Tumor microbiome metabolism: A game changer in cancer development and therapy

Xiaozhuang Zhou1,2, Shruthi Kandalai1,2, Farzana Hossain1,2 and Qingfei Zheng1,2*

1Department of Radiation Oncology, College of Medicine, The Ohio State University, Columbus, OH, United States, 2Center for Cancer Metabolism, James Comprehensive Cancer Center, The Ohio State University, Columbus, OH, United States

Accumulating recent evidence indicates that the human microbiome plays essential roles in pathophysiological states, including cancer. The tumor microbiome, an emerging concept that has not yet been clearly defined, has been proven to influence both cancer development and therapy through complex mechanisms. Small molecule metabolites produced by the tumor microbiome through unique biosynthetic pathways can easily diffuse into tissues and penetrate cell membranes through transporters or free diffusion, thus remodeling the signaling pathways of cancer and immune cells by interacting with biomacromolecules. Targeting tumor microbiome metabolism could offer a novel perspective for not only understanding cancer progression but also developing new strategies for the treatment of multiple cancer types. Here, we summarize recent advances regarding the role the tumor microbiome plays as a game changer in cancer biology. Specifically, the metabolites produced by the tumor microbiome and their potential effects on the cancer development and therapy are discussed to understand the importance of the microbial metabolism in the tumor microenvironment. Finally, new anticancer therapeutic strategies that target tumor microbiome metabolism are reviewed and proposed to provide new insights in clinical applications.

KEYWORDS
tumor microbiome, metabolism, cancer therapy, cancer development, immune response

Introduction

The human microbiota is a broad category consisting of diverse bacteria, fungi, protists, archaea, and viruses that occur in and on the human body (1). The total number of these microbes is believed to be more than 100 trillion, which amounts to 2 kg in mass (2). Due to its important pathophysiological role in human health and disease, the microbiome has also been referred to as “the last human organ under active research” (3)
and “the second brain” (4). Moreover, the number of unique genes from the microbiome is estimated to be 100-fold higher than that from human cells, as noted by the NIH Human Microbiome Project (5, 6). The proteins encoded by these genes and the metabolites biosynthesized by these microbes are able to influence not only their own microbial communities, but also the biological functions of host cells (7, 8). Notably, small molecule metabolites secreted by the human microbiome affect local and systemic bodily functions, including energy generation, metabolism of dietary components, biosynthesis of vitamins, immune responses, behavior, and even mood (9–11).

While microbes were implicated in diseases long ago, the contributions of the tumor microbiome to carcinogenesis, cancer progression, metastasis, and treatment have been poorly understood until recently (12–14). Previous studies have shown that microbes belonging to the genera *Salmonella* and *Helicobacter* affect cellular dysplasia and carcinogenesis (15, 16). Microbiota homeostasis can also play a role in cancer development (17). For instance, dysbiosis is associated with the carcinogenesis of gastrointestinal (GI) and non-GI tumors while also acting as an oncogenic driver of colorectal cancer (CRC) (18). Current research indicates that human-associated microbes interact with host cells and affect disease states, especially cancer, via diverse mechanisms (19, 20). One key mechanism is microbial metabolites serving as small molecule messengers to mediate crosstalk between microbes and host cells (21). Specifically, microbial metabolites can alter the tumor microenvironment (TME) (22), which includes inflammatory mediators, recruited immune cells, fibroblasts, adipocytes, endothelial cells, and pericytes (22, 23), thereby directly influencing cancer progression (23, 24) and the efficacy of immunotherapy (1, 23). One well-studied example of this is the genotoxic metabolite colibactin, produced by pathogenic *Escherichia coli*, that can directly induce DNA double-strand breaks (DSBs) (25), thus motivating CRC development (26).

As the tumor microbiome metabolism exhibits direct and indirect impacts on cancer development, novel therapy strategies may be developed by targeting these unique metabolic pathways (27, 28). Chemical biology, synthetic biology, and biomedical engineering approaches facilitate the remodeling of the microbiome-containing TME and will provide new opportunities for the future development of bacterial, viral, chemical, and immunological therapies.

In this review, we intend to highlight the tumor microbiome and how it affects cancer development and therapy as a new game changer. Among the multiple crosstalk mechanisms between microbes and cancer cells, we specifically focus on the unique metabolites produced by the tumor microbiome. The chemical structures and biochemical mechanisms through which tumor microbiome metabolism affects cancer biology are addressed. Finally, yet importantly, the potential clinical applications of targeting tumor microbiome metabolism through multidisciplinary methods for future cancer therapy have been proposed and discussed.

**What is tumor microbiome?**

The tumor microbiome is an emerging concept that has yet to be clearly defined. It broadly refers to all microorganisms located within the TME (Figure 1) and encompasses bacteria, fungi, archaea, viruses, and other microbes (29) that contribute to the reshaping of the microenvironment. These microbes are widespread in the TME and inhabit inside or outside the tumor cells and immune cells. It has long been in debate whether these microbes constitute a predetermined niche or rather represent a transient stochastic colonization (29).

Within cancer biology, intratumoral bacteria and their effects are a newly raised concept (30). While bacteria were observed in tumor isolates previously, it was assumed that these were contaminants and were not associated with cancer cells...
(31). Recently, a large-scale analysis of over 1,500 clinical samples indicated that the majority of the tumor microbiome is intracellular bacteria that exhibit tumor-site-specific properties (32). Intratumoral bacteria and host cancer cells mutually influence each other through the transcriptome and metabolome (33). Since these intracellular bacteria inhabit cancer cells, direct crosstalk between host and microbes is easily mediated by macromolecules and small molecule metabolites. However, this still leads to a chicken-and-egg situation—is the accumulation of intratumoral bacteria a cause or effect of cancer? Further investigations are required to address this question. Intracellular microbes hiding inside other type of cells, such as macrophages and fibroblasts, have also been shown to remodel the TME (34, 35) and thus affect cancer development and treatment (36, 37).

