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REVIEW

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Microbiota and glioma: a new perspective from association to clinical translation

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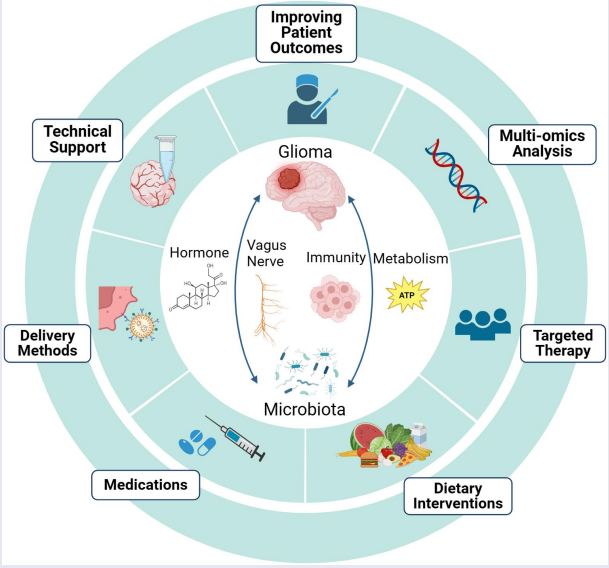
ABSTRACT

Gliomas pose a significant challenge in oncology due to their malignant nature, aggressive growth, frequent recurrence, and complications posed by the blood-brain barrier. Emerging research has revealed the critical role of gut microbiota in influencing health and disease, indicating its possible impact on glioma pathogenesis and treatment responsiveness. This review focused on existing evidence and hypotheses on the relationship between microbiota and glioma from progression to invasion. By discussing possible mechanisms through which microbiota may affect glioma biology, this paper offers new avenues for targeted therapies and precision medicine in oncology.



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1. Introduction

Gliomas, predominantly malignant tumors originating in the brain or spinal cord, pose significant challenges in neuro-oncology due to their rapid progression, aggressive nature, and high propensity for relapse[1]. With the incidence of 6.0 per 100 000 population, gliomas take up 81% of malignant brain tumors,[2,3] varying widely in their aggressiveness and can be classified into grade 1–4 based on their cellular characteristics and rate of growth, which profoundly influences the clinical outcome of glioma patients. Low-grade gliomas may exhibit favorable prognosis after surgery, while high-grade tumors, such as glioblastoma, the most aggressive grade 4 glioma, are associated with dismal survival rates, averaging 14 to 16 months even with comprehensive treatments, and a 5-year survival rate of under 10%.[4]

The diagnostic and therapeutic landscape of gliomas is fraught with hurdles. Early detection of gliomas has been difficult, as they often present nonspecific symptoms in the early stages,

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complicating timely and accurate diagnosis.[5,6] Moreover, chemoresistance and the impermeable nature of the blood-brain barrier (BBB) hampers the detection of tumor components, as well as drug delivery.[7,8] Additionally, the inherent heterogeneity of gliomas contributes to the complexity of managing the disease, as it underpins the variations in treatment response and the emergence of resistance, thereby elevating the risk of disease progression and dissemination.[9]

Recent research has illuminated the significant role of microbiota – communities of microorganisms including bacteria, viruses, fungi, archaea, and protozoa – that inhabit various parts of the human body, in health and disease.[10] Human microbiota has been observed to exert both local and systemic effects on the onset, progression and therapy response to many cancers, including colorectal cancer and and bladder cancer.[11] Notably, the identification of microbial components within the brain introduces the concept of a brain microbiome, implicating its probable involvement in the pathogenesis of glioma.[12,13] Therefore, understanding the intricate relationships between microbiota and glioma holds significant promise for revolutionizing the diagnostic and therapeutic approaches for this formidable disease. [14–16]

This review aims to summarize the potential contributions of microbiota to the development of gliomas. It integrates the possible mechanisms underlying the influence of microbiota on tumor growth and immune evasion, highlights the potential interplay between microbiota and glioma therapies, and discusses the prospective utility of these insights into refining diagnostic and therapeutic strategies for glioma. By integrating the current knowledge on the microbiota-glioma axis, we endeavor to shed light on novel pathways for intervention and ultimately improve outcomes for patients suffering from this challenging condition.

2. Relationship between microbiota and different types of glioma

Glioma may derive from diverse types of cells in the brain or spinal cord, including astrocytes, oligodendrocytes, and ependymal cells. The microbiome may play a pivotal role in the onset, progression, and invasion of different gliomas, possibly through mechanisms such as enhancing proliferative signaling, inhibiting apoptosis, and promoting angiogenesis.[17] Given the diverse nature of gliomas, the varying influences of different microbial communities within the brain, gut, lung, and oral cavity have sparked extensive research into their specific roles across glioma subtypes (Table 1).

2.1. Microbiota and glioblastoma

Glioblastoma, used to be called GBM, is classified as a WHO grade 4 glioma, standing out as the most prevalent and aggressive adult glioma with a poor prognosis.[38] The pivotal role of the human microbiome, particularly the gut microbiome, in glioma development has been a focus of recent research. Studies unveiled significant differences in the gut microbiota composition between glioma patients (or glioma-bearing mice) and healthy controls, highlighting a potential link to disease development.[39] Furthermore, clinical trials have revealed a shift in the concentration of metabolites derived from gut bacteria, suggesting a complex interplay between gut microbiota and glioblastoma progression.[40]

Mendelian randomization studies have advanced our understanding by investigating the association between specific gut microbiota compositions and glioblastoma risk. They identified that an increased presence of certain genera (*Fusobacterium*, *Akkermansia*, *Escherichia/Shigella*) and a decreased presence of others (*Lachnospira*, *Agathobacter*, *Bifidobacterium*) correlate with various malignant glioma types.[18] Interestingly, other research pointed out that the *Ruminococcaceae* family, not previously highlighted, significantly correlates with a reduced glioblastoma risk, indicating the complexity of microbial influences on glioma.[19] The varying results may attribute to limited sample sizes, study design issues or population differences, calling for more comprehensive studies on the underlying associations.

Oral microbiome, where specific microbial features have been associated with glioma malignancy and IDH1 mutation, may also be a potential biomarker of glioblastoma. Notable findings include the ability of certain oral

Table 1. Roles of microbiome in different gliomas.

Condition	Location	Components	Effect/Association
Glioblastoma	Gut microbiome	*Fusobacterium* ↑ *Akkermansia* ↑ *Escherichia/Shigella* ↑ *Lachnospira* ↓ *Agathobactera* ↓ *Bifidobacterium* ↓	Correlation with various malignant glioma types[18]
		Ruminococcaceae	Decreased risk of glioblastoma[19]
		Granulicatella *Rothia mucilaginosa*	Dysbiosis following SARS-CoV-2 infection,[20] potentially accelerating GBM progression[21]
	Oral microbiome	*Porphyromonas* *Haemophilus* *Leptotrichia* TM7x *Capnocytophaga*	Inverse correlation with glioma grades; Accurate discrimination of HGG from LGG and HCs[22]
		Bergeyella, *Capnocytophaga*	Positive associations with IDH1 mutation in glioma (*vs*. IDH1-wild-type group)[22]
		Granulicatella *Rothia mucilaginosa* *Capnocytophaga* *Veillonella*	Dysbiosis following SARS-CoV-2 infection,[20] potentially accelerating GBM progression[21,23]
	Intratumoral microbiome	*Proteobacteria* *Firmicutes*	Discovered by comprehensive histological imaging, Sudan B treatment and a 3D whole-tumor perspective[24–26]
		SARS-CoV-2	Direct infection and high expression of ACE2 in GBM tissues;[27] potential oncogenic effects *via* binding ACE2[28]
Astrocytoma	Gut microbiome	*Parabacteroides distasonis* MRx0005; *Megasphaera massiliensis* MRx0029	Strong capacity to reduce IL-6 secretion *in vitro*;[29] may be associated with low IL-6 level in grade 1-2 astrocytomas[30]
	Brain microbiome	*Brucella abortus*	Potential role of microbes in brain tissue in glioma development[31,32]
	Injection into the dorsal hippocampus	Lentivirus (family *Retroviridae*)	Selective targeting of astrocytes;[33] Manipulation of oncogenic pathways *via* gene transfer[34,35]
Oligodendroglioma	Uncertain	LPS	Damage on astrocytes through activation of TLR4-CD14/TLR2 receptors and NF-κB mediated cytokine surges[36]
DMG	Gut microbiome	*F/B* ratio ↓ *Flavobacteriaceae* ↑ *Bacillales* ↑	Association with higher risk of DMG[37]

