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Targeting stromal cells in tumor microenvironment as a novel treatment strategy for glioma

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Abstract

Glioma is the most common primary malignant tumor of the central nervous system in adults, characterized by high mortality, low cure rate and high recurrence rate. Among gliomas, glioblastoma multiforme (GBM) is the most malignant subtype. Currently, the standard treatment for patients with GBM is maximum surgical excision combined with radiotherapy and chemotherapy. But only a small percentage of patients benefit from this standard treatment. The tumor microenvironment plays an important role in the occurrence and development of most tumors. It is primarily composed of tumor cells, peripheral blood vessels, extracellular matrix, signaling molecules, stromal cells, and immune cells. The role of stromal cells in GBM has emerged as the focus of current research. The interaction among tumor, stromal, and immune cells within the tumor microenvironment can influence tumor development. Traditional research and drug therapy in glioma mainly focus on the tumor cells themselves, but recent studies have found that targeting stromal cells in the tumor microenvironment can also modulate tumor progression in GBM. Here, we review the influence of stromal cells in the tumor microenvironment of GBM on tumor cells and its related mechanism, as well as related molecular targets and signaling pathways, providing new ideas for the treatment and prognosis of GBM.

Keywords Stromal cell, Glioblastoma, Tumor microenvironment, Targeted therapy

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Introduction

Glioma, also known as neuroepithelial tumor, is the most common primary intracranial malignant tumor in adults, accounting for approximately 40–50% of intracranial tumors. It is characterized by a high disability rate and a high recurrence rate, and its five-year mortality rate is second only to pancreatic cancer and lung cancer [1]. The grade of glioma is determined by pathologic examination of the most malignant portion. Glioblastoma multiforme (GBM) is classified as a type of World Health Organization (WHO) grade IV glioma, which is the most malignant type of glioma. With advancements in molecular diagnosis, GBM is now categorized into isocitrate dehydrogenase (IDH) wild type and IDH mutant type according to the 2016 WHO classification of neurological neoplasms [2]. IDH wild type GBM is the most malignant astrocyte tumor, consisting of poorly differentiated neoplastic astrocytes. In the tumor tissue, their cell density is high, with obvious nuclear atypia and frequent mitotic images, with a large number of pathological mitotic images, obvious microvascular hyperplasia, and necrosis. These tumors account for 90% of all GBMs, with the other 10% being of the IDH mutant type, whose molecular characteristics are characterized by the presence of IDH1 or IDH2 gene mutations in the tumor cells. Currently, the standard treatment for GBM is maximum safe surgical excision and a postoperative combination of radiotherapy and chemotherapy [3]. However, with standard treatment, the median survival of GBM patients is only 14.6 months. Immunotherapy represents a new treatment approach for this disease, and immunotherapeutic methods that have been proven to have a beneficial effect on glioma include programmed cell death protein 1/ programmed death-ligand 1 (PD-1/PD-L1) therapy [4] and chimeric antigen receptor T-cell (CAR-T) therapy [5]. However, not all patients respond to immunotherapy, and responses vary among individuals. This implies that improving the efficacy of current treatment regimens and discovering novel treatments for GBM should be the focus of current research.

Tumor microenvironment (TME) refers to the internal and external environment in which tumor cells occur, grow, and metastasize. TME includes the structure, function, and metabolism of the tumor tissue, and an improved understanding of the microenvironment could be of substantial clinical benefit for tumor prevention and treatment. The tumor microenvironment is very complex, but it can be divided into four components: (1) immune cells; (2) stromal cells; (3) extracellular matrix (ECM), and other secretory molecules; (4) blood and lymphatic vascular network [6]. Stromal cells have an important impact on the occurrence and development of glioma and the construction of glioma microenvironment. The stromal cells in the glioma microenvironment are mainly composed of neurons, neuroglial cells, vascular endothelial cells and pericytes. In the TME of glioma, these stromal cells are involved in regulating processes such as tumor proliferation, invasion, angiogenesis, and immune response [7]. Neurons and neuroglial cells can secrete a variety of cytokines and chemicals, which directly or indirectly affect the growth and invasion of glioma by interacting with glioma cells [8]. Vascular endothelial cells and pericytes can promote angiogenesis in glioma and provide sufficient blood supply for glioma [9]. In addition, these stromal cells interact with glioma cells to build a complex intercellular interaction network in the glioma microenvironment, and participate in regulating the biological behavior of glioma cells and the characteristics of TME by secreting cytokines, chemicals and regulating related signal pathways. Given that stromal cells can play an important role in the proliferation, drug resistance, and other aspects of glioma, targeting stromal cells within the TME of glioma is expected to become a future treatment method for glioma [10]. At present, there are few drugs targeting stromal cells, and some studies only mention molecules or molecular pathways that can serve as targets. Therefore, this article aims to provide a review of potential targets that may affect stromal cells and summarize the existing therapeutic drugs targeting stromal cells, which can provide new ideas for improving the therapeutic effect of glioma.

Targeting neurons in TME of glioma

Neurons secrete cytokines to promote proliferation of glioma cells

Research has indicated that neurons can promote the proliferation of glioma cells by releasing cytokines and growth factors. These factors can activate the expression of genes related to cell proliferation through various signaling pathways, thereby promoting the proliferation and survival of tumor cells. Neurotrophic factors are a class of molecular signaling substances that play a crucial role in the development, growth, and repair of the nervous system. Studies have shown that neurons can secrete various neurotrophic factors to promote the proliferation of glioma cells. Nerve growth factor (NGF), typically released by neurons, serves to promote the survival and development of cells within the nervous system. In the microenvironment of gliomas, NGF released by neurons can bind to NGF receptors on the membrane of glioma cells, thereby activating downstream signaling pathways such as Rat sarcoma-mitogen-activated protein kinase (RAS-MAPK) and phosphatidylinositol 3-kinase – protein kinase B (PI3K-AKT) (Fig. 1). The activation of the RAS-MAPK pathway ultimately promotes the proliferation, survival, and enhanced transcriptional activity of glioma

