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Review

Advances in neuroscientific mechanisms and therapies for glioblastoma

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SUMMARY

Gliomas are common primary brain tumors in the central nervous system, characterized by invasiveness, heterogeneity, and drug resistance, posing a threat to patients' lives. Glioblastoma (IDH wild-type) exhibits the highest invasiveness and mortality rate, making it a challenging therapeutic target. This review first outlines the characteristics of gliomas and their impact on the nervous system, then explores the pathological mechanisms and unique behaviors of glioblastoma (IDH wild-type), as well as the influence of the nervous system on its occurrence and progression. In terms of treatment, potential targeted strategies are summarized, and the potential of novel precision therapies, such as immunotherapy and gene therapy, is evaluated. This article underscores the importance of understanding the complex interactions between the nervous system and gliomas, offering new perspectives and targets for treatment. Future research should elucidate these interactions to identify more effective therapeutic targets and improve patient prognosis and quality of life.

INTRODUCTION

Glioma, as the most common primary brain tumor of the central nervous system, is notorious for being highly aggressive, heterogeneous, and treatment-resistant. These tumors not only pose a serious threat to the lives of patients but also pose a major challenge to modern neuroscience and oncology. The complexity of glioma stems from its tight interweaving with normal brain tissue and resistance to traditional treatments. In recent years, with the rapid progress of neuroscience and molecular biology, we have gained a deeper understanding of the biological behavior, molecular mechanisms, and interactions with the nervous system of glioma.

Under normal physiological conditions, the nervous system maintains the normal function of the body through delicate nerve signaling, cell-to-cell communication, and complex neural network activity. However, the occurrence and progression of glioma can have a profound impact on the nervous system, not only directly invading and destroying nerve tissue, but also interfering with nerve signaling, changing the structure and function of nerve cell networks, and leading to a series of neurological symptoms, such as seizures, cognitive and emotional impairment, and impaired sensory and motor function.

Among the many subtypes of glioma, glioblastoma (IDH wt type) is of particular concern. As the most aggressive and lethal subtype of glioma, it is particularly challenging to treat in the clinic. Recent studies have shown that the interaction between the nervous system and glioblastoma (IDH wt type) is not unidirectional, but rather a complex bidirectional relationship (Figure 1). A variety of cellular components in the nervous system, including neurons, glial cells, and so forth, as well as neuromodulation-related factors, such as neurotransmitters,[1] circadian rhythms,[2] sensory stimulation, and mental state, all play an important role in the occurrence and development of glioblastoma (IDH wt type). For example, paracrine signaling from neural cells modulates the biological behavior of glioblastoma cells,[3] and electrochemical synaptic communication between neurons and glioblastoma cells is also involved in the malignant regulation of tumor cells.

This bidirectional interaction brings new challenges and opportunities for the treatment of glioblastoma (IDH wt type). A better understanding of the relationship between the nervous system and glioblastoma (IDH wt) can help uncover its unique pathogenesis and provide a rationale for the development of more effective treatment strategies. Targeting the key link in the interaction between the nervous system and glioblastoma (IDH wt type) may become a new direction for the treatment of this tumor in the future. Therefore, it is of great significance to systematically review the interaction mechanisms between neuroscience and glioblastoma (IDH wt) and explore potential therapeutic targets based on these mechanisms to improve the prognosis of patients with glioblastoma.

THE IMPACTS OF GLIOBLASTOMA ON THE NERVOUS SYSTEM

Direct destruction of neuronal tissues

Glioblastomas, particularly in high-grade malignancies, exhibit remarkable invasive potential by directly infiltrating surrounding

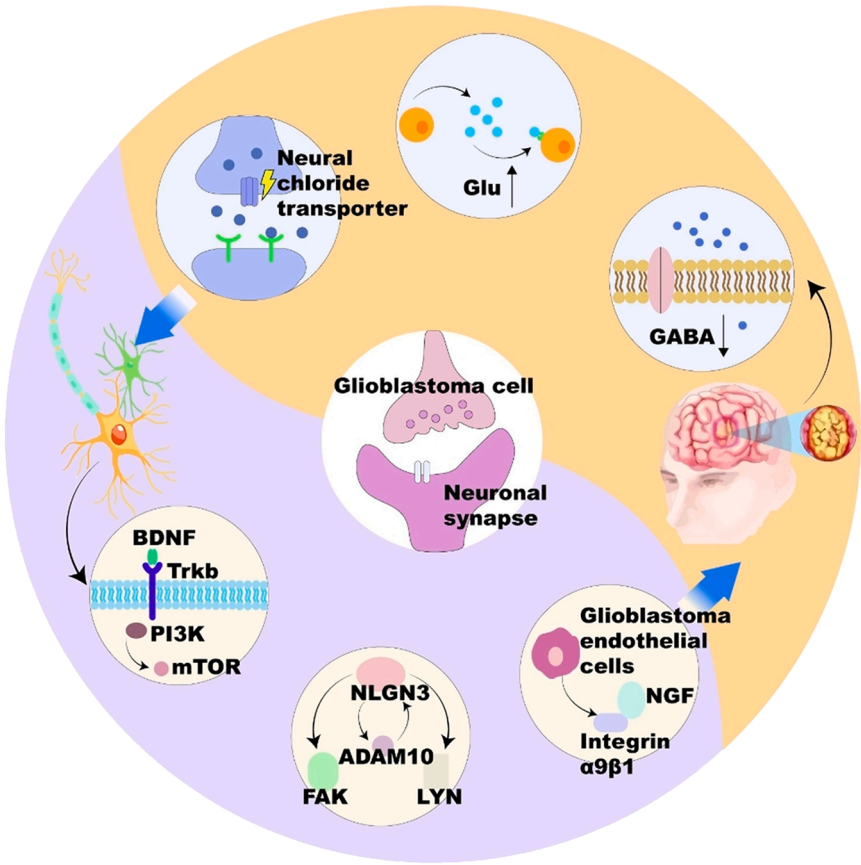

Figure 1. Interactions between glioblastomas and nerves

The middle part of the illustration shows that tumor cells and neurons establish synapses, changing the neural network. Right half of the illustration: gliomas affect nerves by increasing excitatory neurotransmitters, GABAergic neurons, and chloride transporters; Left half of the illustration: Neuroactive secretion factors promote glioblastoma growth and angiogenesis, including the BDNF-mediated activation of the TrkB pathway, the NLGN3-mediated activation of the FAK/LYN pathway, and NGF action on integrin α9β1.

neural tissues through an infiltrative growth pattern. These tumor cells facilitate their spread by secreting various proteolytic enzymes including matrix metalloproteinases (MMPs), which degrade the extracellular matrix to create invasion routes while disrupting the normal structure of neurons and glial cells. A prominent feature of high-grade gliomas is their ability to rapidly breach the blood-brain barrier and invade adjacent brain parenchyma, resulting in structural damage to neural tissues.

Tumor expansion exerts mechanical pressure on adjacent neural tissues, leading to vascular compression-induced local ischemia and hypoxia. Given the high sensitivity of neurons to hypoxia, persistent hypoxic conditions may induce neuronal apoptosis or necrosis. For example, the compression of the primary motor cortex by high-grade gliomas disrupts neural impulse transmission, resulting in clinically significant limb motor impairment.