F/B, Firmicutes/Bacteroidetes.

microbial signatures to distinguish high-grade gliomas from low-grade ones.[22] External factors causing dysbiosis, including viral infections like SARS-CoV-2, may further complicate glioblastoma outcomes by adversely affecting the microbiota.[41]

In addition to external microbiota, the role of intratumoral microbiota in glioblastoma progression has gained attention. Techniques such as immunohistochemistry and RNA fluorescence in situ hybridization have identified bacterial components within glioblastoma tissues, revealing a predominance of *Proteobacteria* and *Firmicutes*.[42] This evidence, supported by advanced imaging techniques, indicates the probable interplay between the microbiome and the tumor microenvironment (TME), offering new insights into glioblastoma pathology and potential therapeutic targets.[24–26]

2.2. Microbiota and other gliomas

Although the role of microbiota in glioblastoma has been the focal point of research, its implications for other glioma types remain less explored. However, emerging studies provide a basis for the investigation of microbial characteristics in the diagnosis and treatment of diverse glioma subtypes.

Previous studies revealed that the dysbiosis of gut microbiome are closely associated with astrocytic dysfunction in mouse models, indicating similar effects on development of pilocytic astrocytoma (grade 1) and diffuse astrocytoma (grade 2).[43] Specifically, *Parabacteroides distasonis* MRx0005 and *Megasphaera massiliensis* MRx0029 demonstrated strong capacity to reduce IL-6 secretion *in vitro*, which may be associated with low IL-6 level in low-grade gliomas mentioned above.[29,30] Furthermore, a recent study revealed the activation of

microglia by *Brucella abortus*-infected astrocytes, suggesting the potential role of brain microbiome in progression and maintenance of astrocytoma.[31,32] In addition to bacteria, lentivirus are also capable of selective targeting and sustained gene expression in astrocytes, demonstrating the potential for microbial components to be involved in oncogenic pathways in glioma.[34,35]

Oligodendroglioma (grade 2 or grade 3), derived from oligodendrocytes which cover and protect nerve cells in the brain and spinal cord, grows slowly and is less common. The impact of lipopolysaccharides (LPS) on oligodendroglioma development and treatment response has been identified, highlighting how LPS-triggered activation of TLR4-CD14/TLR2 receptors may damage oligodendrocytes through NF-κB mediated cytokine surges.[36] This insight into microbe-induced cellular responses opens new avenues for understanding glioma pathology and enhancing therapeutic strategies.

In the case of diffuse midline glioma (DMG), a grade 4 pediatric brain tumor noted for its poor prognosis, recent trials have attempted to integrate microbiome analysis to aid its diagnosis and evaluate its therapeutic efficacy. Key findings suggest that *Firmicutes*/*Bacteroidetes* (*F*/*B*) ratio of gut microbiota, along with the presence of *Flavobacteriaceae* and *Bacillales*, correlates with DMG patients' progression-free survival and overall survival (OS) rates.[37]

These examples underscore the burgeoning interest in the microbiome's role beyond glioblastoma, offering promising diagnostic and therapeutic avenues for various glioma types. As research continues to unfold, the microbiota's multifaceted contributions to glioma pathogenesis and treatment responsiveness are poised to become increasingly significant.

3. Regulatory mechanisms of microbiome-glioma interaction

Recent studies have indicated the possible roles of microbes in modulating the development and the microenvironment of gliomas. These organisms may exert their influence through a combination of direct neural and endocrine pathways, alongside the actions of microbial metabolites. The understanding of the potential microbiota-glioma interaction offers novel insights that have profound implications for the diagnosis and treatment of gliomas (Figure 1).

3.1. Neural and endocrine modulation of glioma progression by microbiota

Research into the regulation of microbiome-glioma interaction has predominantly concentrated on the gut-brain axis, a bidirectional communication network that connects the gut microbiota with the central nervous system (CNS). This axis may impact glioma progression through a variety of mechanisms. Gut microbes and their metabolites, for example, may influence CNS activity and pathologies by modulating neural signaling pathways, including those associated with the vagus nerve.[44] Such modulation may indirectly drive glioma growth and invasiveness by affecting neurotransmitter release and neuroinflammatory responses.[45] Moreover, the gut microbiome's ability to influence neuroplasticity may play a pivotal role in both the prognosis and management of glioma patients.[46,47] The interaction extends further, impacting CNS function through the regulation of hormone levels, including cortisol and sex hormones, potentially altering glioma cell behavior in terms of proliferation and survival.[48,49] This hormonal influence may be exacerbated by increasing levels of LPS, a potent immunogenic component of gram-negative bacteria that induces endotoxemia and compromises the BBB.[50]

The state of dysbiosis, especially the imbalance of bacterial composition and changes in bacterial metabolic activities, introduces additional complexities.[51] Various factors, such as chronic stress, depression, and the prolonged or inappropriate use of antibiotics, can significantly alter the gut microbiota's composition and diversity.[52] This altered microbial environment may facilitate the release of ATP and glutamate from astrocytes, creating conditions conducive to glioma emergence and invasion.[53] Conversely, the development of glioma itself can induce structural changes in the gut microbiota, marked by decreased abundance of *Actinobacteria* and *Bacteroidia* and increased abundance of *Firmicutes*. These shifts may