On the other hand, viruses that directly cause cancer (also known as oncoviruses) have been thoroughly studied. These viruses currently include hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomaviruses (HPVs), Kaposi’s sarcoma-associated herpesvirus (KSHV/HHV-8), human T-lymphotropic virus (HTLV), Merkel cell polyomavirus (MCPV), and Epstein–Barr virus (EBV) (38). They induce cancer through diverse mechanisms, such as the integration of viral DNA into the host genome (39) and the inactivation of tumor suppressor genes like p53 and Rb (40). Globally, these oncoviruses are associated with approximately 10–16% of cancer cases (41, 42). It has also been suggested that other viruses, similar to the bacteria mentioned previously, may play a role in carcinogenesis, without directly causing cancer (37). Other microbes, such as fungi, have also been implicated in cancer (43, 44), although this is less studied.

Extracellular microorganisms in the TME, such as those in the gut microbiota, oral microbiota, vaginal flora, and skin flora, also play essential roles in cancer development (45–47) and have significant impacts on curative outcomes (48). For instance, it has long been known that the colonization by Helicobacter pylori in stomach can directly cause gastric cancer (49), as well as gastric mucosa–associated lymphoid tissue (MALT) lymphoma (50). As a result, H. pylori is associated with approximately 5% of cancers worldwide (42). Multiple studies have shown that the gut microbiota interacts with the host by producing a diverse set of metabolites and toxins from exogenous dietary substrates and endogenous host cellular compounds (51). Host metabolic disorders are systematically associated with alterations in the composition and function of the gut microbiota (52). Specific classes of microbiota-derived metabolites, notably bile acids (BAs), short-chain fatty acids (SCFAs), branched-chain amino acids, trimethylamine N-oxide, and tryptophan and indole derivatives, have been implicated in the pathogenesis of host cell metabolic disorders, some of which directly relate to carcinogenesis (53). In addition, the gut microbiome is essential in shaping the development of innate and adaptive immunity (54) and plays an essential role in the clinical efficiency of cancer immunotherapy (55).

**Crosstalk between tumor microbiome and cancer cells**

The crosstalk between the tumor microbiome and cancer cells is diverse and complex, involving cell–cell direct interactions and messenger molecule-mediated effects (Figure 2). With respect to host cell–microbe direct interactions, intracellular microbe–induced autophagy and extracellular microbe–caused inflammation are two well-studied examples. For instance, it has been shown that Fusobacterium nucleatum modulates the autophagy pathways of CRC cells by targeting TLR4 and MYD88 innate immune signaling and specific microRNAs, thereby promoting CRC chemoresistance and migration (56). Moreover, it has been accepted for decades that inflammation is a critical component of tumor progression (57). Inflammatory cells significantly influence the TME, thereby affecting neoplastic processes and fostering the proliferation, survival, and migration of cancer cells (58). Chronic, dysregulated, persistent, and unresolved inflammation is associated with an increased risk of malignancies, as well as the malignant progression of most types of cancer (58). As microorganisms are one of the major causes of inflammation, the tumor microbiome can manipulate cancer development by remodeling the TME through the recruitment of inflammatory cells. In fact, it has been pointed out that bacterial infections can trigger chronic inflammation that leads to host cell proliferation and tumor development (59).

Messenger molecule–mediated interactions between host cells and microbes are another key machinery linking the tumor microbiome to cancer progression. These messenger molecules involve secreted proteins, peptide toxins, and small-molecule metabolites. For example, the virulence factor cytolysin-distending toxin produced by Campylobacter jejuni is one of the major causes for infectious diarrhea worldwide and has been shown to induce carcinogenesis in vivo (60, 61). Moreover, tumor microbiome–derived small molecule metabolites can reach remote tumor entities through systemic circulation, free diffusion, and active transport (such as the transport of lactate and pyruvate by proton-coupled monocarboxylate transporters) (62). These metabolites are able to stimulate antitumoral or carcinogenic innate immune responses (22) via non-covalent interactions. For instance, evolutionary conserved pathogen-associated molecular patterns (PAMPs) from commensal microbes or pathogens can be systematically sensed by the innate immune system via pattern recognition receptors, such as Toll-like receptors and NOD-like receptors, leading to the host’s innate immune responses (63). There is evidence showing that bacterial PAMPs can boost
antitumor immunity by augmenting Toll-like receptor signaling and serving as cancer vaccine adjuvants (64–66). Additionally, commensal gut bacteria can recruit natural killer T immune cells to control the growth of liver tumors via their unique microbial metabolism of BAs (67). Moreover, chemically reactive metabolites from the tumor microbiome can promote or inhibit tumor growth through the covalent modifications of DNA, RNA, histones, and other essential enzymes involved in host signaling transduction pathways (68). These modifications can be enzymatic or non-enzymatic and are capable of inducing cancer-causing and cancer-promoting epigenetic changes of host cells (69). As a result of this complex crosstalk between the host and tumor microbiome, both cancer and immune cells change their own metabolic status to adapt to the reshaped TME (70).

Furthermore, due to its novel metabolic and catabolic pathways, the gut microbiome is capable of converting human-ingested nutrients into functional microbial metabolites that closely link diet, cancer, and other metabolic diseases (19, 71, 72). These microbial metabolites produced by microbes from diet, such as BAs and SCFAs, have significant impacts on cancer and immune cells (73–78), thereby affecting cancer development and immunotherapies through complex mechanisms (79–81). Based on the important role of the microbiome in connecting diet and different types of cancer, recent research advances have suggested that gut microbiota modulation would become a novel strategy for prevention and treatment of CRC (82). As diet and microbial communities affect one another, dietary interventions have proven to be an efficient approach to modulate the intestinal microbiota, which is in line with the growing recognition of significant impacts of diet and lifestyle on human health through microbiome regulation (83).

