Neuroscience in glioma biology (Review)

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Received May 20, 2025; Accepted September 4, 2025

DOI: 10.3892/or.2025.8999

Abstract. Although our understanding of the molecular and cellular factors involved in the development and growth of glioma has increased, prognosis remains dismal in most patients. The emerging field of cancer neuroscience has revealed the intricate functional interplay between glioma and the cellular architecture of the brain, especially neural circuits. In recent years, studies have revealed that glioma cells integrate and remodel multicellular neural circuits. Neural circuits have thus emerged as critical regulators of glioma from initiation to malignant growth. In the present review, an updated framework was provided for understanding the construction of neuron-glioma networks and the mechanisms by which neurons regulate the malignant phenotype of glioma. Readers will also obtain insights into the construction of glioma-glioma networks formed by tumor microtubes. Furthermore, the present review reveals the complex interconnectivity among the nervous system, immune system and glioma that promotes tumor growth. Finally, some potential areas of clinical translation and new research directions were highlighted.

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Key words: glioma, neuroscience, neural circuits, synapse, neuron

1. Introduction

Cancer is a complex ecosystem that includes malignant cells and non-malignant cells in the internal environment, as well as the stroma, vasculature, and immune, nervous and endocrine systems. These components of cancer coexist and collaborate to boost the survival and proliferation of cancer cells (1). The ecosystem of cancer possesses various core characteristic capabilities, including sustaining proliferative signaling, evading growth suppressors, and avoiding immune destruction (2). However, these core hallmark capabilities do not explain the mechanism by which the nervous system regulates cancer growth. Remarkably, increasing experimental evidence accumulated over the past decade indicates that the nervous system is crucial to cancer initiation and progression (3). The accumulation of data has formed the basis of a new research field called cancer neuroscience.

As an incurable malignant tumor mainly originating in the brain, malignant glioma has become a research paradigm in cancer neuroscience. Malignant gliomas comprise a heterogeneous group of tumors that mainly include glioblastoma multiforme (GBM) and other diffuse gliomas, such as grade 3 anaplastic astrocytoma and oligodendroglioma (4). As the type of glioma with the greatest malignancy, GBM accounts for 50.9% of all malignant brain tumors in the Central Brain Tumor Registry of the United States (5). Patients with GBM have a dismal prognosis with limited treatment options, comprising maximally safe surgery, radiotherapy, and concomitant and maintenance treatment with temozolomide (6-10). Although research has investigated the molecular profiles, genetic mutations, epigenetic reprogramming, tumor cell state, and immune microenvironment of GBM (11-14), effective treatment methods are lacking. A crucial reason for this situation is that the brain is dynamically harnessed as malignant features expand (15), and clarification of these processes could provide further insights for the development of therapeutics.

The present review provides an updated framework for understanding the various aspects of communication between the nervous system and glioma. Readers will obtain insights into the construction of neuron-glioma networks, which are constructed from neurons and glioma cells located at the edge

of the tumor, and the mechanisms by which neurons regulate the malignant phenotype of glioma. Readers will also understand the construction of glioma-glioma networks, which are constructed from glioma cells located inside the glioma by tumor microtubes (TMs), and glioma cell-induced neural hyperexcitability. Furthermore, the present review reveals the mechanism by which the complex interconnectivity among the nervous system, immune system and glioma promotes tumor growth. Finally, some potential areas of clinical translation and new research directions were described.