The impacts of glioblastoma on neuronal survival and excitability

Glioblastomas significantly enhance neuronal excitability, potentially triggering hyperexcitation and neuronal death. This phenomenon can be observed in patients with glioblastomas or metastatic brain tumors, which increased neuronal excitability leads to frequent tumor-associated epileptic seizures. The underlying mechanisms include paracrine factors and abnormally increased neuronal synaptogenesis. Evidence from an adult glioblastoma model suggests that paracrine glutamate elevates neuronal excitability and facilitates tumor progression via the xc-cystine-glutamate transporter system. Furthermore, in the tumor microenvironment of IDH-WT adult glioblastoma, the combined effects of GABAergic interneuron depletion and the glioblastoma-induced alteration of neuronal chloride transporter expression convert the effect of GABA from inhibitory to excitatory, also resulting in an increase in circuit excitability.[4]

The impacts of glioblastoma on neural cell networks and intercellular communication

Glioblastoma cells form nerve-like network structures interconnected through gap junctions and adherent junctions, enabling functional interactions with the surrounding nervous system and modulating the transmission of neural signals. These tumor cells secrete synaptogenesis factors such as thrombospondin-1, which promote aberrant neuronal synaptogenesis and subsequently alter neural network connectivity and functionality. The tumor-induced enhancement of functional neuronal connectivity between neoplastic and normal brain tissue demonstrates a significant correlation with the decreased survival rate of patients with glioblastoma.[5]

In addition, glioblastoma cells are interconnected through adherent junctions between gap junctions (primarily containing connexin 43) and tumor microtubules (TMs), forming a tumor-tumor network. They communicate and exchange small molecules through intercellular calcium waves, similar to the physiological astrocyte network in the brain. This network structure constitutes a critical mechanism for the development of drug resistance in glioblastomas.[6,7] Tumor cells integrated into the TMs network and coupled via gap junction are resistant to radiotherapy and temozolomide chemotherapy, while glioblastoma cells without network-connected are more sensitive to cytotoxic treatments.[8–10]

Furthermore, neuronal activities activate glioblastoma networks via both paracrine signal transduction and glutamatergic synapse formation, significantly promoting tumor cell proliferation and invasion.[7,9,10] These findings suggest that

interconnected glioblastomas can also drive invasion,[11] similar to the collective migration of other cancer entities.

The impacts of glioblastoma on nervous system functions

Research has demonstrated that glioblastoma induces dynamic reorganization in the central nervous system, including language, sensory, and motor networks. Glioblastoma-induced neural plasticity occurs at both network and cellular levels. At the network level, glioblastoma can trigger compensatory reorganizations in the ipsilateral or contralateral hemispheres, facilitating the reconstruction of language and motor pathways. At the cellular mechanism level, these plastic changes involve multiple mechanisms, including reduced cortical inhibition, recruitment of new neural networks, and complex neuron-glia interactions.[12]

Progressive glioblastoma growth exerts an increasingly intense physical compression on adjacent brain tissues, resulting in significant neural damage. This compressive effect can directly affect specific neural function areas. For example, optic nerve compression results in visual impairment or even blindness; motor nerve compression lead to limb motor dysfunction, manifested as weakness or paralysis, and language area compression causes aphasia.[13] Studies have revealed that the bilateral synchrony of neuronal activities in tumor infiltrated cortical areas gradually decreases upon tumor progression, and the neurovascular coupling is also gradually disrupted. Local changes in tumor-affected areas, including high-amplitude discharges and epileptic seizures. Importantly, the alteration of neurovascular coupling may affect the interpretation of functional magnetic resonance imaging data based on blood-oxygen-level-dependent signals, which is of great significance for understanding the relationship between tumor progression and neural functions.[12]

Elevated intracranial pressure constitutes one of the most severe clinical manifestations in patients with glioblastoma, causing diverse neurological symptoms including lethargy, cognitive impairment and epileptic seizures. As a prevalent cause of mortality, increased Intracranial Pressure (ICP) significantly compromises both quality of life and clinical outcomes.[14] A novel model has been developed to simulate the progression of glioblastoma, mass effects and intracranial pressure changes within patient-specific anatomical structures.[14] This model directly derives the intracranial pressure based on tumor dynamics and the individual specific anatomical structures, providing valuable insights for glioblastoma diagnosis and therapeutic management.

The impacts of glioblastoma on cognition and emotion

Glioblastoma-induced structural alterations in the brain often lead to psychological and emotional disturbances in patients, including cognitive decline, memory loss, and emotional instability. In a study on the impacts of glioblastoma on neural circuits, researchers conducted intracranial brain recordings of awake patients engaged in a vocabulary retrieval language task, combined with tumor tissue biopsies and cell biology experiments. The results revealed that glioblastoma functionally remodel neural circuits, causing task-related neural activated in the cortical areas infiltrated by the tumor, beyond the normal recruitment areas of the healthy brain. Further analyses comparing tumor regions with high (HFC) and low (LFC) functional connectivity demonstrated that HFC areas exhibit the elevated secretion of the synaptogenic factor thrombospondin-1 (TSP-1) by tumor cells, promoting neuron-glioblastoma interaction in a TSP-1-dependent manner. In addition, the functional connectivity of the tumor is negatively correlated with the patient's survival period and performance in the language task. Moreover, theinhibition of TSP-1 with gabapentin suppressed glioblastoma cell proliferation and reduced network synchrony. These findings provide new insights into understanding the interaction between glioblastoma and neural circuits and also offer potential targets for the development of treatment strategies.[5]

The impacts of glioblastoma on epileptic activities

Epilepsy is one of the most common symptoms in glioblastoma with glioblastoma. As previously discussed, the electrophysiological alterations of neurons and the metabolic disorders of neurotransmitters caused by glioblastoma provide the pathological basis for epileptic seizures. The frequency and severity of epileptic seizures exhibit considerable variability across individuals, influenced by tumor characteristics and patient-specific factors. Some patients experience only occasional seizures, while others suffer from frequent seizures that significantly impair their quality of life. It has been demonstrated that the infiltrative growth of glioblastoma modifies the electrophysiological properties of the surrounding tissues, mediating neuronal hyperexcitability and the formation of multiple non-continuous epileptic foci that facilitate the initiation and propagation of epileptic-like activities.[4,15] The occurrence of glioblastoma-related epilepsy has been demonstrated to be associated with multiple pathogenic factors, including glutamate excitotoxicity, impaired activity of potassium-chloride co-transporters, and so forth. Furthermore, molecular markers such as IDH-1 mutation, 1p/19q allelic deletion show significant correlations with the occurrence and treatment response of epilepsy.[16,17] These findings provide an important basis for further studying the relationship between glioblastoma and epilepsy. Recent investigations have identified thrombospondin-2 (TSP2) as a critical mediator in this process. Glioblastoma-derived TSP2 promotes the formation of excitatory synapses in the cortex surrounding the glioblastoma, leading to excessive neuronal excitation and offering novel insights into the pathogenesis of glioblastoma-related epilepsy.[18]

A recent investigation employing two glioblastoma mouse models with different synaptic microenvironments and infiltration characteristics revealed that tumor invasion induces the dysregulation of neural assembly function. These functional alterations correlate with both malignant progression and tumor cell proximity. Notably, neural activity modulation varies significantly across different stages of tumor expansion, accompanied by spatial dissociation between the accumulation of glutamate and the neuronal calcium signaling.[18] Therefore, the impacts of glioblastoma on the nervous system are multifaceted and complex.