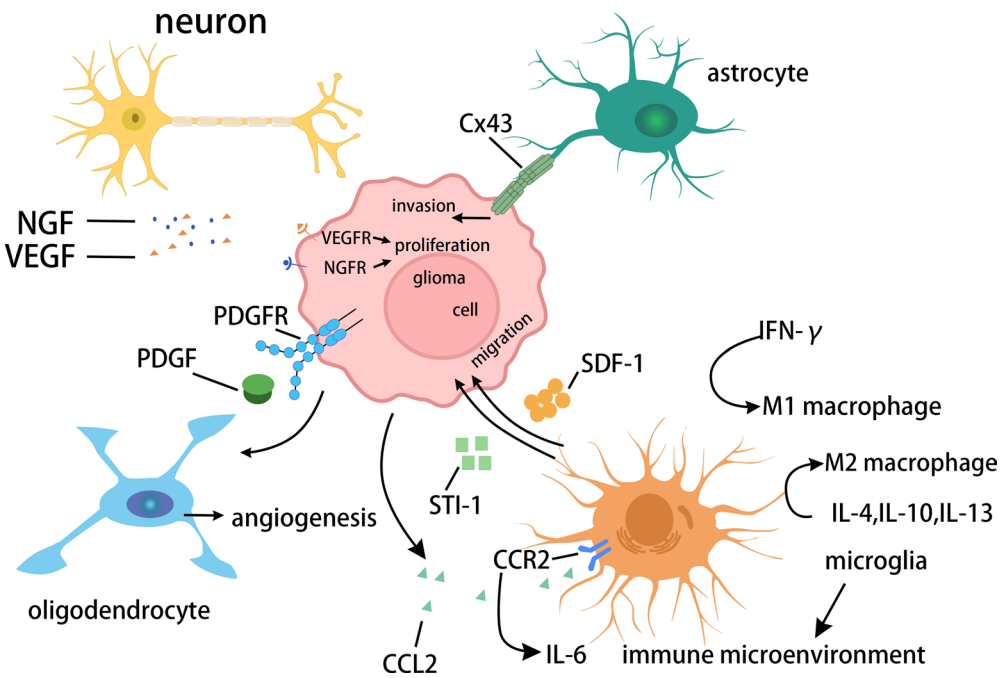


Fig. 1 The role of neurons and neuroglia cells in glioma microenvironment and its possible target. (1) Neurons can promote proliferation of glioma cells through secreting NGF and VEGF. (2) Astrocytes can promote invasion of glioma cells within the interconnection. (3) Oligodendrocytes can affect angiogenesis by PDGF/PDGFR signal. (4) Microglia can influence the formation of glioma immune microenvironment

cells. On the other hand, activation of the PI3K-AKT pathway can stimulate cell cycle progression by regulating proliferative factors and inhibiting apoptosis-related factors, thereby increasing the proliferation of glioma cells [11]. Vascular endothelial growth factor (VEGF) is a type of cytokine that promotes angiogenesis, stimulating the formation of new blood vessels. In the development of glioma, VEGF released by neurons can enhance tumor angiogenesis, providing an ample blood supply and nutrients for the glioma. [12] (Fig. 1). Interleukin-6 (IL-6) is a cytokine that participates in various inflammatory responses and immune regulatory processes. Studies have found that in glioma, IL-6 released by neurons can promote tumor cell proliferation and metastatic capability [13].

Neurons can enhance the invasive ability of glioma cells

Neurons can also influence the invasive and migratory capabilities of glioma cells. Researches have shown that there is interaction between neuronal cells and glioma cells. Through the interaction of cell adhesion molecules and extracellular matrix molecules, neuronal cells can, to some extent, promote the infiltration and migration of glioma cells into surrounding tissues. Additionally, neurons can affect the blood supply and nutrient provision to glioma. The microenvironment formed between neurons and glioma cells can regulate angiogenesis and vascular permeability, thereby providing sufficient blood supply and nutrients to sustain the growth and development of the tumor [14]. It should be noted that gliomas may exhibit variations among different individuals, and the sensitivity and response of neurons to glioma cells can be various. Therefore, further research and exploration are needed to elucidate the specific mechanisms by which neurons interact with glioma cells.

Targeted therapy against neurons in glioma

Research on drugs targeting neurons to inhibit the proliferation of glioma cells is still under exploration, and there are no widely applied specific drugs currently. However, several chemical compounds are under investigation and believed to have the potential to inhibit glioma cell proliferation by targeting neurons. NGF is a crucial factor for the growth and survival of glioma cells, so inhibiting the signaling pathways associated with NGF and its receptors may help slow down the proliferation of glioma cells. Some NGF receptor inhibitors, such as TrkA inhibitors, have shown certain anti-tumor activity in early studies. TrkA is a subtype of the NGF receptor, and inhibitors targeting TrkA can block the effect of NGF on neurons, indirectly affecting the growth and survival of glioma cells. Currently, some drugs targeting TrkA are undergoing clinical trials to evaluate their potential therapeutic effects on gliomas. LOXO-101

(Larotrectinib) is an orally administered small molecule compound and the first drug approved by the FDA for the treatment of tumors with Trk gene fusions, including certain neurotrophic tumors, soft tissue sarcomas, and other solid tumors. Clinical trial results indicate that approximately 80% of patients with Trk gene fusion-positive solid tumors respond to Larotrectinib treatment [15]. SC-514 is a selective inhibitor of I kappa B kinase 2 (IKK-2). In the glioma microenvironment, SC-514 can suppress neuronal secretion of IL-6, thereby inhibiting tumor angiogenesis of glioma within the environmentttt [16]. Additionally, some studies have suggested that specific neurotransmitter receptors play a crucial role in the proliferation of glioma cells. Therefore, inhibitors targeting these receptors may have the potential to suppress the proliferation of glioma cells. For example, drugs targeting glutamate receptors and acetylcholine receptors are currently under investigation in clinical trials. Hence, in the future, treating gliomas may involve targeting neurotransmitter receptors or interactions between factors secreted by neurons and glioma cells (Table 1).

Targeting neuroglial cells in TME of glioma

Astrocytes participate in the proliferation process of glioma cells

Astrocytes are the most common type of glial cells in the central nervous system and constitute the largest volume of glial cells. These star-shaped glial cells extend numerous long, branching processes from their cell bodies, filling the spaces between the cell bodies and processes of neurons, thereby providing supportive and segregating functions for nerve cells. Research indicates that astrocytes play a significant role in the development of gliomas. They provide crucial structural support to gliomas by forming elongated processes that interconnect with glioma cells, constructing a complex network between tumor cells and normal cells, thus providing structural support to gliomas. Astrocytes establish intercellular connections with glioma cells through gap junctions and paracrine signaling. In this process, astrocytes become activated into a reactive phenotype, accompanied by an increase in the expression of proteins such as glial fibrillary acidic protein (GFAP) and matrix metalloproteinase-2 (MMP-2), thereby promoting the migration and invasive capabilities of glioma cells [17]. The characteristic feature of reactive astrocytes in the peritumoral region of gliomas is the upregulation of Connexin 43 (Cx43). This upregulation is crucial for establishing contacts between glioma cells and reactive astrocytes and plays a significant role in promoting the invasion of glioma cells. [18]. To investigate the role of gap junctions between astrocytes and glioma cells in glioma development, researchers employed small interfering RNA (siRNA) to suppress the expression of Cx43 and used 18-α-glycyrrhetinic acid to block gap junctions. They also created gap junction-deficient glioma cells by knocking down Cx43 (Fig. 1). The results revealed that gap junctions between glioma cells inhibited the invasiveness of glioma cells. On the other hand, gap junctions between astrocytes and glioma cells, as well as between astrocytes themselves, promoted tumor expansion [19].

There is also an interaction in energy metabolism between astrocytes and glioma cells. The growth and invasion of gliomas have been shown to rely on the induction of glutamate production and glutamate-dependent motility enhancement. Astrocytes are believed to be metabolically connected with glioma cells, particularly through the establishment of an L-glutamine (Gln)—L-glutamate (Glu) metabolic pool. Researchers have found that glutaminase is highly produced in glioma cells, efficiently converting Gln into Glu, and engaging in an exchange with glioma cells to promote their proliferation [20]. In addition, astrocytes also participate in glioma-related angiogenesis. Experimental results indicate that astrocytes promote the formation of vascular-like structures within glioma, and specific microRNAs such as miR-15b targeting neuropilin 2 (NRP-2) and miR-152 targeting MMP-3 regulate angiogenesis and invasion in glioma cells. In glioma cells, the production of NRP-2 and MMP-3 is negatively correlated with miR-15b and miR-152. In a co-culture system of astrocytes and glioma cells, the expression of miR-15b and miR-152 in astrocytes is upregulated, resulting in the downregulation of NRP-2 and MMP-3 and significantly enhancing the invasiveness of glioma cells [21]. Not only that, but during the development of glioma, astrocytes also participated in immune response regulation. They can release inflammatory mediators and cytokines, attracting and activating other immune cells, and modulate the degree of inflammation, participating in the immune anti-stress response of glioma.