2. Glioma cells remodel the neural circuits into malignant networks

As the host organ of glioma, the brain features structural and functional networks that are organized according to complex topological properties. Signaling and information transfer between neural circuits permeate every facet and spatial scale of brain function (16,17). As they originate from brain cells, gliomas naturally exist in neural circuits. However, the specific type of brain cells from which glioma originates remain controversial. Because oligodendroglia precursor cells (OPCs) and neural progenitor stem cells (NPCs) continue to proliferate throughout life, they are considered the most likely origins of gliomas (5,18). Liu *et al* (19) identified notably aberrant growth prior to malignant tumor in OPCs but not in any other neural stem cell (NSC)-derived lineages or NSCs themselves. Although OPCs are not neuronal cells in the brain, they can receive direct synaptic input from neurons at bona fide synapses. Electrophysiological analyses confirmed that OPCs express multifarious functional neurotransmitter receptors and respond physiologically to presynaptically released neurotransmitters (20-22). This characteristic is likely to be extended to glioma cells originating from OPCs. Moreover, gliomas and neural circuits might interact in a bidirectional manner. In short, higher neural activity induces faster glioma growth, and the presence of glioma increases neural activity (23). Recently, some studies proved that GBM both disrupts neural circuits (24) and remodels neural circuits (25) into malignant networks. These remodeled neural circuits both promote glioma-genesis and their progression (26-29) and determine the type of glioma that arises in different brain tissues. Romero-Garcia *et al* (30) found that distinct glioma subtypes exhibited different spatial profiles of occurrence. Lower-grade gliomas appear to arise more frequently in frontal areas, whereas GBM is often found in temporoparietal areas (30). Their study further revealed that the preferential occurrence of low-grade glioma (LGG) versus high-grade glioma is associated with different regional transcriptomic characteristics and brain connectomic features in normative populations (30), that is, different neural circuits.

To further clarify the close correlation between GBM and neural circuits, GBM data from The Cancer Genome Atlas (TCGA) were analyzed and 4,729 differentially expressed genes in GBM were identified. By implementing the intersections of genes between differentially expressed genes in GBM and synaptic genes from MSigDB, a Venn diagram was generated, demonstrating 860 differentially expressed genes from GBM that are related to synapses (Fig. 1A). The heatmap in Fig. 1B displays the expression changes of differentially expressed genes related to synapses in GBM. The bubble plots in Fig. 1C illustrate that these differentially expressed genes in GBM are significantly involved in neural circuits. From the analysis of TCGA data, it is evident that the initiation and progression of GBM are closely related to neural circuits.

In addition, most glioma cells inside the tumor are interconnected with each other via TMs, which are ultralong, cytoskeletal-enriched membrane tubes. These TMs comprise the anatomical basis of highly functional glioma-glioma networks coupled by gap junctions (31). Some studies consistently revealed TMs and their multicellular networks in incurable gliomas, namely GBMs, WHO grade II-IV astrocytoma, and K27M mutated midline gliomas (32,33). Through TMs, glioma cells at the edge of the tumor can transmit information sent by neurons to every glioma cell inside the tumor (Fig. 2).

Taken together, as presented in Fig. 2, glioma cells and neural circuits jointly construct malignant networks. The malignant networks could be involved in a vicious cycle of neuronal hyperexcitability and glioma progression. Further analysis of these malignant networks will provide a deeper understanding of glioma and accurately predict prognosis. Moreover, such research offers novel therapeutic opportunities.

3. The potential mechanisms by which neurons promote the malignant phenotype of glioma cells

As our understanding of the cancer microenvironment has increased, neuronal regulation has been deemed to play a crucial role in glioma biology (34). Some mechanisms by which neurons regulate the malignant phenotype of glioma cells have been expounded. Through functional neuron-to-glioma synapses and paracrine signaling factors, membrane depolarization in glioma cells drives tumor proliferation and invasion (35). Neural activity-mediated ion channels also promote the proliferation of glioma cells (3,36). In addition, GBM hijacks the neuron-astrocyte glutamate-glutamine cycle to promote tumor proliferation and invasion (37) (Fig. 3).

Neurons promote the proliferation and invasion of glioma cells through synapses. Although the OPC-like and NPC-like populations of glioma cells at the rim of the tumor have been found to be enriched in neuron-glioma synapses (38), the circuit architecture and neural subtype in neuron-glioma networks remain to be further elucidated. Sun *et al* (39) revealed that GBM cells rapidly incorporated into brain-wide neural circuits and displayed different local and long-range connectivity. They also identified miscellaneous neuro-modulatory inputs across the brain, such as cholinergic inputs from the basal forebrain excluding glutamatergic inputs (39). Via comprehensive whole-brain mapping, Hsieh *et al* (40) demonstrated that these glioma-innervating neurons (GINs) constantly arise in brain regions, including different neuro-modulatory centers and specific cortical layers, which project to the locations of glioma. Molecular profiling unveiled that these long-range cortical GINs are mostly glutamatergic, and subsets express both glutamatergic and GABAergic markers. Meanwhile, local striatal GINs are mainly GABAergic. They used electrophysiology to confirm that although GINs share passive