Metabolites produced by tumor microbiome

The consequence of metabolism is the production of small molecule metabolites, which are typically classified into two categories: primary metabolites and secondary metabolites. Primary metabolites are compounds that are directly involved in an organism’s growth and development, while secondary metabolites are not directly involved in these processes and tend to vary more by species (84). There are a number of primary metabolites produced by microbes that contribute to cancer development or suppression, such as methylglyoxal (MGO), SCFAs, BAs, reactive oxygen species (ROS), amines, and methane (CH₄) (85–87). These molecules are biosynthesized...
by diverse human-associated microorganisms, including archaea (88), bacteria (89, 90), fungi (90) protists (91) and parasites (91, 92).

There are several examples of secondary metabolites with well-established functions, such as colibactin, peptide aldehyde, and thiopeptide, that have been known to affect cancer development, and these metabolites have diverse chemical structures (Figure 3). As a well-studied secondary metabolite molecule, colibactin is a cytotoxin mainly produced by pathogenic *Escherichia coli*, as well as other members of the family *Enterobacteriaceae*. The production of colibactin was shown to have a direct and significant association with CRC via the induction of DNA DSBs (25, 26). Peptide aldehydes were discovered as metabolites from a variety of microbes (including *E. coli*, *Bacillus subtilis*, and *Streptomyces* species) and are known to inhibit protease functions (93, 94), which may increase carcinogenicity. Thiopeptides have complex structures and strong antibacterial activities (95, 96), which can affect the distribution of human flora (97). In addition to being isolated from multiple environmental microbes, thiopeptides have been discovered from many microbial species in various parts of the body, including *Lactobacillus gasseri* in the urogenital tract, *Propionibacterium acnes* on the skin, *Streptococcus downei* in the oral cavity, and *Enterococcus faecalis* in the gut (98). Moreover, emerging studies have suggested that thiopeptides may also serve as anticancer agents by targeting proteasomes and transcription factor FOXM1 (99).

**Impacts of tumor microbiome metabolites on cancer development**

Since small molecule metabolites from tumor microbiome play essential roles in cancer development, we would like to summarize some examples in this section to emphasize the neglected but significant impacts of tumor microbiome...
metabolism on the TME (Figure 3). As stated above, colibactin’s ability to cause DNA DSBs allows it to promote tumorigenesis (100). Recently, it has been shown that colibactin also targets bacteria by triggering prophage induction (101), which may explain how this metabolite further affects the communities in the tumor microbiome.

SCFAs are mainly bacterial fermentation products from starch and other polysaccharides (102) and include a wide range of molecules including acetate, propionate, butyrate, and lactate (89). Among these, butyrate has been shown to potently inhibit the activity of histone deacetylases (103–105), whereas propionate does so moderately and acetate has no effect (106, 107). Lactate is known to play significant roles in the Warburg effect and reverse Warburg effect (108–110), as well as affect chromatin biology through histone modification (111, 112). It has also been shown that SCFAs can: 1) modulate macrophage functions by promoting the production of nitric oxide, IL-6, IL-12 (113), and IL-22 (114); 2) induce the differentiation of Treg functions by promoting the production of nitric oxide, IL-6, IL-

...has also been shown that SCFAs can: 1) modulate macrophage functions by promoting the production of nitric oxide, IL-6, IL-12 (113), and IL-22 (114); 2) induce the differentiation of Treg functions by promoting the production of nitric oxide, IL-6, IL-

...has also been shown that SCFAs can: 1) modulate macrophage functions by promoting the production of nitric oxide, IL-6, IL-12 (113), and IL-22 (114); 2) induce the differentiation of Treg functions by promoting the production of nitric oxide, IL-6, IL-
the tumor microbiome metabolism for reshaping TME. Ideally, with a deeper understanding of the tumor microbiome’s function in the TME and cancer development, we could build up an artificial ecosystem of microorganisms in the TME to prevent cancer cells from spreading and enhance the efficiency of immunotherapy.

Based on their functions in suppressing or promoting cancer progression, microbes within the TME can be classified to “good bugs” or “bad bugs” for cancer therapies (171). A straightforward treatment strategy is to take advantage of “good bugs” and get rid of “bad bugs” in the TME. For example, Enterococcus species have been noted to promote responses to immune checkpoint immunotherapy (ICI) (172). Bifidobacterium pseudolongum and Akkermansia muciniphila were observed to produce the metabolite inosine, which enhances ICI through T_{h}1 activation (173). Following biomaterial modulation, mice with increased levels of Peptostreptococcus anaerobius and reduced levels of other bacterial species responded better to oral squamous cell carcinoma ICI (174). Bacteria belonging to the Gammaproteobacteria family have been found to inactivate the chemotherapy drug gemcitabine, which is often used for the treatment of pancreatic ductal adenocarcinoma (175). Overall, modulating the microbial communities in the TME can provide new opportunities for cancer therapies (176). Accordingly, synthetic biology approaches have been applied to engineer specific tumor microbiome species to develop enhanced bacteria-based cancer therapies. For instance, as low concentrations of L-arginine can cause poor responses to PD-L1 ICI, probiotic strain E. coli Nissle 1917 was engineered to
convert ammonia to L-arginine, thereby increasing T-cell infiltration and enhancing ICI (177). Additionally, Nissle 1917 and other *E. coli* strains were engineered to release nanobodies with diverse functions to motivate T-cell infiltration and tumor shrinkage (178, 179). There are also a number of clinical trials in various phases regarding the applications of engineered bacteria for cancer therapies, some of which have shown promising results (180) (Table 1).

Similarly, oncolytic virotherapy has also been applied as an immunotherapy for cancer treatment (181–183). For example, alphavirus M1 was identified for such use, as it specifically targets cancer cells deficient in zinc-finger antiviral protein (184). Engineered oncolytic viruses expressing PD-L1 inhibitors have clinical potentials for curing cancers resistant to PD-1/PD-L1 ICI, as they are able to activate tumor neoantigen–specific T-cell responses (185). Notably, virotherapy has been approved in some countries for use against cancer. Imlygic, which is engineered from herpes simplex virus I (HSV1) and contains granulocyte-macrophage colony-stimulating factor, was approved in 2015 by the US Food and Drug Administration and European Medical Agency for the treatment of melanoma (186). G47Δ, which is engineered from HSV1, was approved in 2021 by Japan Ministry of Health, Labor and Welfare for the treatment of malignant glioma and other brain cancers (187). Oncorine, which is engineered from adenovirus, was approved in 2005 by the China Food and Drug Administration Department in combination with chemotherapy for the treatment of nasopharyngeal carcinoma (186). Moreover, there are other oncolytic virotherapies engineered from HSV1, adenovirus, and measles virus currently in various phases of clinical trials (186) (Table 1).