Oligodendrocytes participate in the formation of abnormal blood vessels in glioma

Oligodendrocytes, also known as oligodendroglia, are distributed in the central nervous system. They are smaller than astrocytes, with shorter and fewer processes. The cell nucleus is round, small, and dense, with high cytoplasmic electron density observed under electron microscopy, mainly containing mitochondria, nuclear bodies, and microtubules. In the gray matter, oligodendrocytes are mainly found near the cell bodies of neurons, while in the white matter, they are aligned between myelinated nerve fibers and contribute to the formation of myelin sheaths. In tissue cultures, oligodendrocytes are observed to be actively moving. In the

Table 1 Drugs targeting the regulation of stromal cells in TME of glioma

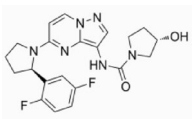
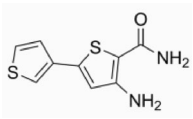
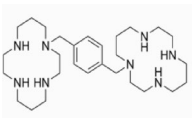
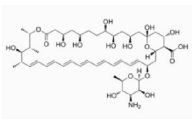
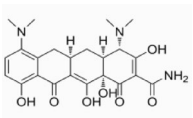
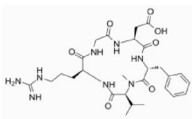
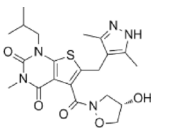
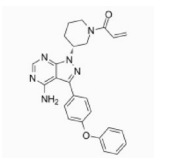
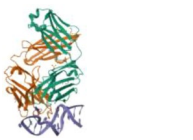
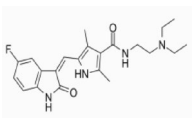
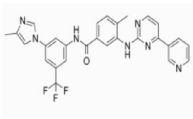
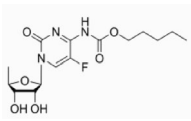
Drug name	Pharmaceutical structure	Drug type	Pharmaceutical affection	Target cell
LOXO-101 [15]		TrkA inhibitor	Inhibit the neurotrophic factor NGF, secreted by neurons, and impede the proliferative effects on glioma cells	Neuron
SC-514 [16]		IKK-2 inhibitor	Inhibit the secretion of IL-6 by neurons to suppress tumor angiogenesis within the glioma microenvironment	Neuron
AMD-3100 [37]		CXCR4 inhibitor	Inhibiting the combination of SDF-1 secreted by microglia and its receptor CXCR4, thereby inhibiting the proliferation and angiogenesis of glioma cells, and increasing the killing effect of radiotherapy on glioma cells	Microglia
Amphotericin B [39]		Antibiotic	Enhance the effect of microglia on cell cycle growth arrest and differentiation of BTIC and interfere with the activation process of microglia	Microglia
Minocycline [40]				
IFN-β [54]		Interferon family	Downregulation of VEGF/VEGFR expression levels in glioma cells and vascular endothelial cells, upregulation of IP-10 expression levels in various cells, inhibition of primary tumor derived angiogenesis activity, and reduction of neovascularization	VEC
Cilengitide [56]		Integrin inhibitor	Destroy the combination of Integrin and extracellular matrix, promote the apoptosis of vascular endothelial cells, inhibit proliferation, and promote the disintegration of cytoskeleton between vascular endothelial cells and glioma cells	VEC
AR-C155585 [57]		MCT1 inhibitor	Inhibiting the uptake of lactate from the extracellular matrix by vascular endothelial cells and glioma cells, thereby inhibiting neovascularization and tumor cell proliferation	VEC
Ibrutinib [70]		Tyrosine kinase inhibitor	Targeting pericyte in glioma, thus inhibiting the formation of BTB, increasing the penetration concentration of chemotherapy drugs in glioma tissue, and improving the efficacy of chemotherapy drugs	Pericyte
Bevacizumab [67]		VEGFR inhibitor	Inhibit the proliferation of vascular endothelial cells and pericyte, and reduce the angiogenesis process within the gliomas microenvironment	Pericyte
Sunitinib [67]				

Table 1 (continued)

Drug name	Pharmaceutical structure	Drug type	Pharmaceutical affection	Target cell
Nilotinib [71]		TGF-β signaling inhibitor	Influence the interaction between pericyte and vascular endothelial cells, and inhibit the formation of tumor neovascularization	Pericyte
Capecitabine [71]				

occurrence and development of glioma, oligodendrocytes play a certain role. Oligodendroglioma is a type of glioma with molecular characteristics such as IDH mutation and chromosome 1p/19q co-deletion. Oligodendrogliomas originate from oligodendrocytes. The incidence of oligodendrogliomas is lower than that of astrocytomas and glioblastomas, but their prognosis is better than the former two. Apart from the mentioned roles, oligodendrocytes also participate in the abnormal vascularization in gliomas. Researchers have found that gliomas are usually associated with enhanced platelet derived growth factor (PDGF) signaling, characterized by overexpression of PDGF-α receptor and PDGF-β ligand (Fig. 1). Activation of the PDGF pathway can recruit precursor cells of Olig261-positive oligodendrocytes and participate in the construction of abnormal vascular structures in gliomas [22]. Additionally, oligodendrocytes play a role in clearing extracellular toxic substances in gliomas. They have the ability to engulf and digest damaged cells and waste materials around the tumor, maintaining normal cellular energy metabolism and clearing metabolic by-products to sustain the homeostasis of tumor tissue. Oligodendrocytes also participate in immune regulation. They can modulate the activity of immune cells by releasing immune-regulatory molecules and participating in inflammatory responses. However, in gliomas, the immune-regulatory function of oligodendrocytes may be limited due to the complexity of the tumor microenvironment.

Microglia can regulate the immune microenvironment within glioma

Microglia are the only cell type in neural tissue that originates from the mesoderm. These cells possess small, rod-shaped cell bodies and extend several thin, ramified processes with a rough surface and visible spines. They have few branches. The nucleus is relatively small, approximately 5μm, and exhibits irregular morphology, such as kidney-shaped, oval, or triangular, with abundant chromatin. Microglia are characterized by multi-synaptic connections and plasticity, serving as intrinsic immune effector cells in the central nervous system. They play a crucial role in physiological processes within the central nervous system and are involved in the occurrence and development of glioma [23]. During the process of glioma development, microglia respond to pathological stimuli, such as the abnormal proliferation of tumor cells, by releasing inflammatory mediators like cytokines and chemokines. These inflammatory mediators can recruit and activate other immune cells, such as macrophages and T lymphocytes, to participate in the inflammatory process. The inflammatory response around the glioma can lead to local vascular dilation, increased vascular permeability, causing plasma proteins and immune cells to infiltrate into the tumor area. The infiltration and activation of immune cells generate more inflammatory mediators, forming a cyclical inflammatory response. This inflammatory reaction can stimulate the proliferation, invasion, and angiogenesis of glioma cells [24]. However, the impact of the inflammatory response on glioma is complex. It can have dual effects, both promoting and inhibiting tumor development. On one hand, cytokines and chemokines in the inflammatory environment can provide the nutrients and growth factors necessary for the growth and survival of tumor cells, promoting the proliferation and invasion of glioma cells. On the other hand, the infiltration and activation of immune cells can also exert anti-tumor effects by killing tumor cells and regulating the tumor microenvironment to suppress tumor development. In low-grade glioma, the number of infiltrating microglia increases with the grade of the tumor and correlates with the patient's survival period. Microglia can secrete stromal-derived factor-1 (SDF-1), promoting the proliferation of glioma cells [25]. In high-grade glioma, microglia are more likely to be polarized into M1 or M2 macrophages, participating in the regulatory role within the immune microenvironment of glioma. When stimulated by IFN-γ and

Toll-like receptor 4 (TLR4), microglia can differentiate into M1-type macrophages, with mTOR or CSF-1 acting as inhibitory cytokines for the transformation of microglia into M1-type macrophages. M2 macrophages, on the other hand, are transformed from microglia activated by cytokines like IL-4, IL-10, and IL-13. In high-grade glioma, M1 macrophages can inhibit the proliferation of tumor cells, while M2 macrophages play a crucial role as promotive immune cells in the occurrence and development of glioma [26].