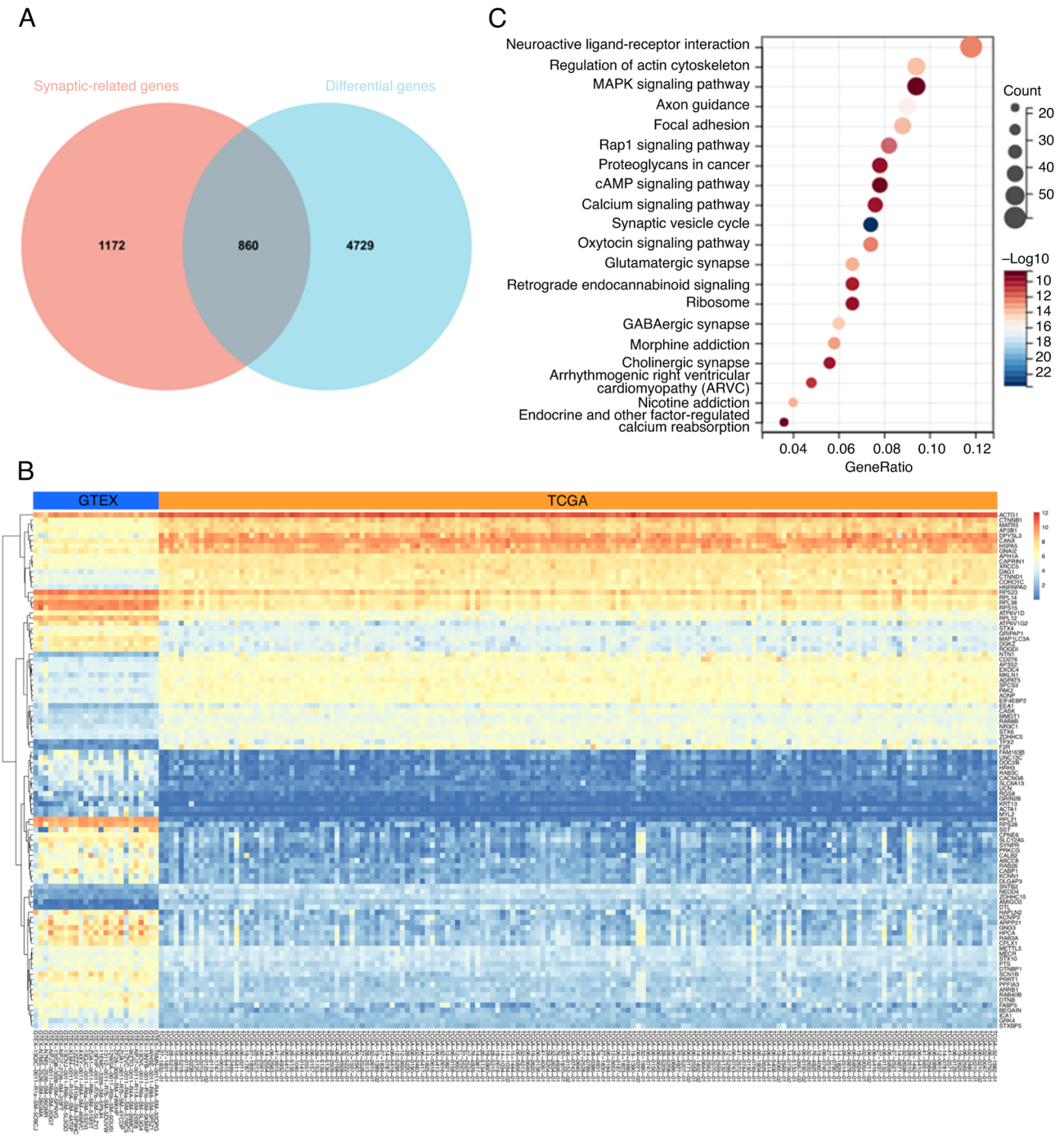

Figure 1. Bioinformatic analysis of The Cancer Genome Atlas data clarified the close correlation between GBM and neural circuits. (A) Venn diagram presents 860 differentially expressed genes from GBM related to synapses. (B) Heatmap displays the expression changes of differentially expressed genes related to synapses in GBM. (C) The bubble plots illustrate the involvement of these differentially expressed genes in GBM in neural circuits. GBM, glioblastoma multiforme.

intrinsic properties with cortex-innervating neurons, GINs possess different action potential waveforms (40).