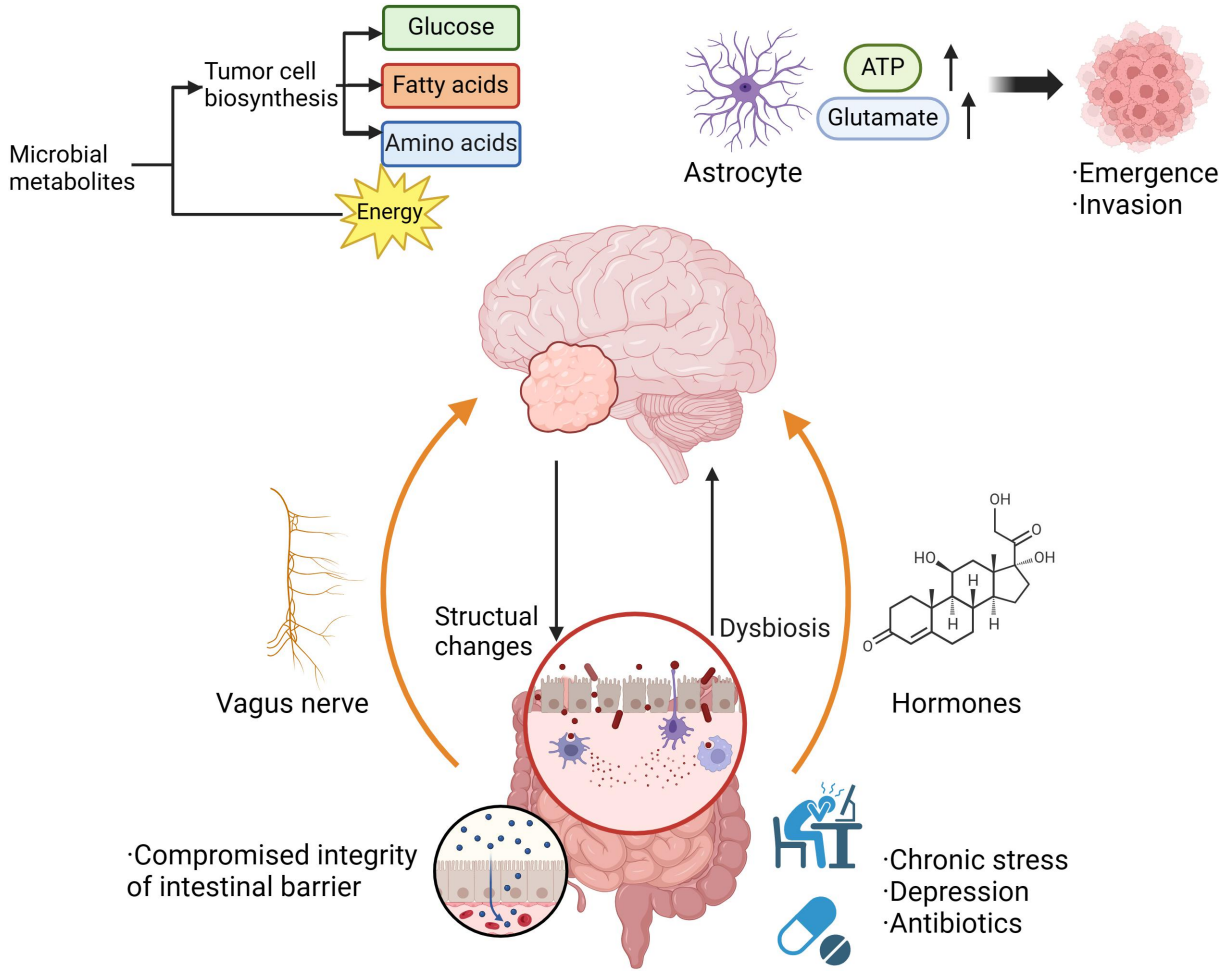

Figure 1. Potential interactions between the microbiome and glioma progression. The illustration delineates the probable modulatory pathway of the gut microbiome, mediated by hormonal release and the vagus nerve. Highlighted are the microbial metabolites' possible roles in synthesizing essential molecules like glucose, lipids, and amino acids within tumor cells. Notably, dysbiosis—triggered by factors such as chronic stress, depression, and antibiotic misuse—facilitates neurotransmitter (e.g., ATP, glutamate) release from astrocytes, may promote glioma onset and invasion. Furthermore, the feedback loop where glioma growth alters gut microbiota composition, indirectly affecting intestinal barrier integrity, suggests the bidirectional interaction between the microbiome and glioma progression.

suppress Foxp3 expression in the brain, further promoting glioma development.[54] By examining these intricate interactions, we gain insight into the possible impact of the microbiome on glioma pathology, offering potential pathways for innovative diagnostic and therapeutic strategies.

3.2. Microbiome and glioma metabolism

Metabolic byproducts from the microbiome, such as short-chain fatty acids (SCFAs), may play a pivotal role in host cell physiology by serving as energy substrates. SCFAs, including butyrate, propionate, and acetate, not only fuel intestinal epithelial cells to support energy metabolism and cellular regeneration, but also impact the integrity of the intestinal barrier. This dual functionality underscores the significance of microbiome-derived metabolites in maintaining host health and their potential implications in disease processes. SCFAs may be harnessed by glioma cells as an energy source, which may contribute to their proliferation and suggest a complex interaction between microbiome metabolites and tumor biology.[55] Additionally, the growth of glioma leads to changes in lipid metabolism, indicating potential avenues for identifying lipid-based biomarkers or therapeutic targets.[56]

The gut microbiome's metabolic pathways possibly intersect with the host's biosynthesis of glucose, fatty acids, and amino acids. This may either directly or indirectly support tumor cell growth and survival. One of the critical pathways affected by SCFAs is the insulin signaling pathway, potentially involved in glioma cells' energy metabolism and growth signal transduction.[57] By activating various G protein-coupled receptors (GPCRs) such as GPR41, GPR43, and GPR109A, SCFAs can modulate insulin sensitivity and inflammation, likely leading to insulin resistance and impacting glioma cells' nutrient absorption and utilization.[58,59]

Moreover, the microbiome may influence the host's fatty acid composition and metabolism, thereby affecting tumor cell fatty acid oxidation and synthesis. Gut microbiota-mediated lipid metabolism, through the production of metabolites like SCFAs, secondary bile acids, trimethylamine, and LPS, can alter fatty acid absorption and transport.[60] This modulation affect the host's fat storage and energy utilization, which may subsequently influence glioma cells' energy supply and growth conditions. The production of essential amino acids such as tryptophan, arginine, and glutamate, or the generation of energy through the metabolism of non-essential amino acids like branched-chain amino acids, further illustrate the microbiome's potential role in glioma proliferation and survival.[61,62]

Microbial metabolites may also have a profound impact on the intestinal barrier's integrity and function. Compromised barrier integrity facilitates the entry of more inflammatory mediators and immune cells into circulation, potentially affecting distant glioma cells.[63] Some metabolites, notably SCFAs like butyrate and secondary bile acids, are key to maintaining intestinal epithelial cell integrity, thereby enhancing barrier function.[64,65] Conversely, other metabolites, including proteases and LPS, can weaken the intestinal barrier by damaging its physical defenses and inducing inflammation, leading to increased permeability.[66,67] This dynamic interplay between microbial metabolites and the intestinal barrier indicates the complexity of microbiome-host interactions and their relevance to glioma development.

4. Role of microbiota in immunomodulation against glioma

The potential interplay between the microbiome and glioma involves a series of molecular and cellular mechanisms which may orchestrate immunomodulation (Figure 2). This interaction may encompass immune activation, immune escape, and the regulation of the immune microenvironment, creating conditions that may either support or hinder glioma progression. Microbiota's possible roles in immune stimulation and escape within the glioma context indicate the intricate balance between oncogenic and oncolytic influences, and underscore the critical potential of leveraging microbiota interactions for developing novel glioma therapies, aiming to boost immune surveillance while counteracting the tumor's strategies for immune evasion.

4.1. Microbiota may enhance immune surveillance against glioma cells

The microbiota, particularly the gut microbiota, may exert a profound impact on the host immune system's surveillance of tumor cells, utilizing its metabolic products and immunomodulatory functions to influence both systemic immune responses and CNS immunity. Some microbial derivatives can activate the host immune system, potentially enhancing its ability to combat gliomas. Notably, bacterial peptides can stimulate tumor-infiltrating lymphocytes (TILs), such as $CD4^+$ T cells and peripheral blood memory cells, to improve immune reactivity against glioblastoma.[68] Flagellin, a whip-like appendage that enables bacterial motility, can reduce the number of myeloid-derived suppressor cells (MDSCs) in tumor tissues and adjust the conversion of tumor-associated macrophages (TAMs) from M2 to M1 type.[69,70] Additionally, the gut microbiota promotes dendritic cell maturation, augmenting their capacity to present tumor antigens to T cells, an effect attributed to the production of SCFAs like butyrate.[71] The microbiome may also engage the host's innate immune system *via* pattern recognition receptors, such as Toll-like receptors, activating innate immune cells (NK cells, macrophages, neutrophils) to enhance glioma cell recognition and elimination.