The toxins and chemicals extracted from microbes can also be used for cancer treatment. This strategy dates back to the late 19th century when Coley’s toxins (a mixture of toxins filtered from killed *Streptococcus pyogenes* and *Serratia marcescens*) were utilized to cure cancer (188). Although this was an unstable approach with poor repeatability, the application of Coley’s toxins led to milestone breakthroughs in immuno-oncology, such as the discovery of tumor necrosis factor α (TNF-α) (189). TNF-α has since been identified to suppress tumor growth and improve the efficacy of immunotherapy by activating cell death pathways (190, 191). Commensal bacteria have been found to play significant roles in CpG-oligodeoxynucleotide immunotherapy, which depend on the increased production of TNF-α (192). Microbial SCFAs have also been shown to improve CAR-T cell therapy by enhancing the levels of TNF-α in different cancer models (193).

Last but not least, recent advances in biomedical engineering have provided new opportunities for cancer treatment by targeting the tumor microbiome. For example, the utilization of biomaterials, such as nanoparticles (194, 195) and hydrogels (174), to modulate and deliver microbial communities to specific sites of the TME opens a new door for future cancer therapies (Figure 4). These novel materials can be designed to be stimuli responsive (196) and utilized for the controlled and targeted release of toxic chemotherapy drugs (197), therapeutic antibodies (198, 199), CAR-T cells (200, 201), or live microbes to reshape the TME (202–204). These applications of new biomaterials will offer a promising platform for basic and translational research and will accelerate clinical outcomes of drugs that may have poor solubility and high toxicity.

**Outlook and perspectives**

In this review, we have summarized the research process of the tumor microbiome, mainly focusing on the impacts of its unique microbial metabolism on cancer development and therapy. Over the past few decades, microorganisms have been regarded only as a cause of infectious disease. The pathophysiological functions of human-associated microbes have long been neglected until recently when the microbiome was identified to manipulate and affect diverse disease states, as well as therapeutic efficacy. The impacts of the human microbiome are so broad that research papers on the topic have exploded in the past few years. Accordingly, a number of new concepts have been raised to describe the omnipotent human microbiota, including the “brain-gut axis” and “second brain.” Despite these, the tumor microbiome still lacks a precise definition. Nevertheless, the tumor microbiome plays constructive roles in cancer biology, some of which are still elusive. Among these macro- and micropathophysiological effects induced by the tumor microbiome, small molecule metabolite–mediated crosstalk appears to be particularly important due to the free diffusion of metabolites that can easily impact local and distant tumor tissues via covalent modifications and/or non-covalent interactions. Here, we have provided representative examples to emphasize the role of tumor microbiome metabolism as a game changer in cancer biology and clinical treatment, as well as its broad biomedical effects that were once disregarded.

Targeting the pathways of microbial metabolism and crosstalk between host and microbes will provide future avenues for cancer diagnosis, treatment, and recovery. Accordingly, therapy strategies have been developed at distinct levels to target tumor microbiome metabolism: 1) directly applying wild-type or engineered live microbes in immuno-oncology; 2) utilizing the microbial-extracted fractions or synthetic chemicals that interfere with corresponding metabolic pathways for cancer treatment; and 3) utilizing rationally designed biomaterials to rebuild a benign TME by modulating the microbial ecosystem. All in all, after having a deeper understanding of the close correlation between the tumor microbiome and human cancer, we would change our perception of these microorganisms’ identities in tumor tissues from “short-term tenants” to “permanent residents.”
| Microorganism                                                                 | Clinical Phase | Cancer Type                                                                 | Status (Trial Identifier)                  |
|------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------|--------------------------------------------|
| *Salmonella Typhimurium VNP20009*                                            | I              | Metastatic melanoma or renal cell carcinoma                                  | Results published (N/A)                    |
| *Salmonella Typhimurium TAPET-CD (VNP20009 expressing cytosome deaminase)*  | I              | Head and neck solid cell carcinoma or esophageal adenocarcinoma              | Results published (N/A)                    |
| *Salmonella Typhimurium* (q4550 expressing human IL-2)                        | I              | Liver metastases of solid tumors                                             | Results published (NCT01099631)           |
| *Salmonella Typhimurium VXM01 (Ty21a expressing VEGFR2)*                     | I              | Pancreatic cancer                                                            | Completed (NCT01486329)                    |
| *Clostridium novyi-NT*                                                        | I              | Solid tumor malignancies                                                     | Results published (NCT01924689)           |
| *Clostridium novyi-NT*                                                        | Ib             | Treatment-refractory advanced solid tumors                                   | Recruiting (NCT03435952)                  |
| *CRS-100* (live-attenuated *Listeria monocytogenes*)                          | I              | Liver metastases of solid tumors                                             | Completed (NCT00327652)                    |
| *Listeria monocytogenes*                                                      | II             | Metastatic pancreatic tumors                                                 | Results published (NCT01417000)           |
| *Listeria monocytogenes*                                                      | II             | Cervical cancer                                                              | Results published (NCT01417000)           |
| *VE800* (11 commensal bacteria strains)                                       | I/II           | Metastatic cancer, melanoma, gastric cancer, or colorectal cancer            | Active (NCT04208958)                      |
| *MET-4* bacterial strains                                                     | N/A            | Locoregionally-advanced oropharyngeal squamous cell carcinoma                 | Recruiting (NCT03838601)                  |
| *Enterococcus strain MNC-168*                                                | I              | Advanced malignant solid tumors                                              | Not yet recruiting (NCT05383703)          |
| *Lactobacillus johnsonii LA1 and Bifidobacterium longum BB536*               | II             | Colorectal cancer                                                            | Completed (NCT00936572)                    |
| *Plasmodium vivax*                                                           | I/II           | Non-small cell lung cancer                                                   | Unknown (NCT02786589)                     |
| *Plasmodium vivax*                                                           | I/II           | Advanced breast cancer or advanced liver cancer                              | Unknown (NCT03474822)                     |
| *Agaricus bisporus extract*                                                   | I              | Breast cancer recurrence                                                     | Completed (NCT00709020)                    |
| *Agaricus bisporus extract*                                                   | I              | Prostate cancer recurrence                                                   | Completed (NCT00779168)                    |
| *Trametes versicolor extract*                                                 | I              | Breast cancer                                                                | Completed (NCT006809667)                  |
| *Ganoderma lucidum spore*                                                     | II             | Non-small cell lung cancer                                                   | Unknown (NCT02844114)                     |
| *Ganoderma lucidum*                                                          | III            | Pediatric cancers                                                            | Completed (NCT00575926)                    |
| *Modified measles virus*                                                      | I              | Mesothelioma                                                                 | Completed (NCT01503177)                    |
| *Modified measles virus*                                                      | I              | Ovarian cancer and peritoneal cavity cancer                                  | Results published (NCT00408590)           |
| *GL-ONCI* (modified vaccinia virus)                                            | I              | Solid tumors                                                                 | Completed (NCT00794131)                    |
| *M032* (modified herpes simplex virus)                                        | I              | Glioblastoma, astrocytoma, or gliosarcoma                                   | Active (NCT02062827)                      |
| *G207* (modified herpes simplex virus)                                        | I/II           | Glioblastoma, astrocytoma, or gliosarcoma                                   | Completed (NCT0028158)                    |
| *H101* (modified adenovirus)                                                  | N/A            | Gynecological cancer                                                         | Recruiting (NCT05051696)                  |
| *Modified fowlpox virus and modified vaccinia virus*                          | II             | Prostate cancer                                                              | Completed (NCT00003871)                    |
| *Talimogene laherparepvec (modified herpes simplex virus)*                    | III            | Melanoma                                                                     | Results published (NCT06769704)           |
| *Pexastimogene Devacirepvec (modified vaccinia virus)*                        | III            | Hepatocellular carcinoma                                                    | Results published (NCT02562755)           |