Microglia can secrete multiple cytokines to regulate the growth and migration of glioma cells. They synthesize and release stress inducible protein 1 (STI-1), a cell surface protein ligand that can enhance the proliferation and migration of glioma cells both in vitro and in vivo [27]. In addition, microglia can release epidermal growth factor (EGF), which stimulates the invasion of glioma cells. This glioma-promoting activity of microglia is triggered by CSF-1, which is released by tumor cells. CSF-1 acts as a chemotactic agent for microglia and transforms them into a pro-tumor phenotype [28]. Chemokine (C–C motif) ligand 2 (CCL2) is another cytokine released by gliomas that acts on microglia through its receptor, CCR2, expressed on microglia (Fig. 1). CCL2 can trigger the release of IL-6 from microglia, thereby promoting the invasiveness of glioma cells [29]. Transforming growth factor β (TGF-β) can facilitate the migration of glioma cells by upregulating the expression and function of integrin family members. In co-culture systems, TGF-β is predominantly released by microglia and induces the expression of MMP-2, resulting in the degradation of the extracellular matrix and promoting the invasiveness of glioma cells [30]. Active MMP-2 is generated by cleavage of pro-MMP2, and the substance responsible for this cleavage is membrane type 1-matrix metalloproteinase (MT1-MMP). Under normal conditions, microglia do not upregulate MT1-MMP expression. However, when exposed to glioma cells, they can upregulate MT1-MMP expression. Increased expression of MT1-MMP in microglia can enhance the growth rate of glioma cells and is positively correlated with increasing malignancy grades of glioma [31]. Microglia also have an impact on angiogenesis within the tumor, promoting intratumoral blood vessel formation through the receptor for advanced glycation end product (RAGE) signaling pathway [32].

Ependymal cells can influence the characteristics of glioma stem cells

In recent years, researches have indicated that the ependymal cells play a crucial role in the development of glioma. The choroid plexus is a specialized tissue covering the ventricles in the brain, comprising both choroid plexus epithelial cells and choroid plexus stromal cells. There exists a complex interaction between ependymal cells and glioma cells, influencing the occurrence, development, and treatment outcomes of tumors. Firstly, as a sanctuary for neural stem cells originating from the central nervous system, choroid plexus cells play a significant role in maintaining the stem cell component of glioma. Neural stem cells, possessing self-renewal and multipotent differentiation capabilities, continuously provide new sub-cells, further driving the growth and development of tumors. Ependymal cells serve as a potential source of neural stem cells, with some studies suggesting that these cells may undergo phenotypic transformation in glioma, acquiring characteristics of tumor stem cells. This implies that choroid plexus cells not only offer a potential source of neural stem cells for glioma but also, through transformation into tumor stem cells, directly participate in the developmental process of glioma [33]. Secondly, ependymal cells regulate the microenvironment of glioma, influencing the tumors' proliferation, invasion, and metastatic abilities. Ependymal cells create a special microenvironment around glioma, providing crucial support for the growth of tumor cells. Research has found that ependymal cells can secrete various growth factors, such as EGF and PDGF. These factors can stimulate the proliferation and invasion of glioma cells, as well as promote angiogenesis, providing ample oxygen and nutrients for the tumor. In addition, ependymal cells can also attract the migration of vascular endothelial cells and immune cells through the release of chemotactic factors, leading to the formation of an inflammatory response, further promoting the development of glioma [34]. Thirdly, ependymal cells in glioma may participate in the immune escape process of tumors. Immune escape is one of the important characteristics of tumor growth and development, which allows tumors to evade attacks from the immune system and protect the survival and proliferation of tumor cells. Ependymal cells can inhibit the activity of immune cells by releasing immune-suppressive factors such as TGF-β and IL-10, thereby causing immune cells to lose their killing effect on glioma. In addition, ependymal cells can also alter the expression of their surface molecules, further reducing the sensitivity of immune cells to glioma [35]. These findings indicate that ependymal cells in glioma not only promote the development of glioma through immunosuppressive effects but also reduce the cytotoxicity of immune cells, protecting the growth of glioma. Finally, the presence of ependymal cells is closely related to the development of glioma and has become a new target for glioma treatment. By studying the role of ependymal cells in glioma

development, new treatment strategies and targets can be identified. Some studies have already begun exploring how to inhibit the proliferation and transformation of ependymal cells in order to suppress glioma development. Moreover, by modulating the interaction between ependymal cells and gliomas, there is also the potential to develop novel immunotherapy strategies to enhance the treatment efficacy of glioma [36]. In summary, ependymal cells play a crucial role in the development of glioma. From providing tumor stem cells to regulating the glioma microenvironment, and even contributing to immune evasion and transformation, the interaction between ependymal cells and glioma is remarkably complex and diverse. Further research on the role of ependymal cells in glioma development will contribute to a better understanding of the pathogenesis of gliomas and provide novel insights and strategies for glioma treatment.

Targeted therapy against neuroglial cells in glioma

Currently, drugs targeting glioma cells for the treatment of gliomas are still in the stage of experimental research and clinical trials, with a particular focus on targeting astrocytes and microglia. One relatively new approach for glioma treatment involves recombinant technology. Germano and colleagues utilized recombinant technology to develop astrocytes expressing the recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Experimental results indicate that the recombinant astrocytes can effectively induce apoptosis in A172 human glioma cells [37]. As previously discussed, SDF-1 and its receptor CXCR4 constitute one of the targeted pathways through which microglia promote the proliferation and angiogenesis of glioma cells. AMD3100, a small-molecule inhibitor of CXCR4, have been shown in clinical trials to enhance the radiosensitivity of glioma cells. The combination of AMD3100 and radiotherapy can lead to more significant therapeutic effects. Another potential approach to target the regulation of glioma growth by microglia is by interfering with CSF-1 signal transduction. A study indicated that CSF-1 receptor inhibitors can improve the survival rate of glioma mice and reduce tumor volume [38]. Some antibiotics seem to also target glioma cells. Amphotericin B has been identified as a molecule that enhances the effect of glioma cells on the growth arrest and differentiation of brain tumor-initiating cells (BTIC) [39]. Minocycline is an antibiotic that interferes with the activation of microglia. At present, Minocycline is being included in the Phase I clinical trial by researchers to explore its effect as an adjuvant treatment for glioma [40]. In the future, more drugs targeting glial cells may be available and become an important means of adjuvant therapy for glioma (Table 1).