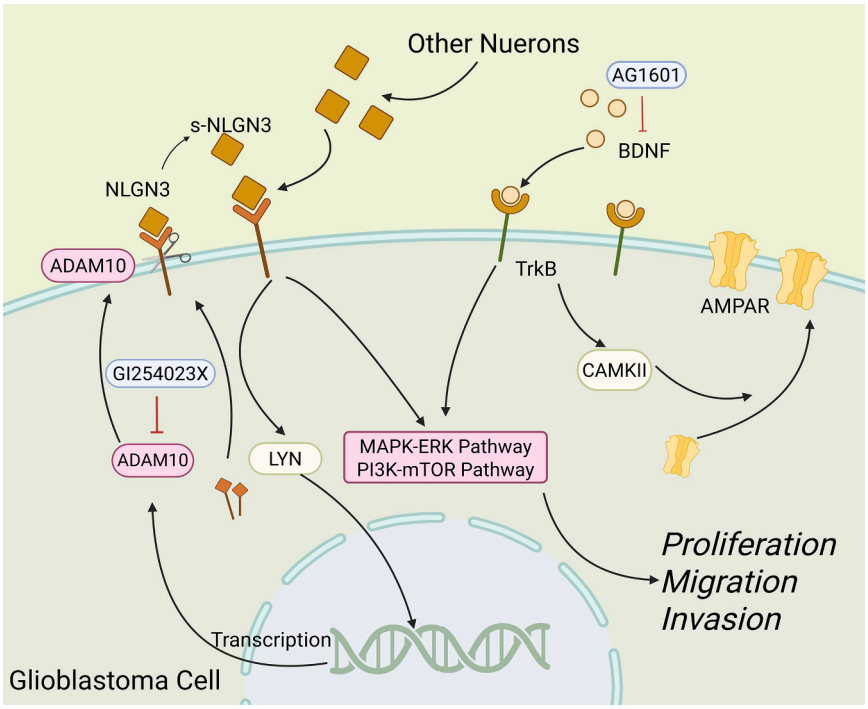

Figure 2. Effect of neuronal paracrine activity on glioblastoma

The figure primarily illustrates the key pathways through which neurons act on glioblastoma cells via paracrine signaling:① NLGN3 Signaling Axis: Neuron-derived NLGN3 activates pro-tumor pathways in glioblastoma cells, including MAPK-ERK, PI3K-mTOR, and LYN. The LYN pathway upregulates ADAM10 expression, which cleaves NLGN3 to form a positive feedback loop. This process can be inhibited by the ADAM10 inhibitor GI 254023X. ② BDNF/TrkB Signaling Axis: Neuron-secreted BDNF exerts dual effects by binding to the TrkB receptor—promoting AMPA receptor membrane localization to enhance tumor proliferation while synergistically activating downstream pathways of NLGN3 (PI3K-mTOR/MAPK-ERK). The BDNF inhibitor AG1601 intervenes in this pathway by inducing apoptosis and suppressing proliferation.

THE IMPACT OF THE NERVOUS SYSTEM ON GLIOBLASTOMA

Impact of the nervous system on glioblastoma via the paracrine pathway

In the nervous system, the paracrine pathway is serves as a vital mechanism of intercellular communication. Paracrine signaling refers to a mode of intercellular communication in which cells secrete signaling molecules (such as hormones, cytokines, growth factors, and so forth) that do not enter the bloodstream but are instead released directly into the extracellular matrix. These molecules then act on nearby target cells, regulating their physiological functions or metabolic activities. During the development of glioblastoma, nerve cells modulate the biological behavior of glioblastoma cells through paracrine factors (Figure 2).[3]

Neuroligin-3 (NLGN3), a synaptic adhesion molecule, is involved in regulating synaptic structure and function and plays a significant role in the formation and remodeling of synapses within the central nervous system.[19] Emerging evidence highlights its role in glioblastoma pathogenesis. Neuronal activity can induce the secretion of NLGN3, which activates the PI3K-mTOR pathway and facilitates the feedforward expression of NLGN3 in glioblastoma cells, ultimately promoting the proliferation of high-grade glioma (HGG). Beyond its role in PI3K-mTOR signaling, NLGN3 has been shown to promote the phosphorylation of focal adhesion kinase (FAK) and its downstream molecules, such as the activation of SRC kinase cascade, SHC-RAS-RAF pathway, and the MEK-ERK cascade. Furthermore, NLGN3 induces thephosphorylation of oncoproteins such as integrin β3 and growth factor receptors, including EGFR, FGFR, and VEGFR, while upregulating synaptic-related genes (NLGN1, NLGN4X, NLGN4Y, and NLGN21) to facilitate the proliferation of HGG cells in both pediatric and adult patients.[20] Glioblastoma-derived NLGN3 promotes the proliferation, migration, and invasion of glioblastoma cells while inhibiting apoptosis by activating the LYN signaling pathway. Additionally, NLGN3 overexpression upregulates Bcl-2 expression and suppresses Bax expression, leading to an increased Bcl-2/Bax ratio. This elevated ratio primarily supports cell survival and proliferation by indirectly inhibiting apoptosis.[19] The sheddase A Disintegrin and Metalloprotease 10 (AMAD10) is crucial for the cleavage and release of NLGN3. The LYN pathway can activate nuclear factors for transcription to upregulate ADAM10 expression and promote NLGN3 cleavage, establishing a positive-feedback loop.[19] Moreover, the ADAM10 inhibitor GI 254023X has been demonstrated to effectively restrain the malignant behavior of glioblastoma cells.[19,20] It has been reported that the loss of the tumor suppressor DAB2IP in glioblastoma stem cells (GSC) can prevent NLGN3 transcription by inhibiting the Wnt/β-catenin pathway.[21] Meanwhile, the expression of NLGN3 is regulated by the deubiquitinase USP7 (which enhances transcription via KPNB1/YBX1), while Gαi1/Gαi3 activates the Akt-mTORC1 and Erk pathways, collectively promoting glioblastoma progression.[22,23] This regulatory network reveals how paracrine signals from the nervous system (such as neuronal activity) influence glioblastoma through protein stability and G-protein signaling, offering new directions for targeted therapy.

Under physiological conditions, brain-derived neurotrophic factor (BDNF) is beneficial to the adaptive plasticity of synaptic connections. Intriguingly, malignant synapses retain this plasticity, regulated by BDNF.[24] BDNF signals to CAMKII through the receptor tropomyosin-related kinase B16 (TrkB), inducing the transport of AMPA receptors to the glioblastoma cell membrane and promoting glioblastoma proliferation by increasing the amplitude of glutamate-induced current.[24] Additionally,

BDNF mediates the expression of multiple downstream targets through the TrkB/PI3K/Akt pathway, promoting tumor growth and chemoresistance. The inhibition of BDNF expression in C6 glioblastoma cells with the small molecule inhibitor AG1601 exerted significant antiproliferative and pro-apoptotic effects.[25] Notably, BDNF expression is regulated by non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Specifically, BDNF serves as a downstream target of hsa-miR-134-5p, which suppresses the BDNF/ERK signaling pathway to hinder the growth, invasion, and metastasis of glioblastoma cells.[26] Additionally, lncRNA TUSC7 inhibits the proliferation and migration of human glioblastoma cells by suppressing the BDNF/TrkB/ERK pathway.[27] LncRNA BDNF-AS is significantly down-regulated in glioblastoma (GBM), and its overexpression inhibits GBM cell growth and promotes apoptosis.[28] BDNF-AS interacts and stabilizes with the RNA-binding protein polyadenylate-binding protein cytoplasmic 1 (PABPC1). This interaction promotes STAU1-mediated decay of the retina and anterior neural fold homeobox 2 (RAX2) mRNA, exerting tumor-suppressive effects. Meanwhile, it increases the expression of discs large homolog 5 (DLG5) and activates the Hippo pathway to inhibit GBM progression.[29] Furthermore, the coupling of BDNF-AS with the RNA-specific adenosine deaminase protein (ADAR), which regulates gene expression, enhances the stability of p53 mRNA and consequently increases p53 protein levels. As a transcription factor of BDNF-AS, p53 activates the transcription of BDNF-AS, establishing a positive feedback loop that reinforces tumor suppression.[28]

Nerve growth factor (NGF) has been found to have a relatively potent oncolytic effect in the C6 glioblastoma cell line even at concentrations less than 10^{-4} M.[30] Moreover, NGF (7.55×10^{-3} μM) inhibits the clonogenic ability of U251 glioblastoma cells within 1–2 days and inhibits cell migration within 3–4 days. These effects may be mediated through the NGF-induced reduction of mitochondrial basal oxygen consumption rate, ATP synthase activity, and maximum respiration capacity in U251 cells.[31] However, NGF also contributes to the malignant behavior of glioblastoma. It has been reported that NGF interacts with integrin α9β1, which is up-regulated in glioblastoma endothelial cells, to promote pathological tumor angiogenesis. Interestingly, the up-regulation of glial cell line-derived neurotrophic factor (GDNF), which can be mediated by testosterone, facilitates the proliferation, migration, and invasion of glioblastoma cells. This hormone-mediated regulatory mechanism may contribute to the observed gender disparity in glioblastoma outcomes, with male patients exhibiting higher mortality rates than females.[32]

This subsection primarily elaborates on the effect of the nervous system on glioblastoma through the paracrine pathway. Current evidence demonstrates that various paracrine factors from the nervous system play a vital role in the development of glioblastoma, providing a theoretical basis for further investigating the pathogenesis and novel therapeutic targets of glioblastoma.