Microorganisms including bacteria (in blue), protists (in orange), fungi (in green), and viruses (in gray) have been utilized in clinical trials for cancer treatment. All information is from ClinicalTrials.gov.
Author contributions

QZ proposed the conception, wrote, and edited the manuscript. XZ drafted the manuscript and figures. SK participated drafting and editing the manuscript as well as references. FH drafted and edited the chemical structures. All authors listed in the paper have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

This study is supported by OSUCCC startup funds for QZ.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Berg G, Rybakova D, Fischer D, Cernava T, Vergès MC, Charles T, et al. Microbiome definition revisited: old concepts and new challenges. Microbiome (2020) 8(1):103. doi:10.1186/s40168-020-00875-0
2. Flint HJ. The impact of nutrition on the human microbiome. Nutr Rev (2012) 70 Suppl 1:510–3. doi:10.1111/j.1753-4887.2012.00499.x
3. Baquero F, Nombela C. The microbiome as a human organ. Clin Microbiol Infect (2012) 18 Suppl 4:2–4. doi:10.1111/j.1469-0691.2012.3916.x
4. Ochoa-Reparaz J, Kasper LH. The second brain: Is the gut microbiota a link between obesity and central nervous system disorders? Curr Opin Res (2016) 5 (1):51–64. doi:10.1016/j.copres.2015.09.011-1
5. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature (2010) 464(7285):59–65. doi:10.1038/nature08821
6. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JJ. The human microbiome project. Nature (2007) 449(7164):804–10. doi:10.1038/ nature06244
7. Koren O. Moody microbes: Do microbes influence our behavior? Eur Neuropsychopharmacol (2017) 27:S478. doi:10.1016/j.eunph.2016.09.561
8. Martin AM, Sun EW, Rogers GB, Keating DJ. The influence of the gut microbiome on host metabolism through the regulation of gut hormone release. Front Physiol (2019) 10:428. doi:10.3389/fphys.2019.00428
9. Van Treuren W, Dodd D. Microbial contribution to the human metabolome: Implications for health and disease. Annu Rev Nutr (2020) 30:345–69. doi:10.1146/annurev-nutres-022119-014559
10. Huang TT, Lai JB, Du YL, Xu Y, Ruan LM, Hu SH. Current understanding of gut microbiota in mood disorders: An update of human studies. Front Genet (2019) 10:98. doi:10.3389/fgene.2019.00098
11. Mercah A, Gauthier A. Microbial metabolites and immune regulation: New targets for major depressive disorder. Brain Behav Immun Health (2020) 9:100169. doi:10.1016/j.bbih.2020.100169
12. Bullman SJ. Emerging roles of the microbiome in cancer. Carcinogenesis (2014) 35(2):249–55. doi:10.1046/j.1365-2967.2013.07929.x
13. von Frielig J, Fink C, Hamm J, Kischies K, Forster M, Bosch TCG, et al. Grow with the challenge - microbial effects on epithelial proliferation, carcinogenesis, and cancer therapy. Front Microbiol (2018) 9:2020. doi:10.3389/fmicb.2018.02020
14. Al-Huda SA, Al-Shujairi WH. Dual role of bacteria in carcinoma: Stimulation and inhibition. Int J Microbiol (2020) 2020:4639761. doi:10.1155/2020/4639761
15. Magter DL. Bacteria and cancer: cause, coincidence or cure? a review. J Transl Med (2006) 4:14. doi:10.1186/1479-5876-4-14
16. Diaz P, Valenzuela Valderrama M, Bravo J, Quest AFG. And intellectual contribution to the work and approved it for publication.

