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Review

Advances in research on glioma microenvironment and immunotherapeutic targets

Aiwei Tang[1], Jianhao Liang[2], Yiying Mai[1], Haitao Sun[1,2,3*]

[1] Clinical Biobank Center, Microbiome Medicine Center, Department of Laboratory Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China

[2] Neurosurgery Center, The National Key Clinical Specialty, The Engineering Technology Research Center of Education Ministry of China on Diagnosis and Treatment of Cerebrovascular Disease, Guangdong Provincial Key Laboratory on Brain Function Repair and Regeneration, The Neurosurgery Institute of Guangdong Province, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China

[3] Key Laboratory of Mental Health of the Ministry of Education, Guangdong-Hong Kong-Macao Greater Bay Area Center for Brain Science and Brain-Inspired Intelligence, Southern Medical University, Guangzhou 510515, China

*Correspondence: 2009sht@smu.edu.cn, msunhaitao1988@126.com

Abstract: The tumor microenvironment is an important regulator in the progression of brain tumors. In the present review, we discussed the roles of various non-cancer cellular components, tumor vessels, and the extracellular matrix in the progression of brain tumors. We also focused on the metabolic remodeling of brain tumors. By providing an overview on the unique and highly complex tissue microenvironment, we hope to support other research groups in finding more available treatment strategies and improving treatment outcomes.

Keywords: Tumor microenvironment, Glioma, Metabolic remodeling

Introduction

Glioma is the most common form of brain cancer. Despite surgical resection, radiation therapy and temozolomide, as well as targeted therapy and immunotherapy, the overall survival rate (OS) of patients remains poor [1,2]. The interplay between cancer cells and the tumor microenvironment (TME) is known to play a pivotal role in tumor progression, tumor angiogenesis and immune sequestration. Distinguished from other tumor tissues, the brain TME possesses unique tissue-resident cell types, including microglia, astrocytes and neurons, and is characterized by the distinct blood–brain barrier (BBB) .

The WHO used to divide gliomas into the following groups based on their histopathological characteristics: low-grade gliomas (LGGs, grades I and II) that are well-differentiated and slow-growing tumors, while high-grade gliomas (HGGs, grades III and IV) that are less-differentiated and evidently infiltrate brain parenchyma [3]. In 2016, WHO classification of tumors of the central nervous system (CNS) was changed into molecular categorization based on genetic and epigenetic features [4]. Mutation of isocitrate dehydrogenase gene (IDH^{mut}) and codeletion of *1p/19q* have become the primary factors by which gliomas are classified. Tissue-resident microglias

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(MGs), bone marrow-derived macrophages (BMDMs), neutrophils and T cells are the main immune cell types in the microenvironment of brain tumors [5,6]. IDH^{mut} gliomas are mainly composed of MGs and a few immune cells; IDH wild-type (IDH^{wt}) gliomas are enriched with BMDMs and a few neutrophils; a small proportion of gliomas are well populated with immune cells, accompanied by the infiltration of T cells and neutrophils [5,6].

In this review, we expound the latest advances in glioma TME and related treatments, aiming to outline a profound and comprehensive picture of TME and provide new insights into the development of alternative treatments to improve the therapeutic efficacy of patients.

Tumor-associated macrophages

Tumor-associated macrophages (TAMs) are the major immune cells in brain tumors, often accounting for up to 30% of the tumor mass [7] TAMs in gliomas include MGs and BMDMs recruited from the peripheral circulation. MGs are derived from $RUNX1^{+}$ yolk sac progenitors and maintain locally through self-renewal, serving as both immune sentinels and homeostatic regulators [8], while BMDMs are replenished through peripheral monocytosis [9]. MGs mainly localize in peritumoral regions, whereas BMDMs preferentially in perivascular areas and necrotic foci where TAMs induce angiogenesis [10,11]. Besides, MGs are predominant in LGGs, while BMDMs prevail in HGGs [6,10,12]. Therefore, BMDMs are more closely related to glioma progression than MGs [12].

Conventionally, TAMs are divided into two phenotypes: M1 and M2 phenotypes. M1 TAMs produce pro-inflammatory mediators including tumor necrosis factor (TNF), interleukin-1β (IL-1β), nitric oxide (NO), and reactive oxygen species (ROS) [13]. M2 TAMs generate anti-inflammatory and immunosuppressive factors, such as IL-6, IL-10 and transforming growth factor-β (TGF-β) [14-16]. IL-6 promotes the phosphorylation of phosphoglycerate kinase 1 in tumor cells, thus facilitating glycolysis and tumorigenesis [16].Oncostatin M (OSM) from TAMs can induce glioblastoma (GBM) cells into mesenchymal-like (MES-like) states [17]. CCL5 from TAMs regulates the migration and invasion of glioma cells via the calcium-dependent matrix metalloproteinase (MMP) 2 [18]. As the malignant degree of glioma increases, the proportion of M2 TAMs increases and the proportion of M1 TAMs decreases [19]. IDH^{mut} patients show lower proportions of M2 TAMs in *1p/19q* codeletion LGGs compared with that in non-codeletion LGGs [20].