Targeting vascular endothelial cells in TME of glioma

Glioma cells promote proliferation of vascular endothelial cells

Vascular endothelial cells (VEC) are a prevalent type of stromal cells within the glioma microenvironment, comprising a significant proportion. They form the inner wall of the newly formed blood vessels in the tumor, playing a crucial role in regulating the occurrence, development, and metastasis of gliomas. VECs bind to their corresponding ligands by expressing angiotensin receptors and vascular endothelial growth factor receptors (VEGFR). This binding activates intracellular signaling pathways, promoting angiogenesis and providing an ample supply of nutrients for glioma cells [41]. The angiotensin receptors are G protein-coupled receptors with angiotensin as their ligand, forming a crucial part of the renin-angiotensin system. The main types of angiotensin receptors include angiotensin type 1 receptor (AT1R) and type 2 receptor (AT2R), in addition to type 3 and type 4 receptors. Angiotensin II (Ang II) is the primary ligand for AT1R and AT2R, formed through the conversion of angiotensinogen by angiotensin-converting enzyme (ACE). In the glioma microenvironment, ACE secreted by glioma cells catalyzes Ang into Ang II, which binds to AT1R and AT2R on VECs. Upon activation by Ang II on endothelial cells, AT1R and AT2R, coupled with G protein receptors such as protein kinase C (PKC), activate phospholipase C (PLC), leading to an increase in intracellular $Ca2+$ concentration. This ultimately promotes vasoconstriction, increases vascular permeability, and induces the growth, migration, and proliferation of VECs [42]. VECs undergo extensive proliferation, forming complex tumor neovessels within the glioma microenvironment, providing ample nutrients for glioma cells and promoting their proliferation. Moreover, glioma cells can also express AT1R, and upon binding with Ang II, multiple signaling pathways within the glioma cells, such as the phosphoinositide pathway, serine/threonine kinase pathway, and mitochondrial pathway, are fully activated, thereby promoting the growth and survival of glioma cells [43] (Fig. 2).

VEGF is also an important angiogenic factor that plays a crucial role in angiogenesis and endothelial cell function. During the development of glioma, VECs can express high levels of VEGFR and activate downstream signaling pathways by binding to VEGF, thereby promoting the progression of glioma [44]. Glioma cells can secrete a significant amount of VEGF, which circulates through the bloodstream to nearby VECs. VEGF binds

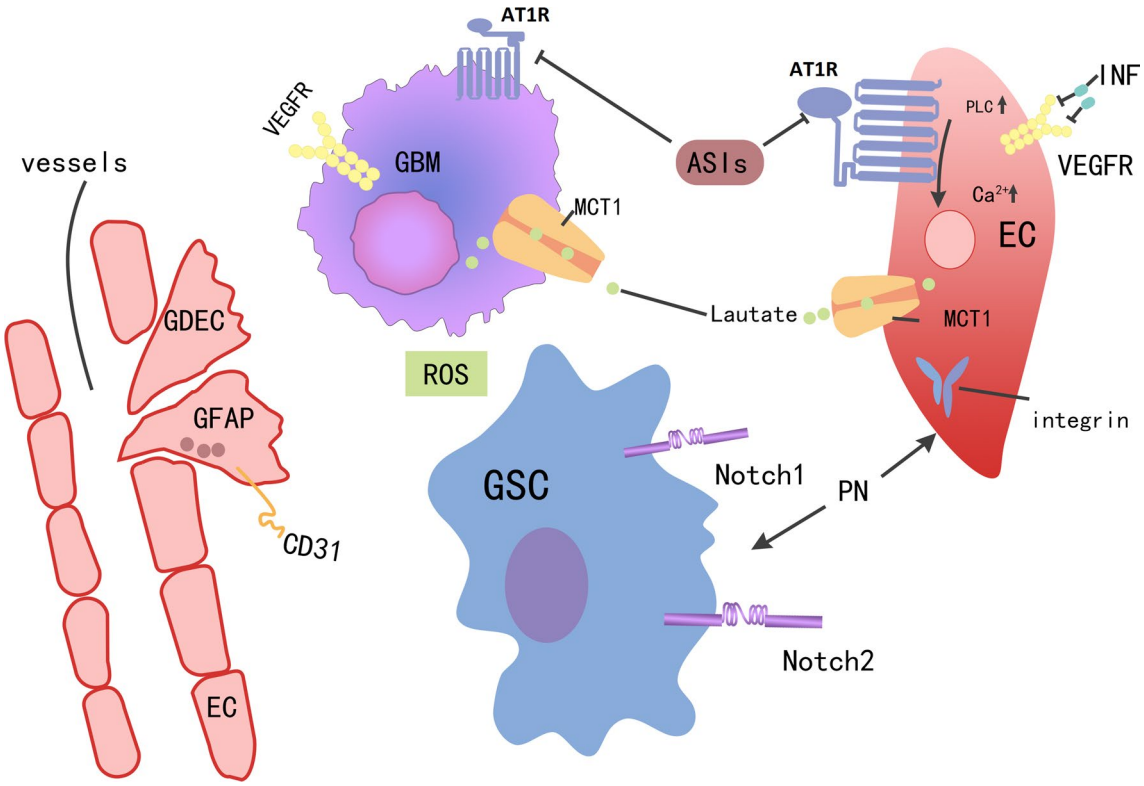


Fig. 2 The role of vascular endothelial cells in glioma microenvironment and its possible target. (1) Normal vascular endothelial cells can be transformed into GDEC and GFAP, and GFAP can express CD31. (2) The interaction of GSC-EC in PN was enhanced during radiation, suggesting that Notch1 on GSC was a therapeutic target. (3) MCT1 on GBM and EC is associated with lautate (4) ASIs can inhibit AT1R and VEGF receptors on endothelial cells. (5) AT1R activate PLC and increase the concentration of cytosolic Ca2+

to VEGFR on VECs, activating the corresponding signaling pathways. VEGFR primarily includes VEGFR-1 (also known as Flt-1) and VEGFR-2 (also known as Flk-1/KDR), with VECs expressing more VEGFR-2. When VEGF binds to VEGFR-2, downstream phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB/Akt) pathways are activated, promoting the growth, migration, and survival of endothelial cells. This leads to neovascularization, providing sufficient blood supply and nutrients for gliomas. Additionally, the binding of VEGF to VEGFR-2 can activate protein kinase A (PKA) and protein kinase C (PKC), causing an increase in vascular permeability in VECs, facilitating the penetration of plasma components into surrounding tissues. This process is known as vascular leakage, providing more nutrients and growth factors for glioma cells [45]. This process, known as vascular leakage, can provide more nutrients and growth factors for glioma cells.

Vascular endothelial cells regulate the growth of glioma cells

The cytoskeleton refers to the protein fiber network system in eukaryotic cells, composed of microtubules (MT), microfilaments (MF), and intermediate filaments (IF) [46]. Initially, researchers used formaldehyde fixation at room temperature before gradually realizing the objective existence of the cell cytoskeleton. The cytoskeleton is an essential structure in eukaryotic cells that helps maintain their basic shape. It is generally considered a type of organelle. The cytoskeleton contains various specific proteins, with integrin being one of the crucial proteins. Integrins, also known as integrin receptors, belong to the integrin protein family. They are a widespread type of protein found on the surface of vertebrate cells, relying on Ca^{2+} or Mg^{2+} to mediate the mutual recognition and adhesion between cells, as well as the interaction between cells and the extracellular matrix. Integrins play a role in connecting extracellular functions with intracellular structures [47]. Integrins are widely expressed in malignant glioma. Within the glioma microenvironment, integrin proteins maintain cell–cell connections between glioma cells and VECs, while playing an important role in maintaining the biological structure of endothelial cells (Fig. 2). Integrins mediate the interactions between VECs, surrounding cells, and the extracellular matrix by binding to the basement membrane and the extracellular matrix. In glioma,

integrins are involved in the interaction between VECs and tumor cells, influencing tumor growth, invasion, and metastasis. Integrin also participates in the regulation of VECs migration and angiogenesis. Under the activation of VEGF signaling pathway, integrin mediates the migration and adhesion of endothelial cells, thereby promoting neovascularization. In addition, the activation of integrin can regulate the permeability of endothelial cells. Its involvement can affect the infiltration of lymphocytes and leukocytes into the glioma tissue, which is important for the entry of nutrients and immune cells [48].