pathology state. Front Immunol (2022) 13:844335. doi: 10.3389/fimmu.2022.844335
17. Shelin AM, Whitney AK, Weir TL. Cancer-promoting effects of microbial dysbiosis. Curr Oncol Rep (2014) 16(10):406. doi:10.1007/s11912-014-0486-0
18. Thomas S, Izard J, Walsh E, Batch K, Chongsothidiket P, Clarke G, et al. The host microbiome regulates and maintains human health. A primer and perspective for non-microbiologists. Carcin Res (2017) 77(8):1783–812. doi:10.1158/0008-5472.CAN-16-2929
19. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nat Med (2018) 24(4):392–400. doi:10.1038/s41584-017-0017
20. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev (2016) 30(14):1589–97. doi:10.1101/gad.284091.116
21. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev (2016) 30(14):1589–97. doi:10.1101/gad.284091.116
22. Hanus M, Parada-Venegas D, Landskron G, Wielandt AM, Hurtado C, Alvarez K, et al. Immune system, microbiota, and microbial metabolites: The unresolved triad in colorectal cancer microenvironment. Front Immunol (2021) 12:612826. doi:10.3389/fimmu.2021.612826
23. Rossi T, Vergara D, Fanini F, Maffia F, Bravaccini S, Pirini F. Microbiota-derived metabolites in tumor progression and metastasis. Int J Mol Sci (2020) 21(16):5786. doi:10.3390/ijms21165786
24. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. Nat Rev Microbiol (2021) 19(2):77–94. doi:10.1038/s41579-020-0438-4
25. Nougayrède JP, Homburg S, Taeb F, Boury M, Brzuza-Kwieciz E, Gottschalk G, et al. Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science (2006) 313(5788):848–51. doi:10.1126/science.1127059
26. Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proc Natl Acad Sci U S A (2010) 107(25):11337–42. doi:10.1073/pnas.1001126
27. Miko E, Kovács T, Sebő É, Tóth J, Csonka T, Ujlaki G, et al. Microbiota-microbial metabolite-cancer cell interactions in addiction and cancer. Int J Mol Sci (2020) 21(16):5786. doi:10.3390/ijms21165786
28. Ting NL, Lau HG, Yu J. Cancer pharmacomicrobiotics: targeting microbiota to optimise cancer therapy outcomes. Gut (2022) 71:1412–25. doi:10.1136/gutjnl-2021-326264
29. Oliva M, Mulet-Margalef N, Ochoa-De-Olza M, Napoli S, Mas J, Laquente T, et al. Tumor-associated microbiome: Where do we stand? Int J Mol Sci (2021) 22(3):1446. doi:10.3390/ijms22031446
30. Poore GD, Kopylova E, Zhu Q, Carpenter C, Fraraccio S, Wandro S, et al. Microbiome analyses of blood and tissues suggest cancer diagnostic approach. Nature (2020) 579(7780):567–74. doi:10.1038/s41586-020-2095-1
31. Robinson KM, Crabtree J, Mattick JS, Anderson KE, Dunning Hotopp JC. Distinguishing potential bacteria-tumor associations from contamination in a secondary data analysis of public cancer genome sequence data. Microbiome (2017) 5(1):9. doi:10.1186/s40168-016-0224-8
32. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science (2020) 368(6494):973–80. doi:10.1126/science.aay9189
33. Qiu Q, Lin Y, Ma Y, Li X, Liang J, Chen Z, et al. Exploring the emerging role of the gut microbiota and tumor microenvironment in cancer immunotherapy. *Front Immunol* (2020) 11:612202. doi: 10.3389/fimmu.2020.612202

34. Ma J, Huang L, Hu D, Zeng S, Han Y, Shen H. The role of the tumor microenvironment in the tumor immune microenvironment: bystander, activator, or inhibitor? *J Exp Clin Cancer Res* (2021) 40(1):327. doi: 10.1186/s13046-021-0218-w

35. Mola S, Pandolfo C, Sica A, Porta C. The macrophages–microbiota interplay in colorectal cancer (CRC)-related inflammation: Prognostic and therapeutic significance. *Int J Mol Sci* (2021) 22(18):6866. doi: 10.3390/ijms22186866

36. Loyayta I, Nejman D, Shenthal N, Straussman R. Characterization of the human tumor microbiome reveals tumor-type specific intra-cellular bacteria. *Oncoimmunology* (2020) 9(1):1800957. doi: 10.1080/2162402X.2020.1800957

37. Jain T, Sharma P, Are AC, Vickers SM, Dudge V. New insights into the cancer–Microbiome–Immune axis: Decrypting a decade of discoveries. *Front Immunol* (2022) 13:501076. doi: 10.3389/fimmu.2022.501076

38. American Cancer Society. Infections that can lead to cancer n.d. Available at: https://www.cancer.org/cancer/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer.html. https://www.cancer.org/cancer/cancer-causes/infectious-agents/infections-that-can-lead-to-cancer.html.

39. Fujiy TR. Oncoviruses and pathogenic MicroRNAs in humans. *Open Viral J* (2009) 3:37–51. doi: 10.2174/1874357900903010037

40. Tornesello ML, Annunziata C, Torresello AL, Buonaguro L, Buonaguro WM. Human oncoviruses and p53 tumor suppressor pathway deregulation at the origin of human cancers. *Cancers (Basel)* (2018) 10(7):213. doi: 10.3390/cancers10070213

41. Zapatka M, Borozan I, Brewer DS, Iskar M, Grundhoff A, Alawi M, et al. Genotoxicity of cytotoxic T-cell lymphocyte Lux protein effecting of colony formation in colorectal cancer (CRC)-related in *Cancer Res* (2020) 80(12):1783–90. doi: 10.1158/0008-5472.CAN-20-1252

42. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Glob Health Sci Policy* (2019) 4(1):720. doi: 10.3748/wjg.v20.i43.16079

43. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal activator, or inhibitor? *Protein Cell* (2020) 12(13):877–919. doi: 10.1007/s13238-021-00846-7

44. Sun X, Wang M, Yao L, Li X, Dong H, Li M, et al. Role of proton-coupled monocarboxylate transporters in cancer: From metabolic crosstalk to therapeutic potential. *Front Cell Dev Biol* (2020) 8:653. doi: 10.3389/fcell.2020.00651

45. Zhou et al. 10.3389/fonc.2022.933407
Inhibition of histone-deacetylase activity by short-chain fatty acids and some pharmaceutical properties.