TAMs secrete pleiotrophin (PTN) and TGF-β1 to promote the maintenance and invasion of glioma stem cell (GSC) [21,22]. $MARCO^{high}$ BMDMs promote the shift of phenotype towards the MES cellular state of GSCs [23]. Extracellular vesicles (EVs) from BMDMs transfer miR-27a-3p, miR-22-3p and miR-221-3p to GSCs, inducing differentiation towards a MES phenotype in proneural (PN) GSCs [24]. In turn, GSCs enhance TAM trafficking and M2 polarization through paracrine periostin and osteopontin [25-27]. Moreover, Wnt-induced signaling protein 1 (WISP1) and prostaglandin E2 (PGE2) from GSCs are critical for GSC maintenance and M2-like TAM polarization [28,29].

Due to the abundance, TAMs are thought to be promising therapeutic targets. Molecules such as CCL2, CCL5, CXCL12, colony-stimulating factor-1 (CSF-1), periostin and osteopontin contribute to macrophage infiltration into the tumor site [15]. Inhibitors or antibodies targeting these molecules or their receptors can inhibit macrophage recruitment.

The reprogramming of phenotypes would be a more effective way than the reduction of TAM numbers [30]. CSF-1 released by glioma cells, is a stimulus of the differentiation, polarization, survival, and recruitment of TAMs [31]. An inhibitor of CSF-1 receptor (CSF-1R) markedly mediates macrophage polarization in a GBM mouse model, suppressing the expression of M2 markers without depleting TAMs [30]. Although CSF-1R blockage prolonges mice survival time in a GBM mouse model, over 50% of them relapse inevitably, which is attributed to the elevated PI3K activity in tumors, driven by macrophage-secreted insulin-like growth factor 1 (IGF-1) [32]. Besides, Bao et al. found that inhibition of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) with MK-893 could reprogram M2 into M1 and promote the macrophage phagocytosis of tumor cells because BACE1-mediated STAT3 activation is required for maintaining M2 [33].

Cancer cells can keep from phagocytosis by upregulating the anti-phagocytic molecule CD47, but CD47 blockage alone is inefficient in activating glioma cell phagocytosis [34]. However, combining CD47 blockage with temozolomide results in a notable pro-phagocytic effect due to the latter's ability to induce endoplasmic reticulum stress [34]. Increased tumor cell phagocytosis therefore promotes antigen cross-presentation and activation of cyclic GMP-AMP synthase-stimulator of interferon (IFN) genes in antigen-presenting cells (APCs), resulting in more T cell priming [34].

Chimeric antigen receptor (CAR) macrophages have been used to enhance tumoricidal function. Characterization of CAR macrophage activity shows that CAR macrophages secrete pro-inflammatory cytokines and chemokines, induce the transformation of bystander M2 macrophages into M1, upregulate antigen presentation, recruit and present antigens to T cells, as well as resist the effects of immunosuppressive cytokines [35].

Lymphocytes

T cell, an important anti-tumor component, is usually rare in gliomas and shows impaired effector function. [36]. GBM is called "cold tumor", referring to the low number of immune cells and insensitivity to immunotherapy [37]. In the setting of intracranial tumors, loss of surface sphingosine-1-phosphate receptor 1 (S1PR1) on T cells directs their sequestration in bone marrow, resulting in a scarcity of infiltrating T cells at the tumor site [38]. Though T cells have successfully reached the tumor site, they are subject to further suppressive influences, such as inhibitory checkpoint molecules. When cytotoxic T lymphocyte-associated protein 4 (CTLA-4) interacts with CD80/CD86, T cells will get anergic [39]. The interaction between the receptor programmed cell death-1 (PD-1) and the PD-1 ligand (PD-L1) expressed on cancer cells, TAMs, etc., suppresses T cells' functions and its proliferation, but has a promoting effect on the proliferation of regulatory T cells (Tregs) [40]. Besides, dendritic cells (DCs) upregulate PD-L1 upon antigen uptake [41]. Other characterized checkpoints are T cell immunoglobulin-3 (TIM-3), Lag-3 (CD223), B- and T-lymphocyte attenuator (BTLA), 2B4 (CD244), CD160, T cell immunoglobulin and ITIM domain (TIGIT), and CD39 [36]. Moreover, Tregs inhibit the activation and differentiation of $CD4^+$ and $CD8^+$ T cells and their reactivity against autologous and tumor-expressed antigens [42]. The TME favors the recruitment and survival of Tregs by CCL2 and indoleamine 2,3-dioxygenase (IDO) [42,43].