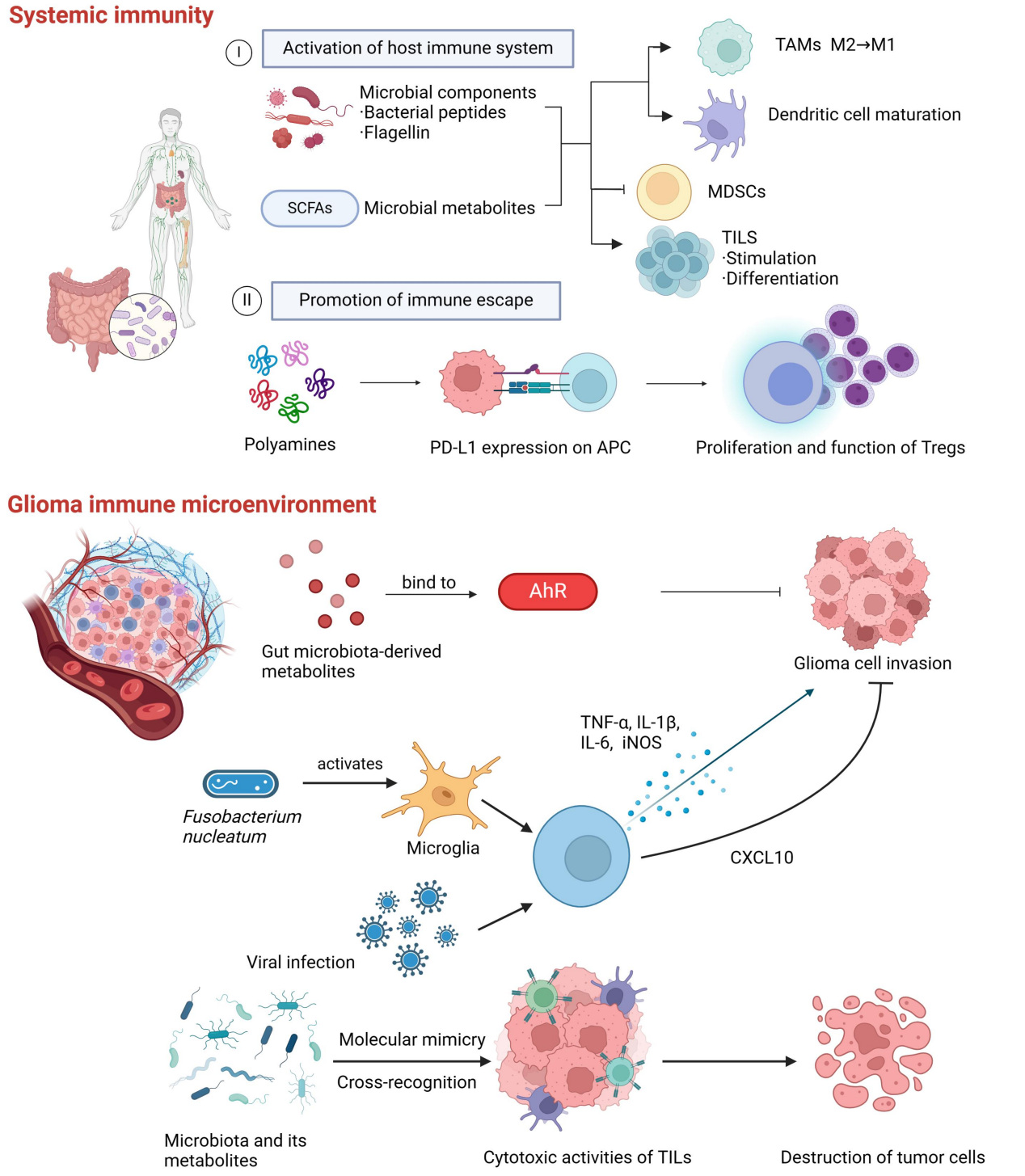

Figure 2. Potential effects of microbiome on immunomodulation. Microbiota may either promote or inhibit glioma growth *via* host immune system and modifications of TME. (1) microbial components and metabolites are able to initiate host immune response, inducing the polarization of TAMs into inflammatory (M1) phenotype, the maturation of dendritic cells, the inhibition of MDSCs, as well as the stimulation and differentiation of TILs. While metabolites such as polyamines potentially upregulate PD-L1 expression on APCs, which may potentiate treg cell expansion and immune escape. (2) AhR, detected in TAMs, can be activated by gut microbiota-derived indole-based metabolites, driving TAMs recruitment into GBM. *Fusobacterium nucleatum* may activate microglia *via* TLR2 and TLR4 pathway, upregulating cytokine (tnf-α, IL-1β, IL-6, and iNOS) secretion conducive to glioma development, which may also be suppressed by the release of CXCL10 induced by viral infection. Some microbe or its metabolites may be recognized as tumor antigen *via* molecular mimicry, promoting cross-reactive immune response, thereby destroying glioma cells.

Moreover, SCFAs contribute to the regulation of both innate and adaptive immunity, guiding the differentiation of T and B cells.[55] Specific strains, such as *Parabacteroides distasonis* and *Megasphaera massiliensis*, have been identified to modulate immune responses, with the latter showing potential in reducing IL-6 secretion and oxidative stress, therefore inhibiting M2-like macrophage polarization.[72,73] To the opposite, the antibiotic treatment and the resulting alterations in gut microbiota may contribute to glioma growth by impairing the function of innate immune cells, such as NK cells and microglia.[74,75]

4.2. Microbiota may promote immune escape of glioma

Certain microbial metabolites may facilitate immune escape, supporting glioma growth. Some gut microbes produce metabolites that inhibit immune cell functions, potentially affecting the PD-L1 response in glioma-bearing mice – a mechanism observed in other non-CNS cancers.[39] Specifically, polyamines from the urogenital microbiota may suppress effector T cell activity by upregulating PD-L1 expression on antigen-presenting cells,[76] suggesting that a similar pathway may promote glioma growth. Additionally, the microbiome may foster an immunosuppressive environment by enhancing the proliferation and function of regulatory T cells (Tregs), mediated by fluctuations in Foxp3 expression, probably reducing immune surveillance against gliomas.[77,78]

4.3. Impact of microbiota on glioma immune microenvironment

The microbiome may exert a profound influence on immune surveillance within the tumor immune microenvironment, a complex assembly of cells, molecules, and signaling pathways that are pivotal in shaping immune responses against glioma. A key mediator of this intricate host-microbiota interaction is the aryl hydrocarbon receptor (AhR). Research indicates that the receptor's ligand, a metabolite produced by gut microbiota, plays a crucial role; its knockdown has been shown to increase glioblastoma cell invasion, indicating the receptor's involvement in maintaining a balance between tumor suppression and promotion.[79]

The microbiome, encompassing both gut and other tumor-associated microorganisms, may dynamically influence the expression of cytokines and chemokines within the TME. *Fusobacterium nucleatum*, an oral commensal organism associated with pathological changes in the brain, activates microglia *via* TLR2 and TLR4 pathway, producing TNF-α, IL-1β, IL-6, and iNOS. These products lead to local inflammation in CNS, potentially promoting the occurrence and progression of glioma.[80] Both DNA and RNA viral infections induce secretion of CXCL10, enhancing the recruitment of adoptively transferred therapeutic T cells to CNS, potentially improves the survival in a mouse model of GBM.[81,82] The shifts in the levels of pro-inflammatory and anti-inflammatory cytokines may directly impact the recruitment, activation, and efficacy of immune cells, which in turn implicates the efficiency of immune surveillance mechanisms targeting glioma cells.[83]