Impact of neurotransmitters on glioblastoma

Glutamate (Glu), the principal excitatory neurotransmitter in the central nervous system, is synthesized by glutaminase (GLS)-mediated hydrolysis of glutamine (Gln). Currently, the role of Glu as a metabolic intermediate in glioblastoma has been documented; its neurotransmitter function in this pathological context remains insufficiently characterized. In radiation-resistant GBM cells, the mitochondrial bidirectional Glu transporter SLC25A22 is up-regulated and exhibits unidirectional mitochondrial-to-cytoplasmic transport rather than the typical bidirectional activity, resulting in the accumulation of intracytoplasmic Glu. This subsequently enhances glutathione (GSH) production and proline synthesis, protects cells from ionizing radiation-induced reactive oxygen species (ROS), and induces extracellular matrix remodeling, resulting in the invasive phenotype of GBM.[33] Another study found that the endogenous dipeptide L-carnosine suppresses the translation of glutamine synthetase (GS), thereby blocking Gln metabolism and inhibiting the colony formation, migration, and invasion of glioblastoma cells.[34] In oligodendroglioblastomas (ODGs), mutations in CIC, which is a conserved transcriptional repressor downstream of the RTK and MAPK pathways, upregulate genes related to Glu release, resulting in extracellular Glu accumulation and neurotoxicity.[35] Furthermore, synaptosomal-associated protein 25 (SNAP25), which is related to synaptic connections, exerts tumor-suppressive effects by promoting GLS-mediated glutaminolysis to regulate synaptic plasticity, as well as inhibiting the proliferation, migration, and invasion of glioblastoma cells.[36]

γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the brain. Studies have found that the reduction of RNA editing during glioblastoma development decreases the stability of gamma-amino butyric acid receptor alpha subunit 3 (GABRA3) RNA, resulting in a decrease in the protein level of the GABRA3. This loss of GABAergic signaling function in neuronal communication promotes the formation of an aggressive phenotype in GBM.[37] Propofol can enhance the characteristics of GSCs and promote the growth of glioblastoma in nude mice through the GABAAR-Src-ZDHHC5-EZH2 signal axis.[38] In addition, it has been reported that histamine secreted by GSCs activates endothelial cells by the histamine H1 receptor (H1R)-Ca2+-NFκB axis, thereby promoting tumor angiogenesis and GBM progression.[39]

These findings indicate that neurotransmitters and their associated signaling pathways play an important role in the initiation and progression of glioblastoma, providing new potential targets for the treatment of glioblastoma.

Influence of neurons on glioblastoma via electrochemical synapses and intercellular communication

In addition to activity-dependent paracrine signaling mediated by neuronal activity-regulated synaptic factors such as NLGN3 and BDNF, the electrochemical signal transmission through functional synapses between presynaptic neurons and postsynaptic tumor cells significantly modulates glioblastoma malignancy.

Upon neuronal activation, miRNAs including miR-200c-3p and miR-184-3p are enriched in neuron-derived exosomes (NDEs). With delivery into microglia, miR-200c-3p reduced the expression of ZC3H13 in microglia and subsequently downregulated DUSP9, promoting the activation of the ERK pathway. This

cascade promotes the M2 polarization of microglia, increasing the production of immunosuppressive cytokines and interleukin-10 (IL-10) and facilitating the growth of glioblastoma cells.[40] Once taken up by GSCs, miR-184-3p induces the proneural-to-mesenchymal transition (PMT) of GSCs through the miR-184-3p/RBM15/DLG3/p-STAT3 pathway, promoting glioblastoma progression and radioresistance.[41] Notably, the antiepileptic drug levetiracetam has been demonstrated to suppress abnormal neuronal activation in GBM and reduce NDE production, thereby inhibiting neuronal activity-dependent GBM progression.[40,41] Additionally, neuronal stimulation can drive infiltration, especially in regions of glioblastoma tumors rich in the axon-guiding gene SEMA4F. It is noteworthy that not only does the neuronal activity near the tumor impact tumor cells, but also the distal neuronal activity promotes tumor infiltration through secreted factors. Moreover, the corpus callosum-projecting neurons (CPNs) on the contralateral side of the primary tumor contribute to this process during early disease stages.[42]

The synaptic connection between neurons and glioblastoma is regulated by SMAD3 and PITX1, the principal transcription factors associated with synaptic organization and axon guidance. Combined inhibition of SMAD3 and neuronal activity synergistically enhances the proliferation ability of GBM cells.[43] Moreover, in diffuse midline glioblastoma (DMG) cells characterized by the oncohistone H3.1K27M, loss of the chromatin remodeler CHD2 impairs cellular viability and disrupts the synaptic connection between neurons and glioblastoma by downregulating the expression of axon-guiding and synaptic-related genes. This weakens the proliferation induced by neuronal activity, inhibits activity-dependent calcium transients *in vivo* and prolongs the survival of H3.1K27M DMG mice.[44]

It has been reported that glioblastoma cells realize multicellular communication through frequent intercellular Ca^{2+} waves. The functional structural basis is the tumor microtubules formed by the membrane-tube protrusions of glioblastoma cells, which interconnect individual glioblastoma cells into an integrated network via gap junctions. These communication networks have been implicated to be closely related to local tumor recurrence and the development of resistance to radiotherapy and chemotherapy.[45] The KCa3.1 channel mediates the generation of periodic Ca^{2+} oscillations. Notably, it has been shown that the growth-stimulating effect of KCa3.1^{high} periodic cells on network neighbors connected by tumor microtubules is achieved through the enhanced activity of the MAPK and NF-κB pathways.[45]

Collectively, these findings disclose the significant role of the interaction between neurons and glioblastoma cells through electrochemical synapses and intercellular communication in glioblastoma development, providing new directions for the exploration of novel treatment strategies.

Impact of glial cells on glioblastoma

In addition to neurons, the nervous system contains numerous glial cells which provide structural support, neuroprotection, nourishment and insulation for neurons, while also participating in the metabolism of neurotransmitters and active substances. These functions significantly influence glioblastoma pathophysiology.

Tumor-associated microglia and macrophages (TAMs) serve as primary mediators of immunosuppression and pathological angiogenesis in GBM. SLIT2 promotes the chemotaxis and tumor-supportive polarization of TAMs through ROBO1&2-mediated PI3Kγ activation.[46] Neurons with NF1 mutations produce midkine (MDK), which activates naive $CD8^+$ T cells to produce CCL4 through the Lrp1/calcineurin/NFAT1 signal pathway. Subsequently, CCL4 induces microglia to secrete CCL5, which binds to CD44 and activates downstream pathways such as AKT/GSK3β/CREB to inhibit apoptosis and maintain the growth of low-grade glioma (LGG) cells.[47] In addition, microglia also convey information to cancer cells by releasing miR-124-enriched small extracellular vesicles (sEVs), which reprogram tumor metabolism by reducing the release of lactate, nitric oxide (NO) and Glu. It significantly reduces the tumor mass *in vivo* and improves the survival rate of glioblastoma-bearing mice.[48]

Interestingly, mitochondrial transfer mediated by astrocytes contributes to GBM progression. GBM cells actively acquire astrocytic mitochondria, leading to an increase in mitochondrial respiration and the up-regulation of metabolic pathways related to proliferation and tumorigenicity. This promotes cell cycle progression into G2/M phase and enhances the self-renewal capacity and tumorigenicity of GBM.[49]

Glial cells play an indispensable part in the development of glioblastoma. A comprehensive understanding of their interaction with glioblastoma cells is beneficial for the development of new treatment strategies for glioblastoma.