In a variety of solid tumors, immune checkpoint blockage targeting the PD-1/PD-L1 or CTLA-4 has achieved great success in a subset of patients. However, in a clinical trial, CheckMate 143 PD-1 blockage in cancer treatment for patients with rGBM failed compared with treating with bevacizumab [44]. The failure of PD-1/PD-L1 monoclonal antibody (mAb) is related to many factors, such as PD-L1 expression intensity, the number of tumor-infiltrating lymphocytes (TILs), the tumor mutation burden, microsatellite instability (MSI), and mismatch repair deficiency (MMR).

The existence of TILs is fundamental to the success of immune checkpoint inhibitors. For example, melanoma brain metastases that harbor a large number of T cells actively respond to checkpoint blockage [5,45]. Additionally, in patients who are insensitive to immune checkpoint blockage (non-responders), PD-1^{high} T cells may be in a fixed dysfunctional condition, contrary to responders whose PD-1^{high} T cells are in a plastic state, amenable to reprogramming [46]. Tumors with TMB and high antigen load are more likely to stimulate immunity. A study showed that a hyper-mutated subgroup identified among IDH^{wt} GBM patients has a better prognosis, and two ultra-mutated cases are characterized by the presence of at least 25% giant cells, MMR mutations, and MSI [47]. Moreover, the existence and upregulation of other immune checkpoints can impair the efficacy of PD-1/PD-L1 mAb. It has been reported that PD-L1 and B7-H4 may serve as complementary immune checkpoint molecules in gliomas [48]. Recently, CD161 expressed on T cells was identified as a new immunotherapy target [49]. Notably, neoadjuvant administration of PD-1 inhibitors enhances anti-tumor immune response locally and systemically, with an upregulation of T cells and IFN-γ-related gene expression and a downregulation of cell cycle-related gene expression within the tumor [50, 51], indicating that drugs given before surgery are more likely to provoke the immune response.

In adoptive immunotherapy, the patient's lymphocytes or Dendritic cells (DCs) are artificially activated to elicit the anti-tumor response, and it can obviate the multiple steps in stimulating the primary anti-tumor immune response. The redirection of CAR-T cells has been the most pioneering and successful work for redirected adoptive immunotherapy. CAR-T cell therapy has shown safety and feasibility in clinical practice for GBM, but its overall results are still unsatisfactory [52,53]. A group investigated the decisive molecules of CAR-mediated GBM cell killing via whole-genome CRISPR screens in both CAR-T cells and patient-derived GSCs [54]. The screening of CAR-T cells identifies dependencies on effector functions, including TLE4 and IKZF2, the knockout of which enhances CAR-T cell effector functions and inhibits the exhaustion responses [54]. Reciprocal screening of GSCs identifies the genes mediating resistance to CAR-T cells, including RELA and NPLOC4, the knockout of which alters tumor-immune signaling and increases the sensitivity of CAR therapy [54]. The high-throughput screening platform established in this study can be extended to CAR-T cells with different targets and other adoptive cell transfer therapies to obtain reliable targets with clinical potential.

Tumor-associated neutrophils

Neutrophils act as key players in defending against infection and in activating and regulating the innate and adaptive immunity. Under different TME conditions, tumor-associated neutrophils (TANs) can be polarized into two distinct functional phenotypes: the anti-tumoral phenotype N1, mostly induced by IFN-β, and the tumor-promoting phenotype N2, elicited by TGF-β1, granulocyte colony-stimulating factor (G-CSF), and IL-6 [55]. N1 TANs mediate anti-tumor reactions by directly killing tumor cells and participating in cellular networks that induce anti-tumor resistance [56]. N2 TANs can be part of tumor-promoting inflammation by driving the angiogenesis, ECM remodeling, metastasis, and immunosuppression [56]. The number of infiltrating TANs is positively correlated with the tumor progression [57,58]. IDH^{mut} gliomas, less aggressive than IDH^{wt} tumors, exhibit low TAN infiltration [59]. Among the molecular subtypes of GBM, MES tumors with poor survival time have higher numbers of TANs than those of other subtypes, including PN, classical, and neural [60].

TANs stimulate the glioma progression through the upregulation of S100A4 expression, supporting cancer invasion and resistance to vascular endothelial growth factor (VEGF) therapies [61]. Increased neutrophil degranulation leads to higher levels of circulating arginase 1 (Arg1) that can potently and rapidly deplete extracellular L-arginine, resulting in T cell anergy and immune dysfunction [62]. TANs can be recruited and can transfer myeloperoxidase (MPO)-containing granules into tumor cells which induce ferroptosis, causing tumor necrosis, indicating a poor prognosis, and the inflammation induced by tumor necrosis will recruit more TANs [57]. Besides, ferroptosis is associated with MES transition and positively correlated with tumor aggressiveness in GBM [57].