As previously mentioned, extensive structural and functional analyses identified glutamatergic synaptic neurons as the main neurons involved in neuron-glioma networks. Similarly as the neuron-OPC synapses that form in the healthy brain, neuron-glioma synapses are mainly mediated by calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, which trigger neuronal activity-dependent currents and membrane depolarization in glioma cells on the postsynaptic side. Glioma cells upregulate AMPA receptors, and the AMPA receptor phenotype of glioma cells differs from that in most neurons of the adult brain, which is not permeable to calcium ions because of the presence of an edited form of the GluR2 subunit. These bona fide neuron-glioma synapses promote the growth and invasion of glioma cells, as evidenced by genetic/pharmacological blockade of AMPA receptors in neuron-glioma co-culture and *in vivo* (41). As another receptor associated with glutamatergic synaptic neurons, N-methyl-d-aspartate receptors (NMDARs)

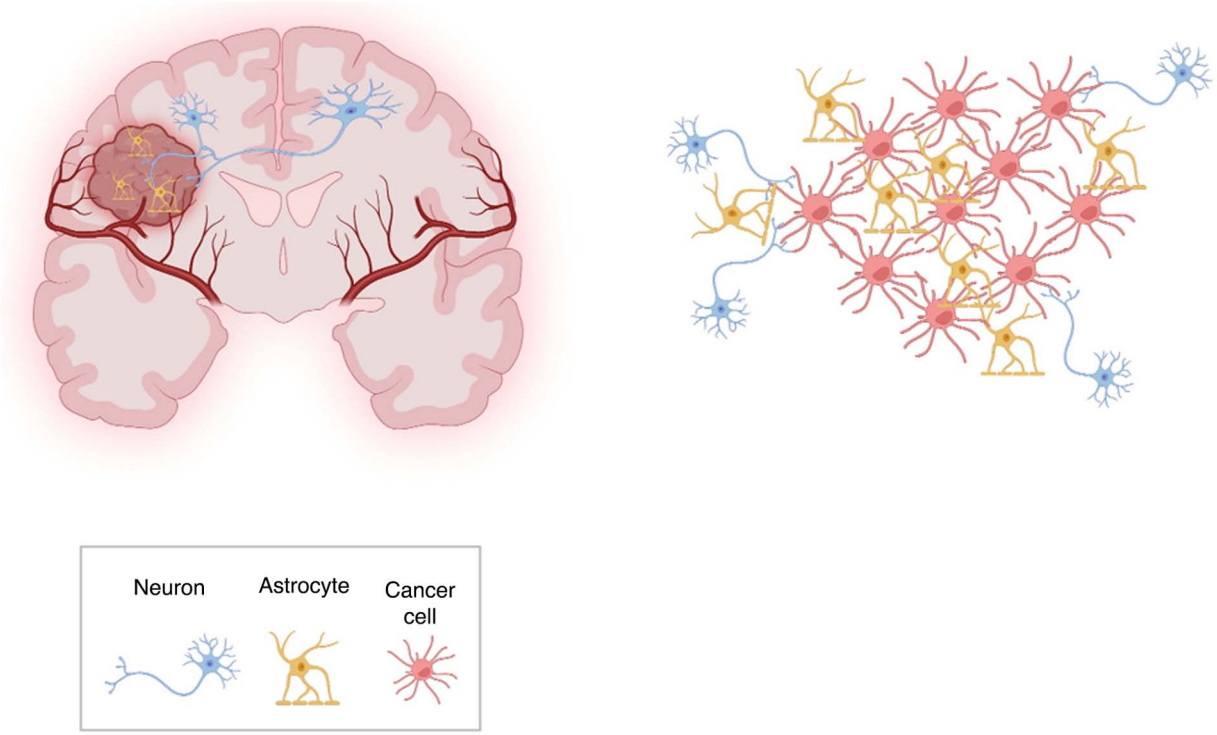

Figure 2. Both glioma cells and neural circuits construct malignant networks, which also include astrocytes.