The influence of circadian regulators, senses and psychiatric disorders on glioblastoma

Circadian rhythm, a conserved biological phenomenon, plays a crucial role in regulating the proliferation, metabolism, and DNA repair of cancer cells. In glioblastoma, the transcriptional complex composed of circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt - like protein 1 (BMAL1) exhibits significant immunosuppressive properties through multiple pathways. First, it enhances the transcription of the novel chemokine OLFML3, which promotes the self-renewal of GSCs and recruits immunosuppressive microglia to the tumor microenvironment (TME), thereby establishing a pro-tumorigenic immune landscape.[50] Second, CLOCK-BMAL1 upregulates CD162 via the CLOCK-OLFML3-HIF1α-LGMN axis, facilitating the infiltration of microglia with an immunosuppressive phenotype into the GBM tumor microenvironment.[51] Moreover, CLOCK mediates the transcriptional up-regulation of the pro-angiogenic factor periostin (POSTN) through the OLFML3-HIF1a axis, subsequently activating TANK-binding kinase 1 (TBK1) signaling in endothelial cells to promote tumor angiogenesis.[52]

It should be noted that certain functional neuronal circuits can modulate glioblastoma initiation and progression of glioblastoma through activity-dependent mechanisms, such as olfactory and visual stimuli. The activity of olfactory receptor neurons (ORNs) can affect the development of glioblastoma originating from oligodendrocyte precursor cells (OPCs). Mechanistically, olfactory excitation modulates mitral and tufted cells (M/T cells) that receive sensory information from ORNs. These M/T cells release the significant mitogen insulin-like growth factor 1 (IGF1) in an activity-dependent manner, which subsequently binds to receptors on OPCs to promote glioblastoma

development.[53] Epidemiological investigations have revealed that olfactory dysfunction is frequently observed in patients with GBM, even without MRI evidence of the interaction between the tumor and the olfactory pathway. This dysfunction may be associated with the poor survival outcome of patients with GBM, although further cohort studies are required for confirmation.[54] In contrast, the impact of visual stimuli on glioblastoma is more complex and less studied. It has been found that complete visual deprivation caused by dark-rearing increases the density of glioblastoma cells, whereas daily exposure to visual stimuli with different spatial frequencies and contrasts suppresses tumor growth. However, the effect of sensory input is region-specific, and visual deprivation has no significant impact on tumor proliferation in mice with glioblastoma located within the motor cortex.[55]

As the most prevalent tumors in the central nervous system, glioblastomas are significantly influenced by stress and psychiatric disorders. Chronic stress up-regulates dopamine (DA) and its type 2 receptor (DRD2) in tumor tissues, promoting GBM progression through the DRD2/ERK/β-catenin axis and the DA/ERK/TH autocrine positive-feedback loop.[56] Mendelian randomization analysis has shown that attention deficit/hyperactivity disorder (ADHD) and insomnia increase the risk of non-GBM glioblastoma, and schizophrenia (SCZ) is significantly and causally associated with non-GBM glioblastoma.[57] These findings underscore the need to comprehensively consider multifactorial interactions in glioblastoma research, offering novel insights into disease pathogenesis and personalized therapeutic strategies.

In summary, this section has explored the multifaceted effects of the nervous system on glioblastoma. It has described the relationships between different nerve-related factors, including paracrine pathways, electrochemical synapses, and intercellular communication, neurotransmitters, glial cells, circadian regulators, sensory inputs, and psychiatric disorders, and the behaviors of glioblastoma cells, such as proliferation, migration, invasion, apoptosis, immunity, and angiogenesis. These research findings contribute to a deeper understanding of the complex relationship between the nervous system and glioblastoma pathogenesis, identifying more potential therapeutic targets and guiding future glioblastoma treatment.

THE INFLUENCE OF GLIOBLASTOMA ON ITSELF VIA THE NERVOUS SYSTEM

Influence on growth and proliferation (a positive feedback loop)

Emerging evidence demonstrates that glioblastoma cells integrate into functional neural networks with neurons through synaptic connections to promote tumor cell proliferation. Both adult and pediatric glioblastomas establish glutamatergic synapses with neurons,[6,9,16,17,24,58] enabling unidirectional neurotransmission from presynaptic neurons to postsynaptic glioblastoma cells. This synaptic connectivity generates excitatory postsynaptic currents (EPSCs) in glioblastoma cells, predominantly mediated by calcium-permeable AMPA receptors (AMPARs).[6,9,16,17,24,58] Research indicates that Glu released by glioblastoma cells activates Glu receptors such as AMPA and NMDA receptors on both neighboring neurons and adjacent tumor cells, subsequently leading to calcium influx and activating intracellular signaling pathways such as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-AKT pathway to facilitate cell proliferation.[6,9,16,17,24,58] Moreover, Glu can activate metabotropic Glu receptors on astrocytes, prompting the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and NLGN3. These astrocyte-derived factors subsequently create a tumor-supportive condition, further promoting glioblastoma cell proliferation.[6,9,16,17,24,58]

Paracrine signals dependent on neuronal activity significantly boost glioblastoma proliferation. Key activity-dependent paracrine factors, including NLGN3, brain-derived neurotrophic factor (BDNF), and 78-kDa glucose-regulated protein (GRP78) have been identified as potent stimulators of glioblastoma growth. The activity-dependent shedding of NLGN3 is mediated by the metalloproteinase ADAM10. Notably, ADAM10 inhibitors significantly suppresses tumor growth in both high-grade and low-grade glioma mouse models. Furthermore, studies demonstrate that glioblastoma cells can induce the synthesis and secretion of NGF through β-adrenergic receptor agonists, which is crucial for maintaining the maturation and function of cholinergic neurons.[59]

Glioblastoma cells can secrete some cytokines and growth factors, such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF), to regulate the synthesis and remodeling of the extracellular matrix, providing support for tumor cell proliferation.[60,61]

Glioblastoma cells can promote the proliferation of adjacent tumor cells through direct intercellular communication. Specifically, they can release Delta-like ligands (DLL) to activate Notch receptors on adjacent cells, thus driving cell proliferation. The activation of the Notch signaling pathway can inhibit apoptosis and simultaneously promote cyclin expression, pushing cells into the division phase. It is noteworthy that this Notch signaling activation mediated by direct cell-to-cell contact not only promotes proliferation but may also enhance the DNA damage repair capacity of tumor cells. Studies have shown that the activation of the Notch pathway can assist tumor cells in coping with DNA damage induced by radiotherapy or chemotherapy, thereby reducing apoptosis and increasing survival rates. This mechanism partially explains the radioresistance of glioblastomas—particularly the CD133-positive tumor stem cell subpopulation. These cells significantly enrich after radiotherapy and exhibit stronger DNA repair capabilities, radioresistance, and tumor regeneration potential [70]. Therefore, targeting the Notch signaling pathway or CD133-positive tumor stem cells may emerge as a novel strategy to overcome treatment resistance in glioblastomas.

Influence on migration and invasion

During the development of the central nervous system, the migration of neural and glial precursor cells is vital for the formation of proper neuronal circuits and nerve myelin sheaths. GSCs, which drive tumor progression and resist conventional therapies, exhibit striking similarities to neural precursor cells in their invasive properties. This shared migratory phenotype suggests that GSCs' invasion may represent a natural extension of the migratory program inherent to neural precursor cells。The migration

and invasion capabilities of GSCs fundamentally contribute to tumor progression, maintenance, and recurrence. Through integrating multiple techniques, studies have found that glioblastoma cells form interconnected networks with astrocytes, while the unconnected tumor cells are the main drivers of brain invasion. These invasive cells possess neuron-like and neural precursor-like features, with an invasion pattern resembling neuronal migration regulated by neuronal activity and synaptic input. Specifically, neuronal activity can stimulate the formation and growth of TMs, increasing the invasion speed. This process involves AMPA-type Glu receptors on TMs, which facilitate both TMs' formation and tumor cell invasion.[4,9]

Studies have summarized that the glioblastoma cells can hijack multiple developmental regulatory signal pathways to promote tumor invasion and metastasis. For example, the non-canonical ligand Wnt5a in the Wnt signaling pathway plays a key regulatory role in the invasive ability of glioblastoma stem cells, and its expression level is positively correlated with the invasive potential. Additionally, the TGF-β signaling pathway induces the mesenchymal transformation of glioblastoma cells by activating downstream transcription factors, enhancing their migration and invasion abilities. Other key contributors to glioblastoma invasion include ion channel activity, critical transcription factors, and epithelial-mesenchymal transition (EMT) processes.[4,60,62]

Furthermore, the extracellular matrix (ECM) plays a pivotal role in facilitating glioblastoma migration and invasion through multiple mechanisms. Glioblastoma cells secrete various extracellular matrix-degrading proteases, such as matrix metalloproteinases, to degrade the extracellular matrix. They also interact with the extracellular matrix through substances such as hyaluronic acid to promote tumor cell migration and invasion. Relevant studies have found that the extracellular matrix glycoprotein tenascin-C (TNC) can regulate the "Go-or-Grow" phenotype conversion of glioblastoma stem cells, promoting tumor invasion.[63] This finding further confirms the direct impact of dynamic changes in the ECM on the invasive capacity of glioblastoma. Meanwhile, it also suggests that interventions targeting key components of the TME may emerge as a novel strategy to impede the progression of glioblastoma.