Researchers designed some treatment strategies based on intrinsic inflammatory chemotaxis and the excellent BBB-crossing capability of neutrophils. A neutrophil-based microrobot ("neutrobot") has been reported to actively deliver cargo to malignancies *in vivo*, exhibiting the biological characteristics and functions of natural neutrophils that are currently unmatched by artificial microrobots [63]. A bioinspired neutrophil exosomes (NEs-Exos) system for delivering anti-tumor drugs to treat glioma has been developed. The mouse model showed that NEs-Exos carrying the drug efficiently penetrated the BBB and migrated into the inflamed brain. Then NEs-Exos showed chemotactic response to inflammatory stimuli and targeted tumor cells in inflamed brain tumors, thus efficiently suppressing the tumor growth [64].

Dendritic cells

DCs are the most effective dedicated Antigen Presenting Cells (APCs). DCs process antigens and present them to T cells and B cells, connecting the innate and adaptive immune systems. In glioma microenvironment, DCs increase the expression of nuclear erythroid 2 p45-related factor 2 (Nrf2) and inhibit their maturation [65]. Besides, fibrinogen-like protein 2 (FGL2) from GSCs and primary GBM cells inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced DC differentiation that is necessary for triggering the activation of killer T cells [66]. Blocking FGL2 prolongs the survival time, and reduces the infiltration of Tregs and M2 macrophages and decrease the expressions of immune checkpoints CD39 and PD-1 [67].

DC vaccination is a promising approach for specific active immunotherapy, showing an excellent safety profile [68,69]. A phase III trial of an autologous tumor lysate-pulsed DC vaccine to standard treatment of newly diagnosed GBM (nGBM) showed significant survival benefits in patients, especially those with an MGMT mutation [68]. In a phase II clinical trial, GBM patients with $IDH1^{wt}$ $TERT^{mut}$ and low B7-H4 expression are more responsive to DC vaccines loaded with GSC antigens [69]. There are many factors that can be taken into consideration to improve the effectiveness of DC vaccines, including the origin of vaccine cells, vaccine antigen and adjuvant selection, vaccine targeting optimization, and migration restriction. Co-delivery of tumor-derived exosomes and α-galactosylceramide (α-GalCer)-pulsed DCs and invariant natural killer T (iNKT) cell adjuvant showed powerful effects in a mouse model [70]. Exosomes were utilized as more potent antigens to load DCs. iNKT cell, as an effective cellular adjuvant activated by α-GalCer, strengthens antigen presentation through their interaction with DCs [70]. Additionally, patients given tetanus toxoid prior to vaccination with cytomegalovirus antigen-loaded DCs exhibit enhanced DC migration bilaterally [71].

Mast cells

Early mast cell (MC) infiltration is crucial in shaping the TME by direct cell-to-cell interaction or releases a range of mediators to remodel the TME [72]. The interactions among MCs, other infiltrated immune cells, tumor cells and the ECM actively promote the angiogenesis and tumor invasion [72]. MCs have been reported on the involvement in glioma, where HGG contains significantly more MCs than LGG [73-76]. MC recruitment may occur nearby glioma-associated vessels and within the tumor mass, where the strong secretion of stem cell factor (SCF), the main growth factor of MCs, can be detected [73]. According to the finding, the detection of MC proliferation in glioma suggests that the expansion of the local MC population results in the MC infiltration in glioma microenvironment [73]. Increased expressions of pro-tumorigenic mediators such as CXCL12, PAI-1/SERPINE1 serglycin and macrophage migration inhibitory factor (MIF) were also found to be positively correlated with MC accumulation [73-76]. Cellular crosstalk between MCs and glioma cells reveals that MCs activated by glioma cells, called "tumor educated" MCs, release mediators to reduce the stemness and inhibit glioma cell proliferation and migration, but in turn induce glioma cell differentiation [77]. However, there are still relatively few studies relevant to targeting MCs to treat glioma.

Astrocytes

Astrocytes are the most abundant cells in the CNS and fulfill a range of other homeostasis, with functions of maintaining BBB integrity, the extracellular ion balance and synaptic neurotransmitter levels, releasing neurotrophic factors, affecting the synaptic plasticity, and transmitting information through gap junctions [78]. In response to threats such as trauma, infection, inflammation, and tumors, astrocytes go through specific molecular, cellular and functional alterations, resulting in so-called reactive astrocytes (RAs) [79].