Zhou et al. 10.3389/fonc.2022.933407
lysine residues as a mechanism for apoptotic cell death by histone deacetylase inhibitors. Cancer Res (2003) 63(24):8948–54.

129. Gore P, Gore ML. Effect of sodium butyrate on the expression of retinoblastoma (RBl) and P53 gene and phosphorylation of retinoblastoma protein in human colon tumor cell line HT29. Cell Mol Biol (Noisy-le-grand) (1993) 39(5):95–97.

130. Cook JW, Kannaway EL, Kunnaway NM. Production of tumours in mice by deoxyacidic. Nature (1940) 145(3677):627. doi: 10.1038/145627a0.

131. Mäger F, Sharma R, Mullins C, Keogh L, Phipps S, Duggan S, et al. New highly toxic bile acids derived from deoxyacidic, chenodeoxyacidic and lithocholic acid. Bioorg Med Chem (2004) 22(1):256–68. doi: 10.1016/j.bmc.2003.11.039.

132. Naraehara H, Tatsuta M, Iishi H, Baba M, Uredo N, Sakai N, et al. K-Ras point mutation is associated with enhancement by deoxyacidic of colon cancerogenesis induced by azoxymethane, but not with its attenuation by all-trans-retinoic acid. Int J Cancer (2000) 88(2):157–61. doi: 10.1002/(SICI)1097-0215(20000115)88:2<157::AID-IJC2>3.0.CO;2-B.

133. Powolny A, Xu J, Loo G. Deoxyacidol induces DNA damage and apoptosis in human colon epithelial cells expressing either mutant or wild-type p53. Int J Biochem Cell Biol (2001) 33(2):193–203. doi: 10.1016/S1357-2725(00)00080-7.

134. Arvind P, Papavassiliou ES, Tsolias GJ, Duceman BW, Lovelace CL, Gong W, et al. Lithocholic acid inhibits the expression of HLA class I genes in colon adenocarcinoma cells. differential effect on HLA-a, -b and -c loci. Mol Immunol (1994) 31(8):607–14. doi: 10.1016/0161-5890(94)90168-6.

135. Gafar AA, Draz HM, Goldberg AA, Bashandy MA, Bakry S, Khalifa MA, et al. Formation of methylglyoxal from sodium butyrate in human colon tumor cell line HT29. J Biol Chem (1993) 268(23):13349–57. doi: 10.1074/jbc.268.23.13349.

136. Martinez JD, Stratagoules ED, LaRue JM, Powell AA, Gause PR, Craven MT, et al. Different bile acids exhibit distinct biological effects: the tumor promoter lithocholic acid. J Biol Chem (1992) 267(7):4364–9. doi: 10.1016/S0021-9258(18)42844-X.

137. Crowle-Weber CL, Payne CM, Gleason-Guzman M, Watts GS, Futschek B, Walmire CN, et al. Development and molecular characterization of HCT-116 cell lines resistant to the tumor promoter and multiple stress-inducer, deoxyacidol. Carcinogenesis (2002) 23(12):2065–80. doi: 10.1093/carcin/23.12.2063.

138. Wu G, Morris SM. Arginine metabolism: nitric oxide and beyond. Biochem J (1998) 336(Pt 1):1–17. doi: 10.1042/bj3660001.

139. Tabor CW, Tabor H. Polyamines in microorganisms. Microbiol Rev (1985) 49(1):81–99. doi: 10.1128/mr.49.1.81-99.1985.

140. Di Martino ML, Campolongo R, Casalino M, Micheli G,-Colonna B, Procida G. Polymaines: emerging players in bacteria-host interactions. JBiolChem (2004) 279(26):27050–8. doi: 10.1074/jbc.M406002200.

141. Khan AU, Mei YH, Wilson T. A proposed function for spermine and spermidine: protection of replicating DNA against damage by singlet oxygen. Proc Natl Acad Sci U S A (1992) 89(23):11246–7. doi: 10.1073/pnas.89.23.11246.

142. Linsalata M, Caruso MG, Leo S, Guerra V, D’Atomma B, Di Leo A. Targeted expression of spermidine/spermine N1-acetyltransferase increases susceptibility to chemically induced skin carcinogenesis. Carcinogenesis (2002) 23(2):359–64. doi: 10.1093/carcin/23.2.359.

143. Linsalata M, Giannini R, Notarnicola M, Cavallini A. Peroxisome proliferator-activated receptor gamma and spermidine/spermine N1-acetyltransferase gene expressions are significantly correlated in human colorectal cancer. BMC Cancer (2006) 6:191. doi: 10.1186/1471-2407-6-191.

144. Smith RC, Litwin MS, Lu Y, Zetter BR. Identification of a novel 120 kDa methylglyoxal binding protein in human prostate cancer cells. J Biol Chem (2004) 279(3):24076–8. doi: 10.1074/jbc.M301990200.

145. Zheng Q, Osunsade A, David Y. Non-enzymatic covalent modification of cancer. Semin Cancer Biol (2018) 49:64. doi: 10.1016/j.semcancer.2017.05.010.

146. Zheng Q, Maksimovic I, Upad A, David Y. Non-enzymatic covalent modifications: a new link between metabolism and epigenetics. Protein Cell (2020) 11(6):401–16. doi: 10.1007/s13238-020-00772-w.