The preceding discussion has delved into how glioblastomas exploit the nervous system to modulate and influence their own biological behaviors. Specifically, we have analyzed the mechanisms by which glioblastomas intervene in the processes of growth and proliferation, as well as how these processes are regulated by the nervous system. Additionally, we have investigated the migratory and invasive characteristics of glioblastomas and the role played by the nervous system in these processes. Collectively, these mechanisms drive the progression and recurrence of glioblastomas.

Given the self-promoting effects of glioblastoma cells on their own growth, proliferation, migration, and invasion through interactions with the nervous system, a profound understanding of these neuro-oncological interactions will lay a crucial foundation for the development of novel therapeutic strategies. Subsequently, we will explore potential treatment approaches targeting these mechanisms.

NOVEL THERAPEUTICS AND POTENTIAL TARGETS FOR GLIOBLASTOMA

Targeted therapy

Glioblastoma-targeted therapeutic approaches are designed against tumor-specific molecular targets that are differentially expressed in glioblastoma cells. The interaction between the nervous system and glioblastoma is of great significance in targeted glioblastoma treatment. Selective inhibitors targeting these glioblastoma-specific molecules exhibit potent antitumor activity while demonstrating minimal toxicity to normal cells. The malignant behaviors of glioblastoma cells, including growth, proliferation, invasion, and metastasis, highly rely on a series of specific molecular targets. Targeted therapeutic agents precisely control tumor progression through multiple mechanisms, including the disruption of oncogenic signaling pathways, the inhibition of tumor angiogenesis, and the induction of tumor cell apoptosis.[64]

Disruption of oncogenic signaling pathways

The epidermal growth factor receptor (EGFR), as a key member of the receptor tyrosine kinase (RTK) family, is a common oncogenic mutation site in GBM.[65] Its abnormal activation can drive the proliferation, migration, and treatment resistance of glioblastoma (GBM) through downstream signaling pathways such as RAS-RAF-MEK-ERK and PI3K-AKT-mTOR. EGFR mutations can be observed in approximately 50% of GBM samples, with EGFRvIII being the most common mutation type. This mutant promotes tumor progression by constitutively activating pro-survival signaling pathways. Although there have been numerous attempts to treat GBM using therapies such as EGFR inhibitors and antibodies, traditional EGFR-targeted drugs (such as gefitinib) have limited efficacy,[66] which may be related to the permeability barrier of the blood-brain barrier (BBB), redundant activation of signaling pathways (such as compensatory upregulation of other RTKs), and sustained activation of downstream effector molecules (such as AKT or ERK), among other factors. Recent studies have found that the third-generation EGFR inhibitor osimertinib, with its ability to penetrate the BBB and effectively block the EGFR signaling pathway, can significantly inhibit EGFR-dependent downstream oncogenic signaling, providing a new treatment direction for patients with EGFR-mutant GBM.[67]

Moreover, BRAF, a member of the Raf kinase family, is an essential serine/threonine kinase that plays a crucial activating role in the Mek/Erk signal transduction pathway, thereby driving cell proliferation. BRAF gene mutations have been detected in various cancer types. Although BRAF mutations are relatively rare in high-grade glioma, including GBM,[68] the combination therapy of dabrafenib and trametinib has demonstrated significant efficacy in glioblastoma patients with the BRAFV600E mutation, providing strong support for further research.[69] Additionally, vemurafenib has shown certain activity against BRAFV600E-mutated glioblastomas, especially in low-grade glioma and pleomorphic xanthoastrocytoma (PXA). However, its application is limited by the number of patients and genomic characteristics. These studies preliminarily confirm that BRAFV600E is a targetable oncogene and suggest the need for further evaluation of the potential of RAF and MEK inhibitors in brain tumors.[69]

It is noteworthy that the PI3K/AKT/mTOR pathway is also a commonly mutated pathway in GBM.[65] However, treatments targeting this pathway often have poor efficacy and low patient tolerance,[70] which restricts its use in GBM treatment. Additionally, neurotrophic tyrosine receptor kinase NTRK gene fusions are rare in GBM. Nevertheless, related treatments such as larotrectinib and entrectinib have shown potential therapeutic value, offering new hope for patients with GBM.

Cell cycle regulation and apoptosis induction

Retinoblastoma (pRB), a key protein encoded by the RB1 gene, plays a central role in the cell cycle transition process. It exerts precise control over the transition of cells from the G1 phase to the S phase by interacting with a diverse array of proteins. However, in glioblastoma, aberrant expression and phosphorylation of pRB mediated by multiple factors impair its tumor-suppressive function. This disruption further compromises cell cycle regulation, ultimately accelerates glioblastoma cell proliferation. Notably, the pRB pathway is frequently dysregulated in GBM due to CDK4/6 amplification, CDKN2A/B deletion, or mutation. However, the therapeutic targeting of the pRB pathway remains clinically challenging due to its ubiquitous expression in normal tissues.[71] While CDK4/6 inhibitors such as palbociclib and ribociclib have been demonstrated to have limited efficacy in GBM clinical trials,[72] emerging discovered inhibitors SPH3643 and TG02 show promise for achieving more significant clinical benefits.[73]

The TP53 gene, a vital tumor-suppressor gene located on chromosome 17p13,[74] which encodes a key protein p53 critical for cell cycle regulation, maintenance of genome integrity, and induction of cell differentiation and apoptosis. Mutations or inactivation of TP53 represent a hallmark of tumorigenesis across multiple cancers, including glioblastomas. These genetic alterations abrogate p53's tumor suppressive functions, compromising both cell cycle regulation and apoptotic induction. Notably, the mutated p53 protein may acquire oncogenic properties by aberrantly regulating specific signal pathways and molecular mechanisms to promote glioblastoma progression. Fortunately, novel compounds capable of reactivating mutant p53 have been developed, among which APR-246 stands out as the most representative one.[75] Preclinical studies have demonstrated significant efficacy of APR-246 against neuroblastoma, with its combination with HDAC inhibitors suggesting a promising targeted therapy approach for patients with neuroblastoma.[76] However, several challenges remain, including elucidating the precise molecular mechanisms of APR-246 action, identifying predictive biomarkers, and screening potential combination drugs, all of which require further research and exploration.

Inhibition of tumor angiogenesis

Vascular endothelial growth factor (VEGF), a master regulator of angiogenesis, mediates crucial biological functions by specifically binding to VEGFR). This ligand-receptor interaction has been well-documented to activate the proliferative and migratory potential of endothelial cells, which promotes the formation of vascular lumens to facilitate the growth of new blood vessels.[77]

In GBM, the rapid proliferation and metabolism of tumor cells create a high demand for nutrients and oxygen, leading to a significant increase in VEGF expression and triggering the angiogenesis signaling pathway. Given VEGF's core role in tumor-associated angiogenesis, both the growth factor and its signaling pathway have become the key targets for anti-angiogenic therapy.[78] Pharmacological inhibition of VEGF/VEGFR significantly blocks tumor angiogenesis, thereby restraining tumor progression and metastasis. This treatment strategy has demonstrated significant efficacy in the clinical treatment of multiple malignant tumors, bringing new hope for the treatment of refractory tumors such as glioblastoma.