At an early stage in glioma development, astrocytes have neuronal protective and anti-tumorigenic properties, such as buffering glutamate [80]. Glutamate causes cytotoxicity when its extracellular concentration is too high [81]. In the context of gliomas, the voltage-gated K^+ channel Kv1.3 that regulates glutamate buffering within astrocytes becomes more active, which disturbs the homeostatic properties of astrocytes [82]. Ammonia released partly by glioma cells induces astrocyte swelling and dysfunction of glutamate uptake [80]. As the glioma develops, astrocytes change towards a pro-tumorigenic RA phenotype. A study showed that a distinct astrocytic phenotype is caused by the coexistence of microglia and astrocytes in the tumor environment, which leads to a large release of anti-inflammatory cytokines such as TGF-β, IL-10 and G-CSF [83]. RAs increase the expression levels of MMP9, which promotes the tumor invasiveness by breaking down the ECM [84]. After radiation, RAs will increase the secretion of transglutaminase 2 (TG2), which triggers the MES trans-differentiation of GSCs [85,86]. In view of the tumor-promoting property of RAs, blocking the signaling of RAs would suppress the tumor growth. A JAK inhibitor has been shown to reduce the number of RAs, impair the recruitment of myeloid cells, and inhibit the tumor growth [83,87].

Neurons

Neurons, a highly specialized cell type, provide mitogenic signals to stimulate the growth of neuronal and oligodendroglial precursor cells within the brain microenvironment. Recent studies uncovered the interactions between neurons and glioma cells, and a new concept of "tumor neuroscience" was proposed [88].

Venkatesh et al. found that activity-dependent cleavage and secretion of the synaptic adhesion molecule neuroligin-3 (NLGN3) stimulates several oncogenic pathways, induces the upregulation of several synapse-related genes in glioma cells, and facilitates glioma cell proliferation [89, 90]. Recently, a group demonstrated that *Nf1* mutation can drive the tumor progression in a mouse model of optic pathway glioma by the aberrantly increased shedding of NLGN3 within the optic nerve in response to retinal neuronal activity [91]. In 2019, the synaptic transmission between glioma and neurons was identified, where neurons release glutamate to activate AMPA receptors on glioma cells, stimulating glioma cell invasion and growth [92]. Incredibly, neural activity-dependent, non-synaptic potassium currents depolarize electrically coupled glioma cell networks, and this depolarization intensifies cancer cell proliferation [93].

Therefore, interrupting the connection between neurons and cancer cells emerges as a potential therapeutic approach. Recent studies have shown several potential therapeutic targets. Some novel driver variants of PIK3CA have been uncovered in a GBM mouse model. These variant-driven tumors upregulate neuronal excitability by secreting glypican-3 (GPC3), thus driving glioma tumorigenesis, network hyperexcitability, and synapse formation [94]. A study reported that olfactory sensory experience directs the gliomagenesis by their corresponding sensory neuronal circuits where insulin-like growth factor 1 (IGF1) from mitral and tufted (M/T) cells is shown to be the key cytokine [95]. However, the selected target should be as tumor-specific as possible to minimize the impact on normal neuronal circuits.

Blood–brain barrier

The BBB is composed of endothelial cells (ECs) connected by tight junctions (TJs) and adherens junctions (AJs), supported by a basal lamina embedded by astrocyte projections and pericytes and sparsely interconnected by neuronal endings and microglia [96], which is important for maintaining CNS surveillance and homeostasis [97]. With the evolution of brain tumors, the blood-tumor barrier (BTB) displays integrity loss, resulting in leakiness, particularly in the high-grade brain tumor (GBM) [98]. However, different types of gliomas and even different regions of the tumor show heterogeneous permeability. WNT-activated medulloblastoma (MB) induces an aberrant and extensively fenestrated vasculature that allows the accumulation of high levels of chemotherapeutic agents in the brain, showing the best response to treatment, whereas SHH MB presents an intact BBB with poor treatment effect [99]. The hypoxic center of the glioma shows a higher degree of BTB leakage than that of the marginal area [100]

Compared to the BBB, the BTB's structural changes generally include astrocyte endfeet displacement, neurovascular decoupling, altered pericyte populations, loss of EC tight junctions and changed transcytosis mechanisms, but the BTB retains the critical expression of active efflux transporters such as ATP-binding cassette transporters in ECs and cancer cells [97,101]. Besides, the BTB shows distinct fenestration of endothelium and basal membrane [100]. Notably, pericyte coverage is negatively correlated with the prognosis of GBM patients, and targeting GSC-derived pericytes selectively disrupts the BTB, impairs BTB TJs, and increases vascular permeability to specifically enhance drug delivery to the tumor site [102]. The loss of BTB integrity is mainly provoked by the upregulation of VEGF through hypoxia-inducible factor-1α (HIF-1α). VEGF induces the permeability of blood vessels, and disrupts the expression and distribution of aquaporin-4 (AQP4) in the astrocytic endfeet, causing extravascular edema and hypoxia [100]. However, high doses of anti-angiogenic drugs may reduce BTB permeability, which may interfere with the delivery of other therapies [103, 104]. Thus, it is a challenge to balance the dose of anti-angiogenic therapy.