Between glioma cells and vascular endothelial cells, there is an important lactate shuttle mechanism. Monocarboxylate transporters (MCTs) play a crucial role in the communication between tumor cells and endothelial cells. MCT belong to the solute carrier transporter family, which consists of 14 members named as MCT 1–14. The MCT protein family consists of 12 transmembrane domains, with subtype-specific tissue distribution and substrate specificity. They are also involved in various physiological and pathological processes. Endothelial cells in blood vessels can produce lactate and transport it into surrounding glioma cells through MCT, thereby influencing the metabolic processes of glioma cells and promoting glioma development [49] (Fig. 2).

Glioma stem cells (GSC) are a population of cells resembling stem cells that exist within gliomas. They possess the ability to self-renew and differentiate into various types of tumor cells, thus playing a crucial role in the development and treatment of gliomas. Research has shown the existence of a local perivascular niche (PN) between GSCs and VECs, which plays an important role in glioma development [50]. PN provides an appropriate microenvironment for maintaining the stem cell state of GSCs. This is achieved through the provision of suitable extracellular matrix, signaling molecules, and supporting cells such as VECs. Within the PN, the signaling molecules released by VECs and other cells can inhibit the differentiation of GSCs, thereby maintaining their stem cell state. The PN provides abundant nutrients and oxygen in the development of glioma, which is achieved through the supply of nutrients and oxygen via blood vessels. GSCs obtain the necessary nutrients and oxygen in PN through interaction and communication with VECs and signaling molecules [51]. PN is also believed to play a crucial role in the invasion and metastasis of glioma cells. In PN, VECs and other cells secrete a series of signaling molecules that promote invasion and metastasis, such as MMP and intercellular adhesion molecules, facilitating the invasion and metastasis of glioma cells (Fig. 2). In conclusion, PN plays an important role in the development of glioma by maintaining the stem cell characteristics of GSCs, promoting GSC proliferation and survival, facilitating GSC invasion and metastasis, and influencing treatment outcomes [52]. In-depth research on PN is helpful in uncovering the pathogenesis of gliobma and providing a basis for the development of novel therapeutic strategies.

Targeted therapy against vascular endothelial cells

As previously discussed, the angiotensin system and vascular growth factor pathway are implicated in glioma development. Therefore, researchers have studied many targeted angiogenesis treatment options Angiotensin inhibitors (ASI) can specifically interfere with the function of the angiotensin system, thereby affecting the growth of glioma cells and the proliferation of vascular endothelial cells. MEDI3617, a neutralizing antibody of Ang II, has been shown to specifically neutralize Ang II within the glioma microenvironment, and reduce its active concentration, which inhibits the growth of GI162 glioma cells and increase the necrosis of U87 glioma cells, thereby effectively reducing the tumor load [53]. Interferon-β (IFN-β) is a type of endocrine interferon in the human body, belonging to the interferon family. Not only can IFN-β regulate immune response and resist viral infection, but it can also down regulate the VEGF pathway in glioma and upregulate the expression of interferon inducible protein 10 (IP-10) to inhibit angiogenesis in glioma. Researchers have found that IFN-β can down regulate the expression level of VEGF/VEGFR in glioma cells and VECs, and up regulate the expression level of IP-10 in a variety of cells, including keratinocyte, fibroblasts, endothelial cells, mononuclear phagocyte and tumor cells, so as to inhibit the activity of primary tumor derived angiogenesis and reduce the generation of new blood vessels [54]. Experimental data shows that IFN-β can inhibit the migration of endothelial Cell migration induced by glioma cells, inhibit the secretion of VEGF by glioma cells, and inhibit the expression of VEGFR and vascular density of glioma cells. Clinical data have shown that systemic administration of IFN-β Injection therapy can cause significant changes in tumor blood vessels within the glioma microenvironment, while significantly inhibiting glioma growth and reversing the microcirculation of glioma tissue to that of non-tumor brain tissue [55]. Jonas et al. created a cross antibody between Ang II and VEGF (A2V CrossMab) to target angiogenesis in the glioma microenvironment. CrossMab is an engineering antibody construction technique that achieves vertical cross assembly by modifying conventional double stranded antibody structures, resulting in the production of a new type of antibody molecule. CrossMab connects the C-terminal of one antibody heavy chain to the N-terminal of another antibody heavy chain, forming a new connection configuration. This cross linked structure

allows CrossMab to bind two different Epitope at the same time. Researchers have found that A2V CrossMab can significantly reduce tumor vascular density in the glioma Gl261 cell line, and may prolong the survival of glioma mice by reprogramming the glioma microenvironment [53].

Cytoskeleton plays an important role in maintaining the junction structure between vascular endothelial cells and glioma cells. Targeting integrin in cytoskeleton can effectively inhibit the development of glioma. Cilengitide, an integrin inhibitor, affects the construction of cytoskeleton by inhibiting the synthesis of integrin, thereby inhibiting the connection between glioma cells and VECs, and damaging the occurrence and development of tumors. Cilengitide has been shown to destroy the combination of integrin and extracellular matrix, promoting the apoptosis of VECs. At the same time, it can detach VECs from the cell Petri dish container wall, and inhibit the proliferation of VECs in a dose-dependent manner. In addition, it can also inhibit Integrin mediated signal transduction pathway, leading to the disintegration of cytoskeleton between VECs and glioma cells, further inhibiting the proliferation of glioma cells, and promoting apoptosis [56]. The clinical observation found that the combination of Cilengitide and Temozolomide could increase the inhibitory effect on glioma cells. Therefore, integrin inhibitors can be used in combination with other drugs to treat patients with glioma in the future. MCT1 also plays an important role in the intercellular connections between VECs and glioma cells. MCT1 can mediate metabolic reprogramming of vascular endothelial cells and promote angiogenesis. Therefore, targeting MCT1 may also be an effective treatment for glioma. Researchers found that the use of the MCT1 specific inhibitor AR-C155585 can effectively inhibit the uptake of lactic acid by VECs and glioma cells from the extracellular matrix, so as to inhibit angiogenesis and tumor cell proliferation [57] (Table 1).

Targeting pericytes in TME of glioma

Pericyte from different sources participate in the genesis and development of glioma

Endogenous pericytes

Pericytes are a type of vascular wall cells embedded in the basement membrane of blood vessels. They have specific local contact with VECs. As an essential component of tumor neovascularization, pericytes play an important role in the development, stability, maturation and remodeling of tumor blood vessels. In the TME, pericyte and VECs jointly act on tumor angiogenesis, with pericytes forming a scaffold in this process, enabling new VECs to form blood vessels and secrete factors that stabilize the new blood vessels [58]. Pericyte participate in the secretion of factors, stimulate the germination of endothelial tip in peripheral blood vessels, recruit vascular endothelial cells and help them to proliferate. When VECs recruit and form vascular structures, pericytes wrap endothelial cells in the glioma microenvironment, leading to the stability and maturation of tumor blood vessels [59]. Therefore, pericyte play an important role in supporting tumor blood vessels in the glioma microenvironment.