Currently, several VEGF inhibitors have demonstrated certain therapeutic effects in glioblastoma clinical trials. Bevacizumab, a relatively well-studied drug whose efficacy has been widely recognized in clinical trials. However, its widespread application has been constrained by drug resistance and adverse effects. Other VEGF inhibitors, including cediranib, have also shown potential in inhibiting tumor angiogenesis and limiting tumor growth, yet face similar limitations regarding resistance and toxicity. These challenges underscore the need for more in-depth mechanistic investigations to elucidate the molecular basis of resistance and adverse effects associated with VEGF inhibitors.

Apart from VEGF, integrin is another important therapeutic target for GBM.[79] Integrin, a transmembrane dimer protein composed of an α-subunit and a β-subunit, binds to ECM and initiates a series of intracellular and extracellular signaling cascades. Widely expressed in various tissue cells, integrin acts as an important participant in the angiogenesis process, providing the necessary nutrients and oxygen support for glioblastoma. Inhibition of integrins may be effective in inhibiting glioblastoma progression by suppressing angiogenesis. Although integrin inhibitors such as cilengitide have shown some efficacy in clinical trials, the overall effect remains relatively limited.

Transforming growth factor β (TGF-β), an important growth factor, directly promotes vascular endothelial cell proliferation and migration. In glioblastoma, high TGF-β expression induces extensive proliferation of vascular endothelial cells, facilitating tumor angiogenesis to meet the increased metabolic demands of growing tumors while promoting glioblastoma progression and invasion.[80] Given the close link between TGF-β and glioblastoma progression, particularly the pivotal role of TGFβ2 as a key T cell suppressor in GBM tumor microenvironment, it has been found that RNA interference-mediated TGF-β suppression not only boosts the anti-glioblastoma immune response mediated by natural killer group 2D (NKG2D), but also effectively inhibits the migration and invasion capabilities of glioblastoma cells, significantly reducing their tumorigenicity *in vivo*. Meanwhile, Microglia-derived TGF-β acts as an important regulator in glioblastoma invasion. This process can be selectively inhibited through blockade of the TGF-β signaling pathway mediated by short hairpin RNA (shRNA), specifically by targeting the human TGF-β type II receptor, providing a new potential intervention strategy for targeted therapy of glioblastoma. Furthermore, galunisertib, a novel anticancer drug and TGF-β inhibitor, provides a potential targeted treatment option for patients with glioblastoma.

Immunotherapy

The fundamental principle of immunotherapy involves harnessing the host immune system to recognize and eradicate

malignant or aberrant cells. The immune system plays a crucial role in the interaction between glioblastoma and the nervous system, the immune system plays a crucial role. It not only recognizes and eradicates glioblastoma cells, but also influences glioblastoma growth and invasion by regulating nervous system functions.[81] The therapeutic challenge in glioblastoma stems from the highly immunosuppressive nature of their microenvironment. Despite progress in conventional treatments, the incidence and mortality rates of glioblastoma remain high.

Immunotherapy, as an emerging strategy in glioblastoma treatment, is gradually transforming the treatment landscape of this disease.[82,83] Regarding the current status of glioblastoma immunotherapy,[84,85] the main types of immune therapy for glioblastoma are as follows.

Firstly, immune checkpoint blockade (ICB) therapy focuses on enhancing the antitumor immune response by blocking immunosuppressive checkpoints such as PD-1/PD-L1[86] and CTLA-4.[87,88] While ICB has shown significant efficacy in other cancers, clinical trial results for GBM have been inconsistent and the effects of ICB alone have been relatively limited. Although ICB has shown remarkable efficacy in the treatment of other cancers, the outcomes of clinical trials in glioblastoma, particularly GBM, have been inconsistent, with monotherapy showing limited efficacy. However, emerging evidence suggests that combined with other treatment methods, such as standard radiotherapy/chemotherapy, targeted therapy, or other immunotherapies, it may improve its therapeutic efficacy.[89–91]

Secondly, vaccine therapy is an important immunotherapy approach, including peptide vaccines and dendritic cell (DC) vaccines.[92,93] These vaccines target tumor-associated antigens (TAA) and tumor-specific antigens (TSA) to stimulate the adaptive immune response. Peptide vaccines are favored for their simplicity and efficiency in manufacturing, while DC vaccines utilize the antigen-presenting function of DCs to effectively activate T cells.[94] Some clinical trials, including the phase III trial of rindopepimut and the phase III trial of DCVax-L, have initially demonstrated the great potential of vaccines in GBM treatment.[95]

Thirdly, chimeric antigen receptor T cell immunotherapy (CAR-T) is a cutting-edge genetic engineering therapy. By modifying T cells to express CAR molecules, they can precisely target specific tumor cell antigens.[96] Although CAR-T cell therapy has achieved significant success in treating hematological tumors, its application in GBM faces numerous challenges, including limited BBB penetration, antigen escape, tumor heterogeneity, and the immunosuppressive TME. However, some phase I clinical trials have initially proven the anti-tumor activity of CAR-T cell therapy in GBM treatment.[90]

In addition, oncolytic virus (OV) therapy, as an innovative immunotherapeutic approach, utilizes naturally occurring or genetically modified viruses that selectively replicate in tumor cells. This mechanism of action of OV therapy not only boosts anti-tumor effects but also simultaneously activates immune responses.[97,98] For example, DNX-2401, a conditionally replicating oncolytic adenovirus, has demonstrated promising therapeutic efficacy in clinical trials when combined with pembrolizumab (an immune checkpoint inhibitor) for patients with recurrent glioblastoma. Although the trial has certain limitations, such as the lack of a control cohort and the evaluation of only a single viral dose, these findings still provide strong evidence for the application of oncolytic viruses in cancer treatment.[99] Notably, OV therapy offers multiple significant therapeutic advantages, including the selective targeting of tumor cells, improvement of the immunosuppressive TME and inhibition of GSCs.[100]

Finally, cytokine therapy is another important immunotherapy strategy. Cytokines, which are secreted by the immune system, possess the ability to modulate the immune response. Tumors exploit these cytokines as protective mediators to weaken the immune system's attack against them. However, with proper utilization, cytokines can induce anti-tumor immune responses. In cancer treatment, commonly used cytokines include interleukins (e.g., IL-2, IL-4, IL-13) and interferons (e.g., IFN-α, IFN-β, IFN-γ). For example, IL-2, a growth factor for T cell activation, has been approved for renal cell carcinoma and melanoma treatment but demonstrates significant side effects in glioblastoma treatment. Targets corresponding to IL-4 and IL-13 have shown certain safety and efficacy in glioblastoma treatment. Among interferons, IFN-α has been used to treat patients with malignant glioblastoma, though reported therapeutic outcomes remain inconsistent. IFN-β can enhance chemosensitivity by reducing MGMT transcription and has shown some efficacy when combined with radiotherapy or chemoradiotherapy in glioblastoma treatment. Although the potential of IFN-γ as an adjuvant therapy in glioblastoma is still under investigation, preliminary studies have shown promising results.[101,102] While the exact efficacy of some cytokine therapies in glioblastoma requires to be further clarification, current treatment regimens show a favorable safety profile. Future research should further explore the effectiveness and application prospects of various cytokines in glioblastoma treatment.

Although so much progress has been made in the immunotherapy of glioblastoma, there are still many challenges in practical application, which are mainly reflected in the blood-brain barrier, tumor antigen heterogeneity, and immune microenvironment.

First, GBM is located in the brain, and the blood-brain barrier (BBB) has a significant impact on the efficacy of immunotherapy. BBB is composed of tight junctions of cerebral capillary endothelial cells and cerebral and ventricular epithelial cells, which can filter regulatory substances, but restrict the entry of T cells from the peripheral blood into the brain parenchyma, and only activated T cells can inefficiently cross specific adhesion molecules. Moreover, while glioblastomas destroy some of the BBB, the BBB that infiltrates areas of normal brain tissue remains intact, further hindering T cell migration.[103] The existence of the blood-brain barrier also restricts the precise delivery of some immunotherapy drugs to the brain tumor site, making it difficult for the drugs to effectively reach the lesion during systemic administration, thus affecting the treatment effect.