In addition to increasing the accumulation of drugs in tumor foci, leaky BTB is also conducive to the infiltration of monocytic and lymphocytic cells, which may help the presentation of tumor-associated antigens [97,105]. Thus, one of the key points of treatment is to enhance BTB permeability. We look forward to the therapeutic benefits of new medical technologies, such as nano-pharmaceuticals and ultrasonic targeted microbubble destruction (UTMD) technology.

Angiogenesis

Angiogenesis is the growth of new capillaries from preexisting blood vessels and is mediated by many angiogenic factors, including HIF-1α, VEGF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), TGF-β, MMPs, and angiopoietins (Angs) [106]. Exosomes with miRNA-9 and miRNA-26a from glioma cells can be absorbed by vascular ECs, leading to an increase in angiogenesis [107,108]. Besides, induced by TGF-β, pericytes generated from GSCs support vessel function and tumor growth [109].

Compared with LGGs, high tumor vascularity is a hallmark of GBM where the vascular network is disorganized and displays a high degree of microvascular proliferation [110]. IDH^{mut} tumors show low VEGF expression compared with IDH^{wt} in GBM [111]. High expression of the microtubule-associated protein TAU (MAPT) in IDH^{mut} tumors impairs the processes of angiogenesis and neovascularization through the stabilization of microtubules, favoring normalization of the glioma vasculature [112].

The tumor vasculature supports the growth of cancer cells, but its aberrant structure often results in high interstitial fluid pressure, edema, hypoxia, and necrosis [113]. The use of antiangiogenic drugs inhibits the formation of complex vascular networks in tumors, makes their structure and blood flow resemble those of normal tissues more closely, and improves the supply of nutrients and oxygen, partly restoring the immune response and their sensitivity to chemotherapeutic drugs [114]. Bevacizumab against VEGFA has an inhibitory effect on tumor neovascularization. For glioma patients, especially those with a large edema range, bevacizumab improves progression-free survival and maintains the baseline quality of life and performance but does not improve the overall survival time [115-117].

Vessel cooption is a non-angiogenic mechanism of tumor vascularization, which means that cancer cells utilize preexisting blood vessels instead of creating new blood vessels. This has been extensively demonstrated in brain metastases arising from melanoma, lung cancer, and breast cancer [118-121]. Vessel cooption is an intrinsic feature of or an adaptive ability of cancers to resist angiogenesis inhibitors, such as bevacizumab [122]. Besides, vasculogenic mimicry (VM) is another way that glioma improves brain blood supply, which mainly forms vascular-like channels independent of ECs and can be enhanced by TGF-β1 from astrocytes [123]. The "EC-like cells" are incompletely differentiated from GSCs, which can be induced by tenascin-C [124-127]. VM is thought to be the major blood supply in the early stages and tumor cells lining the wall of VM vessels are replaced by endothelium as the tumor progresses [128]. These mechanisms provide new perspectives on inhibiting the tumor angiogenesis.

Lymphatic vessels

The lymphatic system is not only essential for maintaining fluid balance and internal homeostasis, but also plays an important role in immune surveillance. It was once widely believed that the brain lacked a lymphatic vessel system, so it was considered as a "immune privileged" organ. However, in 2015, the structure of meningeal lymphatic vessels (MLVs) was discovered in the outermost layer of the mouse's meningeal membrane, the dura mater. It is confirmed that these circuits can directly drain cerebrospinal fluid (CSF) to the peripheral deep cervical lymph nodes (DCLNs) [129,130]. Moreover, vascular endothelial growth factor-C (VEGF-C) and VEGFR3 are shown to be critical for the plasticity and regenerative potential of MLVs [131]. Subsequently, human and nonhuman primate meninges harboring lymphatic vessels were discovered by MRI [132] and immunohistochemical staining of human skull specimens showed that lymphatic vessels from within the skull passes through the dura mater around the jugular foramen and connects to the deep cervical lymphatic network [133].

The discovery of MLVs has led researchers to actively explore the regulatory relationship between the brain tumor and MLVs. In 2020, two teams found that in mouse models, MLVs increase the anti-tumor immune response by promoting the migration of immune cells, improving the efficacy of anti-PD-1/CTLA-4 combined immunotherapy [134,135]. Besides, overexpression of VEGF-C enhances meningeal lymphangiogenesis, facilitating DC drainage to DCLNs, thereby exerting an antitumor effect [134,135]. Recently, Zhou et al. demonstrated the positive role of MLVs in radiotherapy-modulated anti-tumor immunity and highlighted the potential of VEGF-C-mRNA in combination with radiotherapy for the treatment of brain tumors [28].

However, at present, the relevant research on the functions of MLVs is mostly limited to animal experiments and lacks clinical trial data. A lot of work is needed to explore the role and mechanism of MLVs in glioma.