Moreover, the microbiome's regulatory capabilities extend to specific immune cell populations such as TAMs and TILs. Gut microbial bile acids, such as deoxycholic acid, lithocholic acid, chenodeoxycholic acid, and cholic acid, have been observed to induce TAMs to adopt an anti-tumor phenotype, suggesting their potential role in glioma suppression.[84,85] Similarly, these metabolites can augment the cytotoxic activity of TILs, which may bolster their ability to target and destroy glioma cells. For instance, a peptide from *Enterococcus hirae* bacteriophage can be recognized as a tumor antigen by $CD8^+$ T cells *via* molecular mimicry. TIL-derived $CD4^+$ T cell clones (TCCs), such as TCC88, strongly cross-recognizes tumor antigens and microbiota-derived peptides, which are mainly derived from the phyla Firmicutes, Proteobacteria and Bacteroidota.[68] Such mechanisms underscore the microbiome's potential as a therapeutic target, offering pathways to modulate immune responses for more effective glioma treatment.[86]

5. Microbiota and efficacy of glioma therapies

Treatment options for gliomas usually include surgery, radiation therapy, chemotherapy, and

Table 2. Interplay between microbiome and current glioma therapy.

Glioma therapy/Event	Components	Effects and associations
Surgery		
Glioma detection	Gut microbiome: *Escherichia coli*, *Saccharomyces cerevisiae*, etc.	Involvement in host NAD^+ metabolism,[87] potentially associated with assessment of glioma infiltrative margins[88]
Ischemic stroke following craniotomy (stroke *vs*. healthy controls)	Gut microbiome: *Streptococcus* ↑ *Lactobacillus* ↑ *Escherichia* ↑ *Eubacterium* ↓ *Roseburia* ↓ , etc.	Potentially associated with risk factors of stroke;[89] consumption of dietary fibers improves stroke outcomes, likely *via* SCFAs production; stroke can in turn induce intestinal dysbiosis[90,91]
Chemotherapy and radiotherapy		
Immunosuppression	CSF: *Listeria monocytogenes* ↑ *Cryptococcus neoformans* ↑	Exclusion of severe complications of glioma, e.g. leptomeningeal spread with carcinomatous meningitis[92]
Alveolo-interstitial pneumonia in a glioblastoma patient following temozolomide treatment[93]	Gut commensal bacteria e.g. *Bifidobacterium genus*: *Bifidobacterium pseudolongum*; *Bifidobacterium animalis*	Potential role of lung-gut axis: gut microbiome involve in defense against respiratory infections; respiratory infections in turn change gut microbiota composition[94]
Bevacizumab+temozolomide *vs*. temozolomide	*Firmicutes* ↑ *Bacteroidetes* ↑ *Actinobacteria* ↑ *Bacteroidetes* ↓ *Cyanobacteria* ↓	Treatment-induced significant changes in gut microbiota; may foster the development of new glioma therapies, e.g. FMT[95]
Immunotherapy		
ICB	Gut microbiome: *Akkermansia muciniphila* *Bifidobacterium longum* *Faecalibacterium spp.*, etc.	Key taxa potentially associated with a better response to ICB in glioma patients[96]
	Gut microbiome: *Streptococcus* ↑ *Paecalibacterium* ↑ *Stenotrophomonas* ↑ *Faecalibacterium* ↓ *Unidentified Lachnospiraceae* ↓	Potential biomarkers for predicting the occurrence of irAEs[97]
CAR-T therapy	Probiotics, e.g. *Prevotella loescheii*	Preventing and treating irAEs in treatment of malignant glioma[98]
Other glioma therapies		
UniPR1331	Gut microbiome as a whole	Profiling of main metabolites supports a major role in the *in-vivo* clearance of UniPR1331[99]
Dietary polyphenols	*Staphylococcus aureus* ↓ *Pseudomonas aeruginosa* ↓	Anti-bacteria properties influence gut microbiota compositions[100]
Finasteride	*Faecalibacterium* spp. ↓ *Ruminococcaceae* UCG-005 ↓ *Alloprevotella* ↑ *Odoribacter* spp. ↑	Alterations in gut microbiota composition was reported in post-finasteride patients[101]
Yi Qi Qu Yu Jie Du Fang (YYQQJDF)	Gut microbiome (uncertain)	Potential key role in metabolism of core active ingredients[102]
Taohong Siwu Decoction	Gut microbiome as a whole (*in vivo* metabolism in mice)	Active ingredients were yielded from serum of SPF mice, suggesting the role of gut microbiota in TSD metabolism[103]

YYQQJDF: a TCM prescription comprised of "Huangqi" (*Hedysarum Multijugum Maxim.*), "Chuangxiong" (*Chuanxiong Rhizoma*), "Banxia" (*Arum Ternatum* Thunb.), "Baihuashecao" (*Hedyotis Difusae Herba*), "Gancao" (*Liquorice*), "Shancigu" (*Pseudobulbus Cremastrae Seu Pleiones*), "Shichangpu" (*Acoritataninowii Rhizoma*) and "Taizishen" (*Pseudostellariae Radix*). Taohong Siwu Decoction: a TCM prescription composed of "Taoren" (*Persicae Semen*), "Honghua" (*Carthami Flos*), "Shudihuang" (*Rehmanniae Radix Praeparata*), "Danggui" (*Angelicae Sinensis Radix*), "Baishao" (*Paeoniae Radix Alba*), and "Chuanxiong" (*Chuanxiong Rhizoma*).

targeted therapies, depending on the type and grade of the tumor. Emerging research underscores the potential influence of the microbiome, particularly the gut microbiome, on the efficacy of glioma treatments. This body of work puts forward a bidirectional relationship where the microbiome may impact treatment outcomes, and glioma therapies may also modify the composition and abundance of the microbiota (Table 2).

5.1. Microbiota and surgical management of glioma

Gross total excision is the primary treatment strategy for adult and pediatric patients with low-grade glioma. The gut microbiome's role in glioma treatment may extend to its influence on surgical outcomes. For instance, gut microbes are associated with the detection of glioma through their contribution to host NAD^+ pools *via* bacteria-enabled

deamidated pathways and *de novo* synthesis.[87] This interaction may be relevant in the context of intraoperative fluorescence lifetime imaging, which leverages time-resolved NAD(P)H fluorescence to glean metabolic insights from the tumor environment. Such metabolic information may be applied to assessing glioma's infiltrative margins, thereby informing microbiopsy and tumor resection strategies.[88]

Furthermore, the diversity of the gut microbiome can be significantly altered by post-surgical conditions, such as ischemic stroke following craniotomy.[63] Case-control studies have delineated shifts in microbial taxa – identifying 62 upregulated taxa (e.g., *Streptococcus*, *Lactobacillus*, *Escherichia*) and 29 downregulated taxa (e.g., *Eubacterium*, *Roseburia*) in stroke patients compared to healthy individuals. These alterations in microbial abundance are linked to glioma patient risk factors, including vessel injury during brain surgery and anesthesia-induced cardiovascular changes, indicating the possible connections between the microbiome, surgical interventions, and patient outcomes.[89,90]

Microbiome's potential impact on preoperative assessment and surgical outcome illuminates new pathways for therapeutic intervention. By targeting microbiome composition and functionality, there exists a promising avenue for enhancing the multimodal treatment of glioma, underscoring the need for further research in this emerging field.