The characteristic membrane molecule of pericyte is platelet derived growth factor receptor (PDGFR), a tyrosine kinase receptor. After binding to PDGF, it activates a series of signal transduction pathways, eventually resulting in cell proliferation, differentiation or migration. More than half of the PDGFR-β positive pericytes in the glioma microenvironment are provided by the host nervous system. Researchers determined the activation site of endogenous pericytes through experiments and assessed the contribution of endogenous pericytes to the glioma neovascular system. The experimental results confirmed that endogenous pericytes are activated not only in the glioma microenvironment, but also in the brain tissue around the tumor. The endogenous pericytes infiltrating into the glioma microenvironment are mainly located in the tumor vessel wall. Concurrently, these pericytes can co express PDGFR-β and neuronal glial antigen 2 (NG2), suggesting that they originate from other nerve cells in the central nervous system (Fig. 3). This finding confirmed that endogenous pericytes were activated in a wide range of brain regions, and were recruited into glioma, and constituted the main part of the tumor pericytes group, participating in the formation of tumor blood vessels [60].

Pericytes derived from stem cells

There is evidence that some GSCs can differentiate into pericytes. These pericytes seem to have the characteristics of stem cells and have the potential to transform into epithelial cells [61]. Research has shown that vascular endothelial cells in the glioma microenvironment recruit GSCs into tumor blood vessels and secrete TGF by secreting SDF-1, which induces the differentiation of GSCs into pericytes. The pericytes differentiated from GSCs also participate in the construction of blood tumor barrier (BTB). BTB is one of the important structures that block the entry of chemical drugs into tumor tissue and plays an important role in maintaining the drug resistance of glioma cells [62]. Mesenchymal stem cells (MSC) derived from bone marrow are a type of pluripotent stem cells that exist in the bone marrow and can differentiate into various cell types, including pericytes. Research has shown that MSCs can

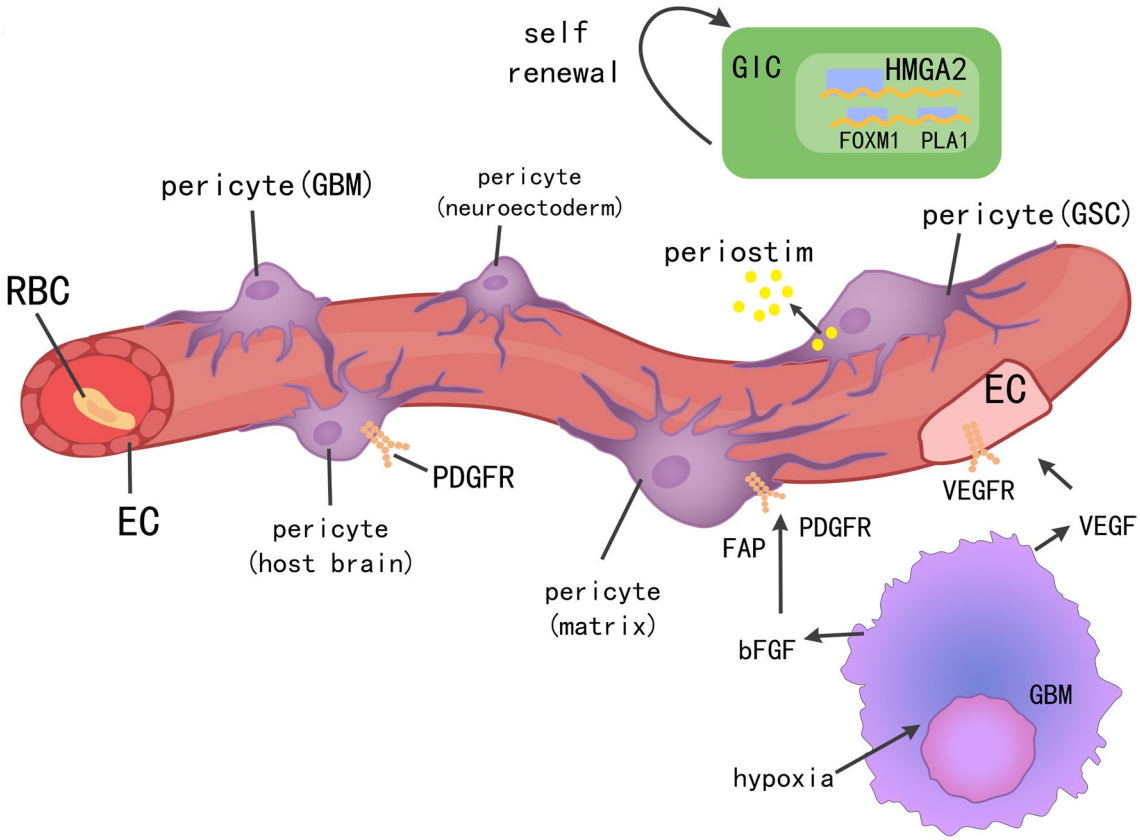


Fig. 3 The role of pericytes in glioma microenvironment and its possible target. (1) Targeting several kinds of pericytes, including glioblastoma-activated pericytes, endogenous brain pericytes, neural crest cell-derived pericytes, tumor-associated pericytes, pericytes derived from glioma stem cells. (2) Targeting protein expression in pericytes (3) Targeting the pericyte rich microenvironment and angiogenesis

differentiate into pericytes to varying degrees in glioma, participating in the formation of tumor blood vessels [63]. MSCs are guided by chemokines to migrate around glioma neovascularization. This migration phenomenon is related to the gradient of chemotactic factors. Once MSCs reach the vicinity of blood vessels, they interact with endothelial and adventitial cells through cross-linked proteins. At this time, MSCs can release a series of growth factors that promote angiogenesis, such as VEGF, basic fibroblast growth factor, bone morphogenetic protein, etc. These factors can induce endothelial cell proliferation and migration, promoting the formation of new blood vessels. At the same time, these factors can stimulate MSCs to differentiate into pericytes. Once MSCs differentiate into pericytes, they tightly bind to the periphery of tumor blood vessels. The main function of periderm cells is to provide support for blood vessels and maintain their stability. They participate in the nutrient supply of blood vessels, regulate vascular permeability, and stabilize vascular structure [64] (Fig. 3).

Pericytes derived from glioma cells

Recent studies have shown that glioma cells can transform into pericytes under certain conditions, which is a complex process and is closely related to tumor microenvironment and signal regulation inside and outside cells. Glioma is a tumor formed by abnormal proliferation of glial cells. These glioma cells typically possess high proliferative capacity and the ability to invade surrounding tissues. In the Tumor microenvironment, there are a series of transforming Signaling molecule that can stimulate glioma cells to differentiate into peripheral cells. These signals may come from other cells around tumor cells (such as vascular endothelial cells, fibroblasts, etc.) or secreted by tumor cells themselves. After receiving appropriate signals, the phenotype and function of glioma cells may change. This includes changes in gene expression, protein expression, and cellular morphology. Transformed glioma cells may begin to express peripheral cell marker molecules such as NG2, PDGFR, etc. The transformation process may involve changes in genetic and epigenetic regulation, including gene mutation, DNA methylation and histone modification. The transformed

glioma cells may begin to function as periderm cells. As pericytes, they can follow the blood vessels to form a covering layer on the tunica externa of the blood vessels, provide support for the blood vessels, regulate the permeability of the blood vessels and stabilize the structure of the blood vessels [65]. In a study conducted by Valdor et al., experimental models in vivo and in vitro showed that GBM cells can transform into pericytes and secrete high levels of anti-inflammatory cytokines, inhibiting the immune system's response to tumor cells. Therefore, GBM related pericytes has immunosuppressive function, which helps to evade anti-tumor response and promote tumor growth [66]. Pericytes derived from GBM may be a feasible target for regulating vascular tumor cell interactions and further enhancing anti-tumor cell behavior [67] (Fig. 3).