Extracellular matrix (ECM)

Different from the ECM of other organs, the ECM in brain tissue only accounts for about 20% of the brain and it has the unique composition: glycosaminoglycans (GAGs) such as hyaluronic acid (HA, hyaluronan), proteoglycans such as chondroitin sulfate proteoglycan (CSPG) and glycoproteins without collagens [136]. Brain tumor ECM shares common components as brain tissue ECM, but glioma cells would overexpress some ECM components, such as HA, tenascin-C and fibronectin as well as specific integrins and other receptors interacting with ECM components [137]. In addition to providing structural and mechanical support and protection for cells, the ECM provides appropriate chemical and mechanical signaling, regulating cell proliferation and survival, cell fate determination, cell migration and invasion, and tissue morphogenesis [138]. Besides, macromolecules such as glycosaminoglycans can store heparin-binding angiogenic growth factors that can be released locally by heparinase [139]. Thus, the growth and metastasis of glioma are inextricably linked to ECM.

The overexpression of HA, tenascin-C, fibronectin, and brevican drives ECM stiffness, but the rising presence of MMPs can erode ECM stiffness by matrix protein degradation [140]. The greater the stiffness of the ECM, the higher the malignancy of glioma, and IDH^{mut} glioma presents decreased TNC expression, ECM stiffness, and mechano-signaling [141]. During the progression of glioma, abnormal mechanical hardness of tumor tissue triggers prominent PIEZO1-dependent currents, activating integrin-FAK signaling and causing increased tissue stiffness. In turn, a stiffer microenvironment elevates PIEZO1 expression, promoting the aggressiveness of glioma [142].

The excessive deposition of ECM components reshapes a stiff ECM, preventing drugs from reaching the lesion, and rich ECM components will interact with the binding proteins of glioma cells, promoting the development of glioma. The highly expressed membrane protein molecules CD44 and RHAMM in glioma cells interact with HA overexpressed in the ECM, mediating the proliferation, migration and invasion of tumor cell [143]. Besides, the elevated CD151 and α3β1 integrin interact with laminins, which work synergistically with EGFR-dependent signaling pathways to accelerate tumor cell motility and invasiveness [144].

In short, ECM alteration is critical for driving glioma progression and its invasiveness. In the future, it can be seen that many inhibitors will be screened out via the tumor models based on hydrogels.

Metabolism

The metabolic pathways of glioma cells are abnormally activated or reprogrammed through direct or indirect mutagenic effects, giving glioma cells malignant biological characteristics.

As one of the signs of tumorigenesis, IDH^{mut} is an independent prognostic factor for glioma and heralds a better survival [145,146]. IDH mutant results in the conversion of proteins from α-ketoglutaric acid (α-KG) to 2-hydroxyglutarate (2-HG) and contributes to genome-wide histone and DNA methylation alterations [147,148]. IDH^{mut} significantly upregulates HIF-1α expression that helps glioma tumorigenesis [149]. In addition, the effect of IDH^{mut} on the immune microenvironment of glioma is complicated [150]. A study demonstrated that there are significantly fewer TAMs in IDH^{mut} GBMs, but they are more pro-inflammatory [151]. However, another study showed that IDH^{mut} glioma exhibits a more immunosuppressive phenotype than IDH^{wt} glioma [152]. Compared to IDH^{wt} tumors, IDH^{mut} glioma shows a major reduction of Tregs, which may be related to the concomitant dearth of pro-inflammatory cells [153]. Besides, the infiltration of NK cells in IDH^{mut} glioma is higher than that of IDH^{wt} and IDH mutant promotes the recruitment of NK cells through CX3CL1/CX3CR1 chemotaxis [154]. Counterintuitively, IDH^{mut} in LGG suppresses the accumulation of $CD4^+$T cells and $CD8^+$T cells in tumor sites [153,155]. Tumor cell-derived R-2-HG is taken up by T cells where it can induce a perturbation of nuclear factor of activated T cells transcriptional activity and polyamine biosynthesis, resulting in suppression of T cell activity [156].

Glioma cells often metabolize glucose into lactate to enable cancer cells to use glucose-derived carbons for the synthesis of essential cellular components, while still generating sufficient ATP [157], leading to a metabolite-depleted, hypoxic, and acidic TME [158], which places infiltrating effector T cells in competition with the tumor for metabolites and renders them functionally impaired [159]. In GBM, glycolytic rate-limiting enzyme hexokinase 2 and phosphofructokinase 1 platelet isoform are upregulated, enhancing lactate production and promoting tumor growth [160,161]. Tregs are able to maintain their tumor-suppressive identity by using lactate as fuel [162]. In addition, lactate induces TAM polarization into M2 phenotype as well as the increase of Arg1 and VEGF expression of TAMs, which is mediated by HIF1α [163]. Due to the enhanced glycolytic activity of cancer cells and hypoxia in the TME, carbonic anhydrase IX (CAIX), which maintains intracellular pH, is highly expressed in GBM [164,165]. A study showed that anti-CAIX CAR T treatment is a promising strategy to treat GBM [166].