147. Zhou et al. eLife.19375.
virotherapy.

Zhou et al. 10.3389/fonc.2022.933407

Front Oncol (2023) 13:101. doi: 10.3389/fonc.2022.933407

170. Makisimovic I, Finkin-Groner E, Fukase Y, Zheng Q, Sun S, Michino M, et al. Derepression of the PAK1 oncogene by CD200R1 inhibitors. RSC Med Chem (2021) 12(7):1232–8. doi: 10.1039/D1MD0082D

171. Garrett WS. Cancer and the microbiota. Science (2013) 340(6138):80–6. doi: 10.1126/science.aaa4872

172. GriffM ME, Espinosa J, Becker JL, Luo JD, Carroll TS, Jha JK, et al. Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy. Science (2021) 373(6585):1040–6. doi: 10.1126/science.abf9113

173. Mager LF, Burkard R, Pet N, Cooke NCA, Brown K, Ramay H, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science (2020) 369(6510):1481–9. doi: 10.1126/science.abb3421

174. Zheng DW, Deng WW, Song WF, Wu CC, Liu J, Hong S, et al. Biomaterial-mediated modulation of oral microbiota synergizes with PD-1 blockade in mice with oral squamous cell carcinoma. Nat BioMed Eng (2022) 6(1):32–43. doi: 10.1038/s41551-021-00807-9

175. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Nat Rev Cancer (2021) 21(12):727–43. doi: 10.1038/s41580-021-00486-4

176. Chowdhury S, Castro S, Coker C, Hinchliffe TE, Arpaia N, Danino T. Characterization of alphavirus M1 as a selective oncolytic virus targeting ZAP-77+ cells. Proc Natl Acad Sci U S A (2020) 117(10):5130–8. doi: 10.1073/pnas.1905928117

177. Canale FP, Basso C, Antonini G, Perotti M, Li N, Sokolovska A, et al. Programmable bacteria induce durable tumor regression and systemic antitumor effect in murine models of colorectal cancer. Nat Biomed Eng (2020) 4(11):1156–60. doi: 10.1038/s41551-020-0456-8

178. Gurbatzi CR, Lia I, Vincent R, Coker C, Castro S, Treuting PM, et al. Deglycase-activity oriented screening to identify DJ-1 inhibitors. Nat Commun (2021) 12(7):1232. doi: 10.1038/s41467-021-00704-z

179. Mager LF, Burkhard R, Pett N, Cooke NCA, Brown K, Ramay H, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science (2021) 373(6585):1040–6. doi: 10.1126/science.abb3421

180. Zhou S, Gravekamp C, Bermudes D, Liu J, Hong S, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science (2017) 357(6356):1156–60. doi: 10.1126/science.aah5043

181. Russell SJ, Masner M, Ferreira FA, Hoffman RM. Bacterial therapy of cancer: Promises, limitations, and insights for future directions. Front Microbiol (2018) 9:182. doi: 10.3389/fmicb.2018.00016

182. Canale FP, Basso C, Antonini G, Perotti M, Li N, Sokolovska A, et al. Metabolic modulation of tumours with engineered bacteria for immunotherapy. Nature (2021) 598(7882):662–3. doi: 10.1038/s41586-021-04003-2

183. Chen AY, Wolchok JD, Bass AR. TNF in the era of immune checkpoint inhibitors: friend or foe? Nat Rev Rheumatol (2021) 17(3):213–23. doi: 10.1038/s41586-021-00584-4

184. Lin Y, Zhang H, Liang J, Li K, Zhu W, Fu L, et al. Identification of the molecular basis of tumor necrosis factor resistance in breast cancer cells. J Control Release (2021) 380:101366. doi: 10.1016/j.jconrel.2021.10.019

185. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Nat Rev Cancer (2021) 21(12):727–43. doi: 10.1038/s41580-021-00486-4

186. Zell E, Hwang D, Hirata M, Yoneda T, Shi J, Shiina S, et al. Microbial short-chain fatty acids modulate CDR. Nat Commun (2021) 12(1):4077. doi: 10.1038/s41467-021-24331-1

187. Chowdhury S, Castro S, Coker C, Hinchliffe TE, Arpaia N, Danino T. Characterization of alphavirus M1 as a selective oncolytic virus targeting ZAP-77+ cells. Proc Natl Acad Sci U S A (2020) 117(10):5130–8. doi: 10.1073/pnas.1905928117

188. Ye QN, Wang Y, Shen S, Xu CF, Wang J. Biomaterials-based delivery of therapeutic antibodies for cancer therapy. Adv Healthc Mater (2021) 10(11):e2002139. doi: 10.1002/adhm.202002139

189. Smith TT, Stephane SB, Moffett HF, McKnight LE, Ji W, Reiman D, et al. In situ programming of leukema-specific T cells using synthetic DNA nanocarriers. Nat Nanotechnol (2017) 12(8):813–20. doi: 10.1038/nnano.2017.57

190. Salomon BL, Leclerc M, Boselli J, Ronin E, Pugno E, Cohen JL. Tumor necrosis factor-α and regulatory T cells in oncimmunology: Front Immunol (2018) 9:444. doi: 10.3389/fimmu.2018.00444

191. Chen AY, Wolchok JD, Bass AR. TNF in the era of immune checkpoint inhibitors: friend or foe? Nat Rev Rheumatol (2021) 17(3):213–23. doi: 10.1038/s41586-021-00584-4

192. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat Rev Drug Discovery (2008) 7(9):771–82. doi: 10.1038/nrd2614

193. Fodor P, Albert M, Boehler R, Wu C, Aebi M, Oertli C, et al. Tumor microenvironment. Science (2018) 357(6356):1156–60. doi: 10.1126/science.aah5043

194. He P, Zhou D, Guo J, He P, Zhou D. Recent advances of oncolytic virus in cancer therapy. Hum Vaccin Immunother (2020) 16(10):2389–402. doi: 10.1080/21645515.2020.1723363

195. Fujihara H, Takeshima Y, Todo T. Triple-mutated oncolytic herpes virus for treating both fast- and slow-growing tumors. Cancer Sci (2021) 112(8):3293–301. doi: 10.1111/cas.14981