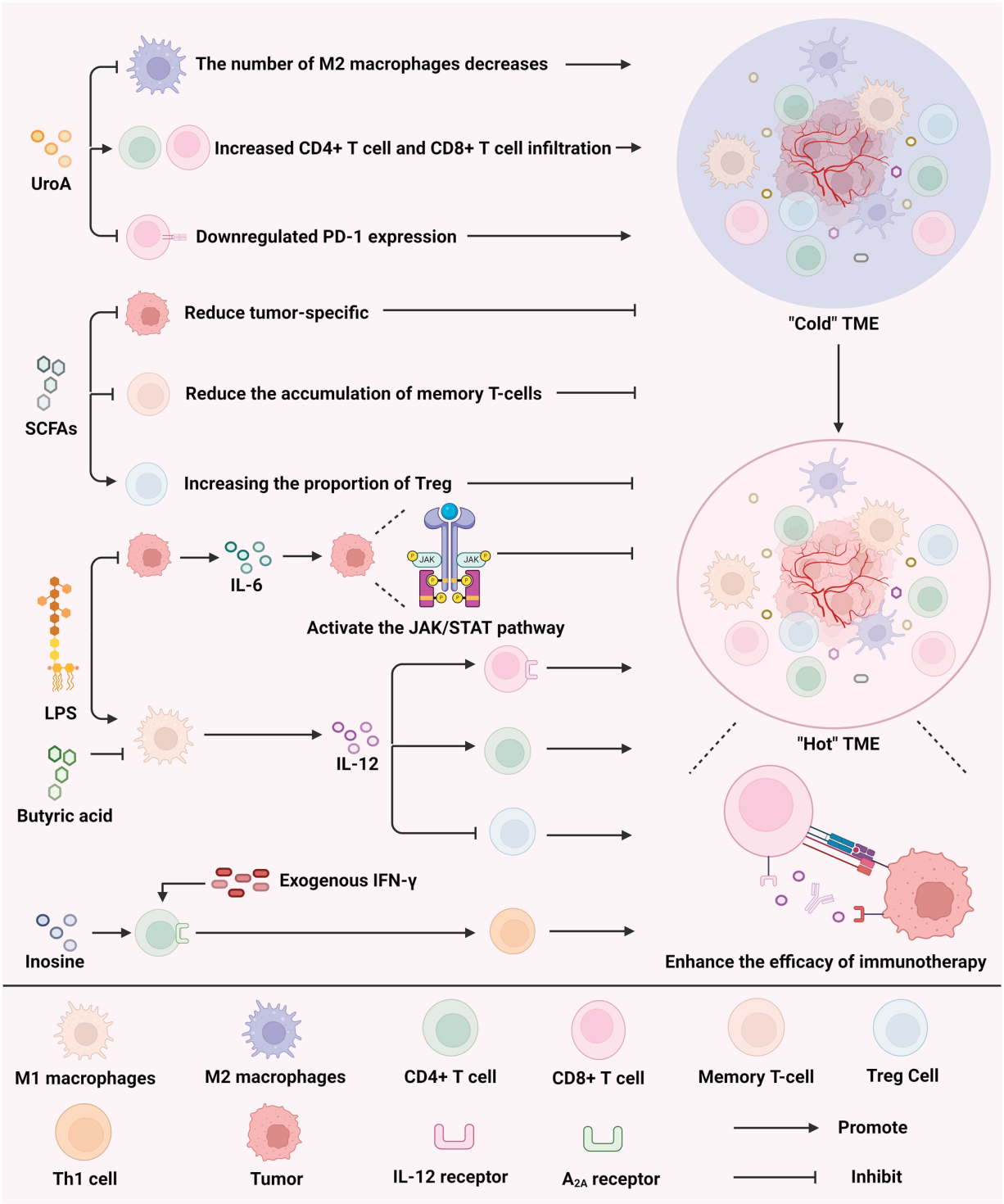

Figure 4. Microbial metabolites promote the transformation of the TME from a 'cold' environment to a 'hot' environment, enhancing the efficacy of immunotherapy. When used alone, UroA can reduce the number of M2 macrophages in the TME, increase the infiltration of $CD4^+$ T cells and $CD8^+$ T cells, and downregulate the expression of PD-1 on $CD8^+$ T cells. SCFAs can directly reduce the accumulation of tumor-specific and memory T cells, increase the proportion of Tregs and inhibit the efficacy of immunotherapy. LPS promotes the secretion of IL-6 by tumor cells, activates the JAK/STAT signaling pathway and reduces efficacy of immunotherapy. LPS and butyric acid respectively promote and inhibit the secretion of IL-12 by M1 macrophages, affecting the differentiation of $CD8^+$ T cells and $CD4^+$ T cells, and regulating the infiltration of Tregs. Adenosine, in the presence of exogenous IFN-γ, binds to A2AR on $CD4^+$ T cells, promoting the accumulation of memory T cells. The figure was created using BioRender.com. TME, tumor microenvironment; UroA, urolithin A; PD-1, programmed cell death protein 1; SCFAs, short-chain fatty acids; Treg, regulatory T cell; LPS, lipopolysaccharide; IL, interleukin; IFN, interferon; $A_{2A}R$, adenosine A2A receptor.

immunotherapy, chemotherapy and radiation, and can also strengthen the immune system in patients with cancer, lessen the negative effects of drugs and fight drug resistance. Meanwhile, by promoting the immunosuppressive TME, microbial metabolites can also lessen the effectiveness of therapies.

There is a limitation in the current review of microbial metabolites and cancer, as research on gut microbiota

metabolites is primarily focused on colorectal cancer, resulting in previous reviews being confined to the impact of microbial metabolites on colorectal cancer. However, in the present review, studies on colorectal cancer were not only examined but research on the association between microbial metabolites and other cancer types such as melanoma, breast cancer, liver cancer and pancreatic cancer, were also included (140-142). Furthermore, in reviews concerning microbial metabolites and cancer, researchers tend to focus more on summarizing the connection between microbial metabolites and antitumor immunity, while overlooking the negative impact that microbial metabolites may also have in promoting tumor progression. In contrast to previous reviews, the present review supplements the understanding of the influence of microbial metabolites on tumor progression (143). With the rapid advancement of immunotherapy, reviews focusing on microbial metabolites have increasingly emphasized their impact on immunotherapy. However, considering the high cost of immunotherapy, the majority of patients with cancer still undergo chemotherapy and radiation therapy. Therefore, research on microbial metabolites in the fields of chemotherapy were further explored to assess their potential in mainstream cancer treatments (144). However, the present review has limitations. Given that clinical trials investigating microbial metabolites are currently either recruiting or are in the experimental stages, clinical trial results were not reviewed to assess the potential of microbial metabolites as adjunctive cancer therapeutics.