Fatty acid oxidation (FAO), another energy-producing pathway, is also critical for the proliferation of glioma cells [167]. Carnitine palmitoylotransferase 1 (CPT1), as well as high-affinity carnitine transporter SLC22A5, affects the FAO rate, mediating glioma cell survival [168] .

For amino acid metabolism, glutamine is a nitrogen and carbon source for the biosynthesis of nucleotides and amino acids,

which is indispensable for glioma growth [157,169]. When glioma cells are starved of glutamine, the conversion of glutamate into glutamine via upregulation of the enzyme glutamine synthetase is promoted [157]. Glutamine blockade in tumor-bearing mice suppresses the oxidative and glycolytic metabolism of cancer cells, accompanied by effector T cells with activated phenotype [170]. Besides, tryptophan catabolic route closely affects tumor development. Gliomas enhance cell motility by highly expressing IDO1, tryptophan-2,3-dioxgenase (TDO2) and interleukin-4-induced-1 (IL4I1), leveraging tryptophan catabolite (indole metabolites and kynurenic acid)-mediated aryl hydrocarbon receptor (AHR) activation [171]. AHR activation in TAMs drives their recruitment via overexpressing CCL2, suppresses NF-κB activation, and increases their expression of the ectonucleotidase CD39 that prompts $CD8^+$T cell dysfunction by producing adenosine in cooperation with CD73, which can be intensified by 2-HG and kynurenic from glioma [152,172].

Cancer cells can increase the rate of autophagy to maximize their energy gains when they feel stressed in the TME [169, 173]. Autophagy, the recycling of metabolic organelles, generally helps to meet the energy demands of cancer cells [174,175]. The nuclear hormone receptors REV-ERBα and REV-ERBβ are responsible for the synthesis of lipids and autophagy, controlling cellular energy metabolism [176]. REV-ERB agonists impair the GBM growth *in vivo* and improve the survival without causing overt toxicity in mice by blocking energy access [177].

In summary, gliomas abnormally activate multiple metabolic pathways, which may compensate each other to meet metabolic requirements for energy. Therefore, for treating energy metabolism disorders, it is necessary to find out the key targets or choose the method of multi-target inhibition. Given the impact of metabolism on the immune microenvironment, treatment of targeted tumor metabolism combined with immunotherapy is also a good choice.

Conclusion

We discuss recent advances in the research on the brain TME and related treatment strategies. The interaction between tumor and various elements in the TME deeply affects the initiation and development of tumor, local drug resistance, and immune escape. Intercellular communications, including secretory factors, EVs, direct contact and cell metabolism, strongly shaping an immunosuppressive TME. Adaptive immunity, including exposure of tumor antigens, antigen presentation by APCs, and activation of sufficient numbers of infiltrating T cells to kill tumor cells, plays an irreplaceable role in tumor suppression, and the meningeal lymphatic vessels as well as normal drainage are necessary for this process.

Though many studies of the TME have provided many therapeutic targets, many clinical trials failed due to significant intertumoral and intratumoral genetic instability and resultant heterogeneity, which generates diverse aberrant signaling pathways within and across tumors [178]. This forces scientists to develop new treatment strategies, such as tumor-treating fields (TTFields), multitarget therapy, and combination therapy. Clinical data have shown that patients can gain benefits from TTFields, a physical method affecting cancer cell mitosis by electric currents [179]. Regorafenib is an oral multifunctional inhibitor of angiogenic, stromal, and oncogenic receptor tyrosine kinases. The phase II clinical trial REGOMA shows an encouragingly beneficial effect of regorafenib on overall survival time in rGBM patients, and it is currently being tested in a phase III clinical trial [180]. Clinical trials of multi-peptide vaccines aimed at multiple glioma antigens have also been investigated. However, a phase III trial of personalized peptide vaccination for $HLA\text{-}A24^+$ rGBM met neither the primary nor the secondary endpoints [181].

Although current treatment approaches involving immunotherapy are often ineffective, some specific patients can benefit from them. A subgroup of patients with GBM with *MGMT* promoter methylation and no baseline corticosteroid dependence may be most likely to benefit from PD-1/PD-L1 immune checkpoint inhibitors [44]. Hence, it is beneficial to accurately identify the molecular subtypes of patients' pathological tissues. Besides, future studies to increase the local drug concentration, through local injection or nanoparticle delivery, are necessary.

In conclusion, our dissection of the TME in glioma has provided potential therapeutic targets from multiple perspectives, but the huge gap between fundamental research and clinical application needs to be bridged.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Authors' contributions

The work presented here was carried out in collaboration

among all authors. H. S. and A. T. conceived and designed the review; A. T. wrote the paper; J. L. and Y. M.helped with literature searching and summarizing. All authors read, commented on, and approved this manuscript.

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