5.2. Microbiota in chemotherapy and radiotherapy for glioma

In the management of glioma recurrences or progression, adjuvant therapies such as chemotherapy and radiotherapy are indispensable. These treatments, however, can profoundly affect the body's microbiome and immune system. The immunosuppression induced by chemotherapy and radiotherapy can diminish the diversity of the gut microbiota, consequently increasing the permeability of the BBB. This alteration is exemplified by a case report, where systemic immunosuppression from glioblastoma chemotherapy prompted the need for comprehensive molecular microbiology testing of cerebrospinal fluid (CSF). Such testing is crucial not only for typical bacterial and viral pathogens but also for pathogens linked with immunosuppression, such as *Listeria monocytogenes* and *Cryptococcus neoformans*. This comprehensive analysis can aid in excluding severe complications like leptomeningeal spread with carcinomatous meningitis.[92]

The effects of treatment on the microbiome extend to the gut-lung axis, illustrated by a case of a 56-year-old woman who developed alveolo-interstitial pneumonia following treatment with temozolomide.[93] This condition indicates the potential interactions between the lung microbiome and the oropharynx and gut microbiome. Furthermore, temozolomide treatment induces notable changes in gut microbial composition, with distinct differences between combination therapy with bevacizumab and monotherapy. Increased abundance of *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and decreased abundance of *Bacteroidetes* and *Cyanobacteria* were found in the patients who received combination treatment.[95]

Conversely, the microbiome's composition and diversity may play a crucial role in shaping responses to chemotherapy and radiotherapy. The gut microbiota, through immunomodulation, may influence the efficacy of Temozolomide in treating glioma.[104] Pilot clinical trials have highlighted the potential of the gut microbiota in shielding cancer patients from radiation injuries.[105] The intratumoral microbiota also emerges as a promising player in modulating chemotherapy efficacy. Researchers found that intratumoral microbes, such as *Gammaproteobacteria*, mediate tumor resistance to the chemotherapeutic drug gemcitabine by converting it into an inactive form *via* the bacterial enzyme cytidine deaminase, which may be associated with decreased efficacy of glioma therapy.[106,107] Comparatively, research on the role of intratumoral microbiome in radiotherapy remains scant.[108,109] This underscores the microbiome, particularly the gut and intratumoral microbiota, as potential therapeutic targets in glioma treatment, offering avenues to enhance treatment effects and reduce side effects.

5.3. Microbiota may modulate immunotherapy efficacy in glioma

Evolving evidence indicates the microbiota's possible role in modulating glioma patients' responses

to immune checkpoint blockades (ICBs), such as anti-PD-L1 and anti-CTLA-4 therapies. The potential of gut microbiome modulation through fecal microbial transplantation (FMT) to either initiate or suppress the response to ICB therapies have been confirmed in the treatment of epithelial tumors such as melanoma.[110] This intricate interplay suggests the gut microbiome's possible influence on the therapeutic landscape of gliomas.

Moreover, the advent of chimeric antigen receptor (CAR) T-cell therapy has introduced new therapeutic potentials for gliomas, evidenced by p32-specific CAR T cells. Although phase I clinical trials for CAR T-cell therapy in glioblastoma have only recently commenced,[111] the gut microbiome's correlation with CAR-T therapy's effectiveness has been well-documented in B-cell lymphoma and leukemia.[112] However, the specific impact of the gut microbiome on CAR-T therapy for glioma remains to be fully elucidated.

The microbiota's role extends beyond modulating therapy effectiveness to influencing immunotoxicity. For instance, antibiotic use, which reduces gut microbiota diversity, has been associated with exacerbating CAR T cell-induced cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[113] In this context, probiotics such as butyrate-producing *Prevotella loescheii* emerge as promising agents for preventing and treating immune-related adverse events (irAEs) in novel immunotherapies against malignant glioma.[98]

These examples indicate the underlying dual role of the microbiota in both enhancing and mitigating responses to advanced glioma therapies. As research continues to unravel the complex relationships between the microbiota and cancer therapy, it becomes increasingly clear that targeting the microbiota may offer novel avenues for improving therapeutic outcomes and managing treatment-related side effects.

5.4. Drug-microbiota interaction in glioma therapy

The microbiome, particularly the gut microbiota, may play a crucial role in both directly and indirectly affecting the metabolism and efficacy of drugs used in glioma treatment. The capability of gut microbiota to metabolize certain drugs may significantly influence their bioavailability and therapeutic outcomes. For instance, the gut microbiota is involved in the *in-vivo* clearance of UniPR1331, an antagonist of the Eph-ephrin system shown to be effective *in vivo* in a murine orthotopic model of GBM.[99] Additionally, natural compounds like polyphenols, which hold promise for the prevention and therapy of glioma, encounter poor intestinal absorption challenges attributed to the individual's intestinal microbiota content.[114]

Conversely, the administration of drugs can lead to modifications in the gut microbiota composition, which may impact the therapeutic efficacy of glioma treatments through the mechanisms described. Finasteride, known for its antioxidant and antiproliferative activity against glioblastoma cells, has demonstrated long-term effects on gut microbiota composition.[115]

The interplay between traditional Chinese medicine (TCM) and the microbiota also implicates the possible relationship between glioma treatments and the microbiome. While the herbal ingredients of TCM are not directly absorbed by the host, they can be transformed into active metabolites by the gut microbiota,[116] some of which exert anti-glioma effects. Specifically, derivatives of Yi Qi Qu Yu Jie Du Fang have been applied in GBM treatment, illustrating the potential therapeutic impact of microbiota-mediated metabolism.[102] The gut microbiota's ability to regulate the metabolism of compounds such as those in Taohong Siwu Decoction, which inhibits glioma cell proliferation and enhances autophagy, indicate the potential influence of the microbiome on the efficacy of glioma therapies.[103]

Although further prospective controlled trials to confirm this potential interaction are required, these examples suggest the possible role of the microbiome in the metabolism and efficacy of glioma treatments, indicating that the microbiome itself, through its dynamic interaction with therapeutic agents, may offer novel avenues for enhancing treatment outcomes or mitigating adverse effects.

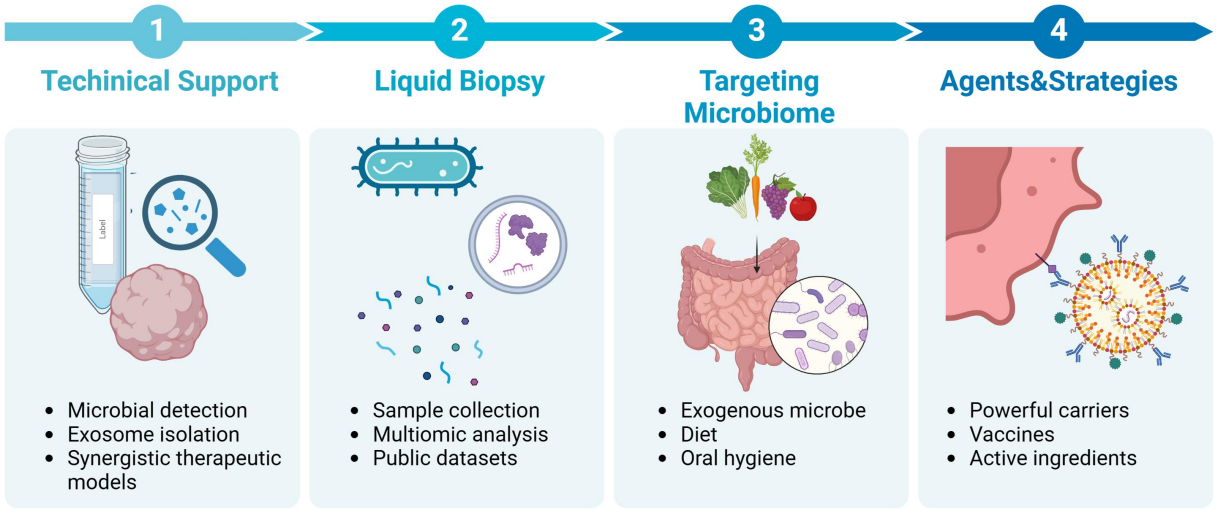

Figure 3. Microbiome-based strategies for glioma. Front techniques for detection, extraction, and analysis of microbe and its derivatives are advancing, and models for TME simulation are being built, enabling in-depth investigation of the interaction between microbiome and glioma. These progresses also facilitate non-invasive diagnosis of glioma, where body fluids, stool and tumor samples are collected for multi-omics analysis, hopefully building a model for glioma diagnosis in combination with public datasets. Microbiota and its derivatives may act as not only a therapeutic target, but also a weapon for killing glioma cells due to their biocompatibility, immune characteristics, and/or cytotoxicity.