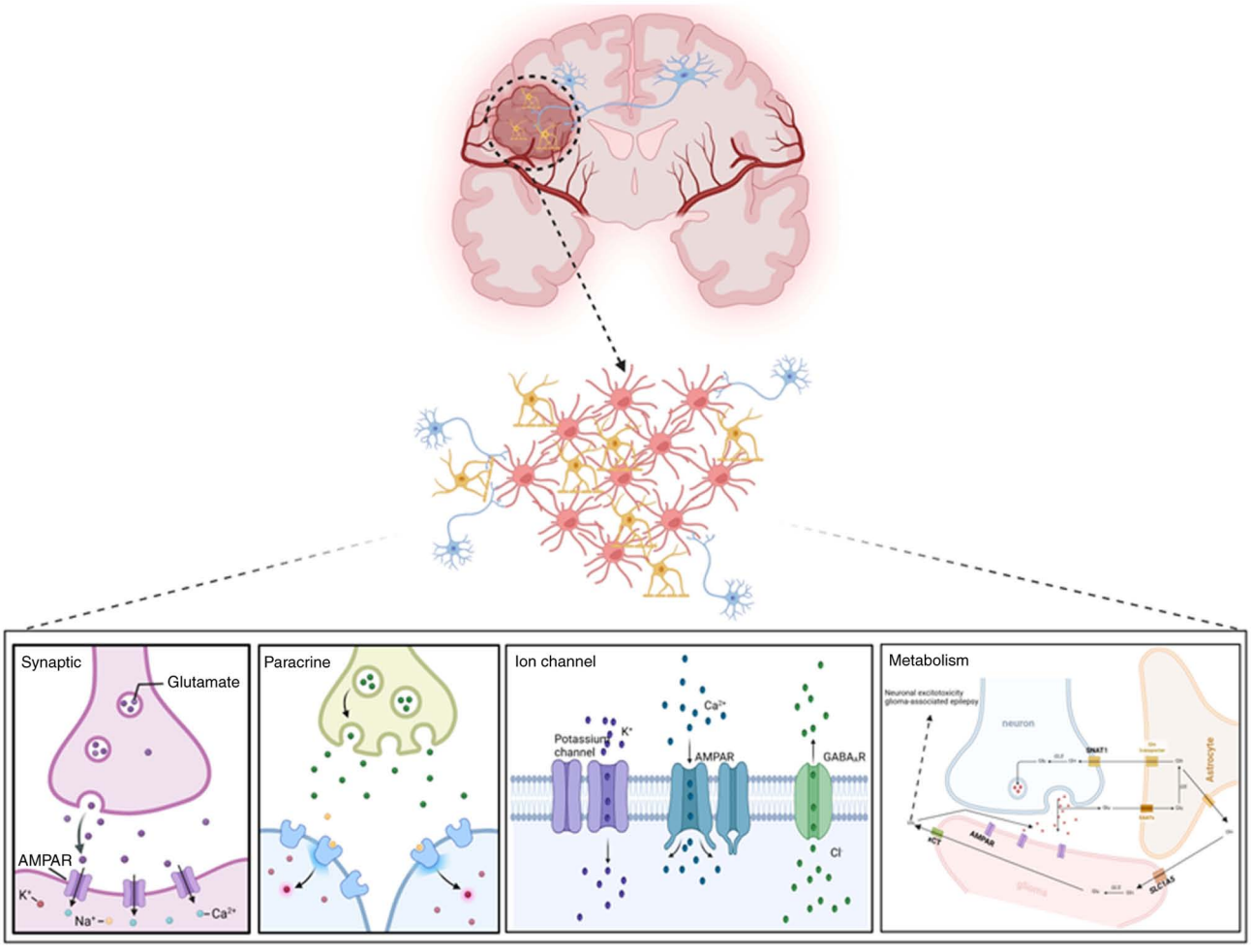

Figure 3. Neural activity promotes the proliferation and invasion of glioma cells by various mechanisms, including functional neuron-to-glioma synapses, paracrine signaling factors, neural activity-mediated ion channels, and hijacking of the neuron-astrocyte glutamate-glutamine cycle.

have been less studied in gliomas. Müller-Längle *et al* (42) reported that treatment with NMDAR antagonists abated the growth and migration of glutamate-releasing glioma cells and increased their radiosensitivity by inhibiting double-strand break repair. These findings suggested that NMDAR activation facilitates the growth and radio-resistance of glioma (42). However, the expression of NMDARs on glioma cells and the mechanism by which neurons regulate the phenotype of glioma cells need to be further delineated in the future.