Pericytes derived from neural crest stem cells

In the process of ontogenesis, pericytes originate from two main embryonic germ layers, mesoderm and ectoderm. Therefore, pericytes of different origins may be found in different organs of ontogenesis. However, pericytes of different origins may gather and colonize in adjacent areas of the same organ. Pericytes derived from neural crest stem cells (NCSCs) originate from mesoderm. NCSCs initially exist in the ectoplasm layer between the surface ectoderm and the developing central nervous system, where they differentiate into pericytes and are associated with endothelial precursor cell derived from mesoderm that express VEGFR. The pericytes derived from NCSCs are involved in the formation of meningeal blood vessels, which surround the deeper network of meningeal capillaries, a process necessary for the late development of cerebral vascular [68]. Research has shown that pericytes derived from NCSCs participates in the construction of glioma neovascularization, which to some extent affects the proliferation and migration ability of glioma cells. However, the specific mechanism by which they exert their effects remains uncertain [69] (Fig. 3).

Targeted therapy against pericytes

Pericytes and vascular endothelial cells both have the function of regulating vascular properties, and contribute significantly to the construction of glioma neovascularization and maintaining its structural stability. Therefore, targeting pericytes is a potential treatment for glioma. At present, there is relatively limited research on direct targeted chemical drugs targeting pericytes within the glioma microenvironment. Ibrutinib is a chemical that targets to regulate PKB signaling pathway. It is a small molecule Tyrosine kinase inhibitor and is widely used to treat specific types of leukemia and lymphoma. It is found that Ibrutinib can target pericytes of glioma, thus inhibiting the formation of BTB, increasing the penetration concentration of chemotherapy drugs in glioma tissue, and improving the efficacy of chemotherapy drugs [70]. However, there are some drugs that can indirectly affect or regulate the pericytes in the glioma microenvironment. Some drugs can inhibit the angiogenesis of glioma, thereby indirectly affecting pericytes. These drugs include VEGFR inhibitors, such as Bevacizumab and Sunitinib. They can inhibit the proliferation of vascular endothelial cells and pericytes, and reduce the angiogenesis process in the glioma microenvironment. Research has shown that the combined use of Bevacizumab and cytotoxic drugs brings significantly better therapeutic effects than the use of cytotoxic drugs alone [67]. In addition, some drugs can regulate and affect the interaction between peripheral blood cells and vascular endothelial cells. For example, TGF-β Inhibitors of signal pathway can affect the interaction between pericytes and vascular endothelial cells, such as Nilotinib and Capecitabine [71].

The expression of periosteal proteins is related to the progression of glioma. Some studies have shown that pericytes are the main source of periosteal proteins in glioma, and periosteal proteins play an important role in the growth and branching of blood vessels. Therefore, periosteal proteins should become a new target for anti angiogenic therapy of glioma. The mesenchymal phenotype is a marker of tumor invasiveness in GBM. HMGA2 is a structural transcription factor that promotes mesenchymal phenotype in many solid tumors. It is highly expressed in mesenchymal subtypes of GBM and marks pericytes of glioma and glioma initiating cells (GIC). The loss of HMGA2 in GICs results in impaired self-renewal and tumorigenicity, as well as impaired differentiation of mesenchymal cells or pericytes. In vitro and in vivo, HMGA2 allows the expression of FOXM1 and PLAU, thereby maintaining GIC proliferation, glioma occurrence, and invasion. Therefore, inhibiting HMGA2 mediated GIC self-renewal and invasiveness may be an effective method for treating GBM [72] (Table 1).

Conclusion

As the survival place of glioma cells, Tumor microenvironment plays a key role in the occurrence and development of glioma, and more and more studies have also focused on therapeutic drugs targeting TME. In glioma TME, neurons, neuroglial cells, vascular endothelial cells and pericytes constitute the majority of non-tumor stromal cells. Among them, neurons and Glia provide nutrition and cytokines for glioma cells to proliferate, while vascular endothelial cells and pericytes participate in the construction of glioma neovascularization, providing a channel for glioma cells to deliver nutrition. At the same

time, these cells are also interconnected and influence each other's proliferation and migration. Therefore, this article summarizes the specific roles and molecular pathways involved in the occurrence and development of glioma by the four types of stromal cells mentioned above. At the same time, we have also summarized corresponding targeted drugs for different molecular pathways of different stromal cells, providing effective information for the development of specific drugs targeting stromal cells in the glioma microenvironment.

Abbreviations

A2V	Ang II and VEGF CrossMab
ACE	Angiotensin converting enzyme
AKT	Protein kinase B
Ang II	Angiotensin II
ASI	Angiotensin inhibitor
AT1R	Angiotensin type 1 receptor
AT2R	Angiotensin type 2 receptor
BTB	Blood tumor barrier
BTIC	Brain tumor-initiating cell
CAR-T	Chimeric antigen receptor T-cell
CCL2	Chemokine (C–C motif) ligand 2
CSF-1	Colony stimulating factor 1
Cx43	Connexin 43
ECM	Extracellular matrix
EGF	Epidermal growth factor
FDA	Food and Drug Administration
GBM	Glioblastoma multiforme
GFAP	Glial fibrillary acidic protein
GIC	Glioma initiating cell
Gln	L-glutamine
Glu	Glutamate
GSC	Glioma stem cell
IDH	Isocitrate dehydrogenase
IF	Intermediate filament
IFN-β	Interferon-β
IFN-γ	Interferon-γ
IKK-2	I kappa B kinase 2
IL-6	Interleukin-6
IP-10	Interferon inducible protein 10
LOXO-101	Larotrectinib
MCT	Monocarboxylate transporter
MF	Microfilament
miRNA	MicroRNA
MMP-2	Matrix metalloproteinase 2
MSC	Mesenchymal stem cell
MT	Microtubule
MT1-MMP	Membrane type 1-matrix metalloproteinase
mTOR	Mammalian target of rapamycin
NCSC	Neural crest stem cell
NG2	Neuronal glial antigen 2
NGF	Nerve growth factor
NRP-2	Neuropilin 2
PD-1	Programmed cell death protein 1
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PD-L1	Programmed death-ligand 1
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
PLC	Phospholipase C
PN	Perivascular niche
RAS-MAPK	Rat sarcoma-mitogen-activated protein kinase
RAGE	Receptor for advanced glycation end product
SDF-1	Stromal derived factor 1
siRNA	Small interfering RNA
STI-1	Stress inducible protein 1
TGF-β	Transforming growth factor β
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TrkA	Tropomyosin receptor kinase A
VEC	Vascular endothelial cell
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization

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Author contributions
Zhu C and Geng ZA made substantial contributions to the conception. Zhang ZY, Wang MH and Yu ZX made acquisition of references. Wang SQ, Lu J, Wang SS and Guan S analyzed and made contributions to interpretation of data. Geng ZA, Zhang ZY, Wang MH and Yu ZX were major contributor in writing the manuscript. Zhu C, Liu TC and Li JN critically revised the article and ensured that all listed authors have approved the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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