6. Novel microbiome-based strategies for glioma diagnosis and therapy

Microbiota, or microbial community, has shown its research and application potential in multiple medical fields in recent years, especially in the diagnosis and treatment of glioma. Researches on the microbiota provide new perspectives and strategies for understanding the pathogenesis of glioma, improving the accuracy of diagnosis, and developing new treatment methods (Figure 3).

6.1. Technical supports for unraveling microbiota-glioma interactions

In recent years, the field of medical research has significantly benefited from advancements in microbial detection and application, contributing to understanding glioma's pathogenesis, diagnosis, and treatment strategies. The past decade has seen remarkable progress in the development of techniques for detecting microbes and their interactions with host cells. For instance, luminogens with aggregation-induced emission properties have revolutionized rapid and specific imaging of bacteria and fungi, further enabling the monitoring of bacteria-cell interactions. This advancement may be pivotal for understanding the microbial influences within the glioma TME.[117]

Moreover, bacterial extracellular vesicles (BEVs) have shown promising potential in clinical applications, serving as diagnostic markers or therapeutic agents. Effective methods for BEV separation and extraction have been proposed and established, highlighting the growing importance of microbial components in medical research.[118,119] Similarly, two-dimensional porphyrin-based Metal-Organic Frameworks (MOFs) and their derivatives have become increasingly vital for biomedical sensing and drug delivery, facilitating the detection and transport of microbial components.[120]

The exploration of microbiota-glioma interactions may also be enhanced by new techniques and models. Synergistic therapeutic models, such as 3D cultures simulating the GBM TME,[121] and the development of organoids for GBM, medulloblastoma, and high-grade glioma,[122,123] may enable in-depth studies on the intricate relationships among microbes, glioma, and the TME.[124] Additionally, 3D neuronavigation utilized during surgical resection may offer a comprehensive view of GBM evolution and heterogeneity,[26] while microbiome engineering introduces novel solutions for glioma therapy by improving the functions of the existing microbial community through the introduction of new microbes.[125]

These advancements underscore the microbiota's research and application potential across multiple medical fields, offering new perspectives and strategies for diagnosing and treating glioma. The continuous development of techniques to investigate the associations and interactions between microbiota and glioma may pave the way for innovative diagnostic and therapeutic approaches, demonstrating the potentially significant role of microbiota in the medical realm.

6.2. Employing microbiome in liquid biopsy of glioma

The complexity of glioma's biological characteristics has traditionally posed challenges for distinguishing it from other brain diseases using standard diagnostic methods. Consequently, there is an urgent need for early, precise, and noninvasive detection techniques. Emerging research has identified distinct differences in the microbiome's distribution between glioma patients and healthy individuals, implicating the microbiota's involvement in glioma pathogenesis.[39] Specific types of bacteria, viruses, and fungi have been associated with the occurrence of glioma, suggesting their potential as biomarkers.[126] Furthermore, variations in the microbiome can reflect the tumor's development stage and prognosis, offering new avenues for patient monitoring. For instance, differences in the gut microbiome between benign meningioma, malignant glioma, and healthy controls have been observed, indicating the microbiota's relevance in glioma's biological landscape.[18]

The concept of a microbiome-derived liquid biopsy has emerged from these findings. This promising approach includes not only microorganisms but also their derivatives, components, and metabolites as biomarkers, necessitating multi-omics analysis for more comprehensive evaluation. By analyzing the composition of a patient's blood, CSF, or gut microbiome, this method may complement traditional imaging and histopathological diagnoses, hopefully enhancing the accuracy of early diagnosis.[127] The analytical process incorporates whole-genome and transcriptome sequencing, alongside machine learning models based on microbial signatures,[128] further refined by nanopore sequencing technology.[129] Moreover, the correlation between oral microbiota and glioma introduces saliva as a potential medium for liquid biopsy,[130] although the relationship between salivary microbiota and glioma warrants further exploration. Additionally, public cancer genome sequence data analysis has identified bacteria associated with glioma, such as the detection of *Mycobacterium tuberculosis* complex in GBM samples, revealing associations with the sequencing center of the samples.[131]

These advancements highlight the microbiota's significant research and application potential in glioma, offering new strategies for understanding pathogenesis, improving diagnostic accuracy, and developing innovative treatment methods.

6.3. Harnessing the microbiome for glioma prevention and therapy

Insights into the microbiota-glioma relationship may inform new preventive and therapeutic strategies for glioma. Specific examples of current clinical trials and proposed interventions have demonstrated that microbiota may act as not only a therapeutic target, but also a weapon for glioma growth inhibition (Table 3).

6.3.1. Microbiota as a therapeutic target for glioma

In the realm of glioma prevention and therapy, directly modulating the composition of the microbiota presents a promising approach. This modulation can be achieved through dietary adjustments and changes in living habits. Notably, recent studies have highlighted the potential of probiotic combinations, such as *Bifidobacterium lactis* with *Lactobacillus plantarum*, in inhibiting glioma growth in mice. This effect is mediated by suppressing the PI3K/AKT pathway and regulating the composition and metabolism of the gut microbiota.[132]

Prebiotics may also play a crucial role in enhancing the response to ICBs and reducing immunotoxicities by fostering the growth of beneficial microbial species. For example, fructooligosaccharides (FOS) and

Table 3. Promising preventive and therapeutic approaches based on microbiota-glioma relationship.

Associations	Strategies
Microbiota as a therapeutic target	
•*Bifidobacterium lactis* and *Lactobacillus plantarum* inhibit glioma growth in mice	Probiotic combination[132]
•FOS and GOS improve the microbial profile and neuroplasticity through the gut-brain axis	Fostering the growth of beneficial microbial species via prebiotics[133]
•Intake of tea and vegetables may reduce the risk of glioma, while the intake of grains and processed meat may increase the risk[134] •Ketogenic diet is associated with improved outcomes of GBM patients[135] •A high-glucose drink was observed to increase $CD4^+$ T cells in GBM mice through regulation of the gut microbiota[136]	Dietary interventions, e.g. nutritional adjuncts[137]
•Oral microbiota is associated with glioma malignancy[22]	Attention to lifestyle factors, e.g. oral hygiene[138]
•Transferring healthy bacteria from a carefully screened donor to the recipient's colon ameliorates cognitive impairment, suggesting interconnectedness of the gut, blood, and brain	Exogenous microbial therapies, e.g. FMT and LBPs[139,140]
Microbial derivatives as vehicles for targeted therapies	
•Oncolytic viruses can infect glioma cells and elicit anti-tumor immune responses in patients with malignant glioma[141] •The *filamentous bacteriophages* are effective vehicle for delivering displayed peptides toward the tumor target[142] •Virus-like particles hold promise for delivery of glioma mRNA-based therapeutics[143]	Virotherapy
•EVs derived from probiotics can be applied to glioma treatment through genetic manipulation and/or dietary interventions[144] •Nanovehicle mimicking tumor-colonizing bacteria overcomes chemoresistance in mouse models of established breast cancer[145] •Microglia is a potential therapeutic target which may be modulated by exosomes[146]	EVs as vehicles for targeted glioma therapy
Development of new drugs	
·p28 secreted by *Pseudomonas aeruginosa* has been approved for glioma treatment by FDA[147] •Extracts from mushrooms exhibit anti-glioma potential[148]	Microbial derivatives or components

galactooligosaccharides (GOS) not only improve the microbial profile and neuroplasticity through the gut-brain axis, but also mitigate leaky gut syndrome in the distal colon.[133]