In addition to glutamatergic synaptic neurons, other neurons have been found to participate in the proliferation and invasion of glioma cells. Sun *et al* (39) revealed that GBM cells express multiple types of neurotransmitter receptors, including ionotropic and metabotropic glutamatergic, GABAergic and cholinergic receptors, as well as serotonergic, adrenergic and dopaminergic receptors. Furthermore, they found that acute acetylcholine stimulation induced uninterrupted calcium oscillation and long-lasting transcriptional reprogramming of GBM cells into a more invasive state by the metabotropic CHRM3 receptor. *In vitro* and *in vivo* experiments proved that knockdown of CHRM3 can inhibit GBM cell invasion, proliferation, and survival (39). These results were confirmed by Drexler *et al* (43), who demonstrated that cholinergic neurons in the midbrain have long-range projections to midline structures that foster activity-dependent growth of diffuse midline glioma (DMG) via CHRM1 and CHRM3 cholinergic receptors. Regarding inhibitory neuron synapses, GABAergic synaptic neurons release GABA, which activates $GABA_A$ receptors in neural precursors to attenuate NSC proliferation (44). As a modulator of GABAergic synaptic neurons, diazepam-binding inhibitor (DBI) suppresses $GABA_A$ receptor-mediated currents. Prior research illustrated that GBM lacks $GABA_A$ receptor expression. The expression of $GABA_A$ receptors is negatively correlated with the tumor grade of glioma, and high $GABA_A$ receptor expression predicts improved prognosis in different types of gliomas (45). Recently, Barron *et al* (46) found that GABAergic neuron-to-glioma synapses promoted the growth of DMG by $GABA_A$ receptors. Via NKCC1 chloride transporter function to elevate intracellular chloride concentrations in DMG malignant cells, GABAergic input has a depolarizing role on DMG cells. By inducing glioma cell membrane depolarization, the activity of GABAergic interneurons boosts DMG proliferation. By contrast, the activity of GABAergic interneurons did not affect the growth of hemispheric GBM (46). In addition, DBI is overexpressed in glioma, and it inhibits GABA signaling, thereby promoting glioma growth. However, DBI is upregulated in GBM, thereby driving tumor growth through a GABA-independent pathway (47). Therefore, further detailed research is needed to clarify the mechanism by which GABAergic synaptic neurons regulate the growth of different glioma subtypes.

Neural activity boosts the proliferation of glioma cells via paracrine signaling. In addition to neuron-glioma synaptic communication, paracrine signaling also mediates neural activity-induced glioma growth through brain-derived neurotrophic factor (BDNF) and the soluble synaptic adhesion protein neuroligin-3 (NLGN3) (48-52). Venkatesh *et al* (51) confirmed that neural activity promotes the proliferation of glioma cells through secreted factors. Via mass spectrometry, they identified some secreted proteins that increased the proliferation of glioma cells in an activity-dependent manner. More unexpectedly, it was found that NLGN3 is an important activity-regulated paracrine growth factor, and 10 of 11 different glioma models exhibited increased proliferation in response to NLGN3 (48). This dependance on microenvironmental NLGN3 was proved in patient-derived xenograft models of diffuse intrinsic pontine glioma, pediatric GBM and adult GBM. This phenomenon did not occur in a patient-derived model of brain metastasis from breast cancer, suggesting specificity for gliomas (51). However, with prolonged observation, some xenografted tumors in mice began to grow in the NLGN3-deficient brain within each experimental cohort (51). The reason for this finding is unclear, and further research is needed. Mechanistically, neural activity increases the expression of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), which cleaves membrane-bound NLGN3 to generate a soluble bioactive protein, inducing the proliferation of glioma cells. Both Nlgn3 knockdown and pharmacologic ADAM10 inhibition suppress the growth of glioma (51). Likewise, neural activity-regulated BDNF also promotes the proliferation of glioma cells via a paracrine pathway (53). In addition, NLGN3 and BDNF promote synaptic connectivity between neurons and glioma cells and regulate the strength of neuron-glioma synapses (35). They play their respective roles in various types of gliomas. Specific details still need to be studied.