Secondly, the tumor antigenic heterogeneity of glioblastomas also seriously affects the efficacy of immunotherapy. There is significant heterogeneity in antigen expression in tumor cells, such as EGFRvIII is expressed only in some tumors, and negative subclones coexist within tumors, which can easily lead to failure of targeted therapy due to antigen loss (especially in the case of recurrence) after treatment. In addition, other antigens such as IL-13Rα2 and HER2 also have similar down-regulation issues.[104,105] This heterogeneity in intratumoral and antigen

expression can directly lead to the absence of immunotherapy targets and hinder the therapeutic effect.

Finally, glioblastomas have an immunosuppressive tumor microenvironment, which is also not conducive to immune-therapy. On the one hand, there are a variety of immune-suppressive factors in its micro-environment, such as TGF-β2 and IL-10, which will inhibit the proliferation and function of T cells and hinder the production of immune responses. On the other hand, patients have severe systemic T cell depletion, and the number of regulatory T cells in tumor tissue is relatively high, which can inhibit effector T cell activation, and tumor hypoxia will activate related signaling pathways and promote the proliferation of immunosuppressive cells, resulting in tumors in an immunosuppressive state, which is not conducive to immunotherapy.[106,107]

Gene therapy

Gene therapy holds great promise in the treatment of cancer, particularly in brain tumors. In the context of brain tumors, the non-metastatic nature of gene therapy enables targeted delivery of genetic material to tumor cells for therapeutic genetic modification.

Gene therapy for glioblastoma represents a strategy that harnesses new biotechnologies to intervene directly in the gene expression or function of glioblastoma cells for therapeutic purposes. Suicide gene therapy is among the most promising gene-based treatment approaches.[108] Specifically, suicide gene therapies based on TK[109] and CD have been the subject of extensive research. The TK-based therapy inhibits tumor replication and cell division through an enzyme-prodrug system,[110] while the CD-based approach causes tumor cell death by converting 5-fluorocytosine into its toxic derivative.[111] These therapies have demonstrated certain efficacy in both pre-clinical studies and clinical trials.

Gene delivery systems for brain tumor therapy employ both viral and non-viral vectors. Viral vectors, such as retroviruses, adenoviruses, and adeno-associated viruses, have been widely investigated, issues such as immunogenicity and transduction efficiency persist. In contrast, non-viral vectors including liposomes, stem cells, polymer nanoparticles and extracellular vesicles.[112] offer advantages of reduced toxicity and favorable biocompatibility.

Gene therapy for glioblastoma faces many challenges, and there are prominent problems at the level of vector technology. Viral vectors have low transduction efficiency, such as retroviral vectors that need to be implanted into packaging cells to deliver genes, but have low titers and short cell survival time; Although adenovirus vectors have high titers, the genome can exist in the form of extrachromosomal elements, which are easily lost in dividing cells, which affects the persistence of transduction efficiency. Different vectors also have their own hidden dangers, such as strong immunogenicity, abnormal cell migration, limited loading capacity, genetic damage and carcinogenic risks in viral vector gene therapy, for example, adenovirus can trigger a strong immune response, resulting in transgene expression for a short time; Although non-viral vectors have low immunogenicity, they face problems such as nuclease degradation, systematic clearance, and low efficiency across the blood-brain barrier, and there are many obstacles in the process of gene delivery and avoiding degradation by lysosomes.[113] In addition, in glioblastoma gene therapy, nanoparticles are mainly used as gene delivery carriers, but the stability of nanoparticles is not good, unmodified nucleic acids are easily degraded by nucleases,[114] and there is a contradiction between size and clearance, less than 10 nm is easy to be cleared by the kidney, and more than 200 nm may activate the complement system and be cleared by the blood.[115,116]

Second, neural stem cells (NSCs) are prone to the accumulation of chromosomal abnormalities and genomic instability, which is at risk of immortalization, and their biology and fate are not fully understood, and may stimulate tumor growth or cause non-specific toxicity to normal cells.

Although a variety of gene therapies (suicide genes, tumor suppressor genes, immunomodulatory genes, and oncolytic therapies) have made significant progress in the treatment of brain tumors, more clinical trials are needed to verify their safety and efficacy.

Other innovative treatment strategies

As an emerging treatment method for glioblastoma, TTFields has made significant progress in clinical application by interfering with the mitotic, cell cycle, and migration processes of tumor cells through low-intensity, medium-frequency alternating electric fields, inducing apoptosis and enhancing anti-tumor immune responses.[117] In newly diagnosed glioblastoma (ndGBM), TTFields in combination with temozolomide (TMZ) significantly prolonged overall survival and progression-free survival[118–120]; In recurrent glioblastoma (rGBM), TTFields monotherapy has comparable overall survival compared with systemic therapy, with a better safety profile and quality of life. Its efficacy is closely related to the duration of use, dose, power density, and field strength, and the efficacy can be further improved by optimizing the delivery method. TTFields has a good safety profile, with mild to moderate skin reactions as the main adverse event, with little impact on patients' quality of life, and is not hindered by the blood-brain barrier, and is suitable for a wide range of people.[121–123] However, further research is needed on cost-effectiveness issues and efficacy in low-grade glioma. Future research directions include improving equipment to improve patient compliance, expanding combination therapy options, expanding tumor types, and optimizing personalized treatment plans to overcome current clinical application challenges and further improve treatment outcomes.

CONCLUSIONS AND FUTURE PERSPECTIVES

The pathogenesis and targeted therapies of glioblastoma have long been the research focus in related fields. Among these, the interaction between the nervous system and glioblastoma represents a significant advancement in the mechanistic understanding that distinguishes glioblastoma from other solid tumors. Through a systematic review of relevant studies, this article demonstrates the bidirectional influence of this interaction. The nervous system affects tumor progression through paracrine signaling, synaptic interactions, and tumor migration and invasion. Conversely, glioblastoma also impacts the nervous system's manifestations by influencing neuronal survival and

excitability, as well as neural cell networks and intercellular communication. These interactions offer new perspectives and potential targets for glioblastoma treatment. Emerging treatment modalities, including targeted therapy, immunotherapy and gene therapy, have demonstrated potential in addressing key aspects of glioblastoma pathogenesis, especially in precisely targeting tumor proliferative and invasive mechanisms, activating immune responses and directly modifying the genetic components of tumor cells. While these treatment methods have shown some efficacy in pre-clinical studies and early-stage clinical trials, numerous challenges remain, such as drug delivery, drug resistance, and the immunosuppressive tumor microenvironment.

Future research directions should focus on elucidating the neurobiological mechanisms underlying glioblastoma pathogenesis to identify more effective therapeutic targets. Additionally, more clinical trials are needed to validate the safety and efficacy of existing treatment methods and to explore optimal treatment combination strategies. With the continuous integration and development of neuroscience, oncology, and biotechnology, glioblastoma treatment strategies based on neural regulation are expected to achieve more substantial breakthroughs and progress. For glioblastoma treatment, it is necessary to comprehensively consider the interaction of multiple factors and deeply study the mechanisms of various potential therapeutic targets and methods to overcome the limitations of current therapeutic approaches. For example, in targeted therapy, further exploration of methods to overcome the blood-brain barrier, enhance drug efficacy, and reduce adverse reactions is required. In immunotherapy, Ment of continued development of innovative therapies to strengthen the immune system's ability to target glioblastoma and overcome the immunosuppressive microenvironment is essential. In the field of gene therapy, the optimization of gene-delivery vectors to improve treatment safety and efficacy is crucial. Simultaneously, the in-depth exploration of the complex relationship between neuroscience and glioblastoma is expected to uncover more novel therapeutic targets, providing more effective treatment options for patients with glioblastoma and improving their prognosis and quality of life.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.T.H. and Y.X.Z.; methodology and visualization, K.L., and M.Y.D.; Writing—review and editing, K.L., M.Y.D., Q.L., and J.Q.L.; Supervision, M.T.H. and Y.X.Z. All authors have read and agreed to the published version of the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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