Additionally, dietary interventions have demonstrated potential for glioma prevention and treatment by controlling the nutrients supply to the intestinal microorganisms.[149] Statistics showed that intake of tea and vegetables may reduce the risk of glioma, whereas the intake of grains and processed meat may increase the risk.[134] Nutritional adjuncts like the ketogenic diet have shown multiple benefits at the synaptic level, including reducing oxidative stress and neuroinflammation. Its influence on the gut microbiome-brain axis has been associated with improved outcomes for glioblastoma patients.[135] A recent systematic review confirmed the therapeutic benefits of such nutritional adjuncts, indicating an increase in the median OS for both newly diagnosed and recurrent glioma cases compared to historical data. However, the absence of a statistically significant difference in OS highlights the need for further research to elucidate the mechanisms underlying these benefits.[150] Interestingly, a high-glucose drink, typically linked to metabolic diseases, was found to increase $CD4^+$ T cells in GBM mice through modulation of the gut microbiota,[136] suggesting the immunomodulatory potential of dietary interventions.[137]

The relationship between oral microbiota and glioma malignancy also underscores oral microbiota as a potential therapeutic target. Lifestyle factors, such as oral hygiene, could influence glioma occurrence and progression,[138] indicating a broader context in which microbiota modulation may impact glioma therapy.

Exogenous microbial therapies, like FMT, offer another avenue for microbiota modulation. FMT involves transferring healthy bacteria from a carefully screened donor to the recipient's colon, successfully treating *Clostridioides difficile* infections[151] and ameliorating cognitive impairment in Alzheimer's disease models by modulating intestinal macrophage activity and circulating blood inflammatory monocytes.[139] This technique sheds light on the interconnectedness of the gut, blood, and brain and its potential application in glioma therapy. Live biotherapeutic products (LBPs), either oral, topical, or injectable, represent a future direction for employing live organisms in disease prevention and treatment. By consuming

harmful compounds and delivering therapeutic agents to the TME, LBPs may prevent antibiotic-induced dysbiosis, modulate gut microbiota, and regulate intratumoral microbiota to combat solid tumors.[140,152]

6.3.2. Glioma therapies based on viral vectors and microbial derivatives

The development of glioma vaccines has marked a significant research milestone, with various vehicles discovered or synthesized to carry therapeutic effectors across the BBB. Virotherapy stands out as one of the most promising strategies, with several oncolytic viruses, such as herpesvirus, demonstrating the capability to infect glioma cells and elicit anti-tumor immune responses in patients with malignant glioma.[141] Additionally, *filamentous bacteriophages*, which specifically infect bacteria and are harmless to humans, have been recognized for their biocompatibility and high carrying capacity. These bacteriophages may be powerful carriers for glioma therapy, targeting tumor cells or molecules within the TME.[153] It is noteworthy that virus-like particles hold promise for mRNA delivery targeting APCs,[154] which may enhance the potency of glioma mRNA vaccine currently in clinical trials.[143]

Extracellular vesicles (EVs), including outer membrane vesicles derived from bioengineered bacteria, have also shown promise as delivery tools for glioma therapy. These exosomes can be loaded with various tumor antigens to stimulate an anti-tumor response, successfully inhibiting the growth and metastasis of lung melanoma and colorectal cancer.[155] Glioblastoma cell-derived exosomes, for instance, can promote chemotherapy resistance by delivering long non-coding RNAs that induce microglia to produce complement C5,[146] suggesting microglia as a potential therapeutic target to mitigate chemotherapy resistance, which may be modulated by exosomes. Moreover, EVs derived from probiotics like *Akkermansia muciniphila* offer promising avenues for glioma treatment through genetic manipulation and/or dietary interventions.[144] A novel type of nanovehicle mimicking tumor-colonized *Fusobacterium nucleatum* has been developed to overcome chemoresistance by targeting tumor-colonizing bacteria, a strategy tested in mouse models of established breast cancer.[145] Notably, the presence of tumor microbiome in glioma has been confirmed,[24] indicating that synthesized nanoparticles mimicking intratumoral microbes might also be applied to inhibit glioma growth and invasion. These vehicles can carry a wide range of cargos, including antibodies, peptides, proteins, as well as naturally occurring compounds like diosgenin and polyphenols, which have been shown to modify gut microbiota composition and may influence glioma development.[114,156]

In addition to vaccines, an increasing number of new drugs based on microbial derivatives or components are emerging. Bacterial peptides like p28, secreted by *Pseudomonas aeruginosa* and capable of crossing the BBB, have received FDA approval for glioma treatment.[147] Furthermore, active ingredients from fungi, including extracts from mushrooms like *Cantharellus cibarius*, *Coprinus comatus*, *Lycoperdon perlatum*, and *Lactarius delicious*, have shown anti-glioma potential by inhibiting cancer cell DNA synthesis.[148]

These advancements suggest the potential of microbial components and engineered delivery systems in advancing glioma diagnosis and treatment, although challenges in translating these findings from bench to bedside are also emerging. The specific roles of microorganisms in occurrence, development, and treatment of glioma still need to be confirmed, limiting their clinical application.[126] Additionally, strict control is required to avoid microbial contamination and degradation in samples.[157] Furthermore, moving from laboratory research to clinical application requires extensive clinical trial validations. Addressing these challenges calls for more efforts in in-depth research, standardization of preprocessing methods, and further evaluation of feasibility and effectiveness of these strategies.

7. Conclusions

This review has illuminated how leveraging the microbiota, particularly from the gut, could possibly advance glioma management, introducing noninvasive diagnostics, targeted therapies, and even preventive strategies. However, the focus on glioblastoma and gut microbiota to date

represents just the tip of the iceberg. The most critical areas for future research include the broader spectrum of gliomas and the diverse microbiota across different body sites. The interconnectedness of microbiota across these sites hints at a complex, systemic relationship with glioma, urging a more holistic approach to future studies.[158] Moreover, the exploration of non-bacterial microbiota components, such as viruses and fungi, promises to deepen our understanding of the microbiome-glioma nexus, unveiling new targets for intervention. As we move forward, it is imperative to identify the gaps of current literature, including the nuances of pediatric versus adult gliomas, tailoring interventions to the unique microbiota profiles of these populations.[159] New methodologies or approaches for liquid biopsy and glioma therapy, such as multi-omics analysis and microbiome-based therapeutics, require improvement and evaluation for further application. In conclusion, the burgeoning field of microbiota research in glioma heralds a new era in oncology, which may promise more effective, personalized, and less invasive options for diagnosis and treatment. The synergy between microbiota and glioma research not only offers hope for breakthroughs in glioma management, but also emphasizes the need for interdisciplinary research, combining oncology, microbiology, and neurology to unravel the complexities of human health and disease.

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Wenhui Wang and Zihao Ou wrote and edited the manuscript; Wenhui Wang collected published papers and generated the figures; and Zihao Ou and Lei Zheng revised the manuscript. All authors have read and approved the article.

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