In recent decades, cancer has come to be seen as a serious threat to the safety of human life. Nonetheless, cancer treatment has proven to be difficult due to the intricate and varied characteristics of the TME. To find a solution, scientists are continuously experimenting with novel approaches and enhancing current therapies. As research on the gut microbiome continues, researchers are beginning to recognize that there is a significant relationship between the gut microbiome and cancer. Scientists have found microbial colonization within the TME, attributed to the rapid progress of next-generation sequencing technologies and analytical resources. The metabolites of this group of bacteria do not require the employment of various intricate transporters to reach the tumor. Instead, they directly release metabolites, resulting in the heterogeneity of the TME. However, additional research is necessary to clarify the relationship between microbial metabolites and cancer. Advancements in this area will provide new research ideas and therapeutic strategies for the prevention and control of cancer.

Prior research has discovered microbial metabolites that impact tumor treatment and advancement by influencing the immune system of the patient, cancer or immune-related signaling pathways, protein epigenetic alteration and DNA damage. Notably, microbial metabolites have dual impacts on both tumor development and tumor immunology. As a result, developing a more intricate comprehension of microbial metabolites will facilitate their utilization as supplementary therapeutic agents, as well as in conjunction with anticancer drugs, thereby enhancing effectiveness. Furthermore, recent studies have focused on the influence of certain microbial metabolites on cancer, with particular emphasis on metabolites that exhibit notable disparities in metabolomics analysis. This could potentially neglect the significant contribution of other metabolites or the combined and opposing impacts of metabolites.

Future research should aim to gain a comprehensive understanding of the processes by which microbial metabolites operate in the TME and explore how these microbial metabolites can be harnessed in clinical settings to develop more effective cancer treatments. These studies should specifically investigate the combined impact of microbial metabolites with current treatments. Furthermore, it is necessary to investigate the synthesis and modification of microbial metabolites to optimize their effectiveness and guarantee their safety. These studies will therefore extensively investigate the potential of microbial metabolites as supplementary therapeutic agents and present new opportunities for cancer treatment.

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Authors' contributions

YZ, WH, YF and YW performed the literature review and wrote the manuscript. YZ and JX revised the figures and tables. YZ, WH and JX revised the manuscript. YZ, WH, TS and JX were involved in the conception of the study. All authors have 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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