Neural activity activates ion channels to regulate the malignant phenotype of glioma cells. In addition to synaptic activity-dependent currents, neural activity also evokes the depolarization of glioma cell membranes via non-synaptic activity-dependent currents mediated by ion channels. Accumulating evidence indicates that ion channels act a pivotal part in the progression of glioma by mediating communication between neurons and glioma cells. In the central nervous system, Na^+, K^+, Ca^{2+} and Cl^-channels are involved in regulating various biological behaviors of cells (54). It was recently indicated that ion channel mediated-electric currents direct the migration and invasion of glioma cells. Glioma cells regulate their volumes through ion channels for migration. Through NKCC1, glioma cells accumulate Cl^- intracellularly, whereas Cl^- channel protein 3 (CLC3) regulates Cl^- efflux. To balance Cl^- efflux, glioma cells regulate K^+ influx *via* Ca^{2+} activation by expressing KCa1.1 and KCa3.1 channels (55). Chlorotoxin, which causes the internalization of CLC family members, inhibits the invasion of glioma cells (56). Barish *et al* (57) developed chimeric antigen receptor (CAR) T cells incorporating chlorotoxin and evaluated the primary objectives of feasibility and safety in four patients with MMP-2-expressing recurrent GBM (NCT04214392). The result showed that three of the four participants exhibited a best response of stable disease, and the therapy was well tolerated with no dose-limiting toxicities (57). Likewise, blockade of KCa1.1 or KCa3.1 channels also inhibits the invasion of GBM cells (55). A preclinical study identified that KCa3.1 channel inhibition sensitized malignant gliomas to temozolomide (58). Recently, Dong *et al* (59) found that GBM cells predominantly express EAG2 and Kvβ2 at the GBM-neuron interface. EAG2 and Kvβ2 physically interact to form a K^+ channel complex. Disruption of the EAG2-Kvβ2

interaction mitigates growth and temozolomide resistance in GBM (59). However, the mechanism by which neural activity regulates the proliferation of glioma cells by ion channels remains incompletely understood. The activity of ion channels involving neuron-mediated electric signals is essential for downstream pathway signaling, whereas neural activity promotes glioma cell proliferation. Based on these facts, it was hypothesized that ion channels act as important bridges between neural activity and glioma progression. However, these assumptions need to be further confirmed.

Neural circuits promote the growth of glioma by supplying nutrients. After integrating into neural circuits, GBM cells also hijack brain metabolism, co-opting neurons and glia to obtain nutrients. As a dominant anaplerotic carbon source for the TCA cycle, glutamine is rapidly consumed by GBM cells *in vitro*. However, the *in vivo* glutamine metabolism of GBM differs from that in cell culture. *In vivo*, some GBM cells integrate into the neuron-astrocyte glutamate-glutamine cycle, allowing these cells exploit astrocytes as an exogenous source of glutamine. It has been revealed that glutamine catabolism through the GLS-initiated pathway is absent in IDH1 wild-type GBM *in vivo*. GLUL-positive glioma stem cells (GSCs) can produce glutamine, whereas GLUL-negative GBM cells lack this ability. *In vivo*, GLUL-negative GBM cells reside in close proximity to astrocytes, which are GLUL-positive (37). This phenomenon indicates that GLUL-positive astrocytes are the primary sources of glutamine for anabolism in GBM. By expressing the high-affinity uptake transporter SLC1A5, GBM cells potentially outcompete neurons for glutamine (37). After depleting glutamine, astrocyte-derived glutamine is adequate to maintain the proliferation of GLUL-negative GBM cells *in vitro* (60). IDH wild-type GBM cells produce and secrete high levels of glutamate, and consequently, the extracellular glutamate concentration in the tumor microenvironment (TME) surpasses that in normal brain tissue. Excessive glutamate promotes the growth of GBM and triggers epilepsy in patients with GBM.

In addition to glutamate, GSCs can acquire and hydrolyze N-acetylaspartate (NAA), which is synthesized and secreted exclusively by neurons, into acetate and aspartate to promote proliferative metabolism. In particular, NAA both boosts GSC proliferation and suppresses GSC differentiation *in vitro* (61).

4. Glioma-glioma networks formed by TMs promote the malignant phenotype of glioma

In the tumor core, glioma cells are interconnected with each other through TMs, thereby forming glioma-glioma networks (Fig. 4). Astrocyte-like and MES-like tumor cells enriched in TMs construct the gap junction-coupled glioma-glioma networks (38). Moreover, most of these cells contain multiple TMs. Additionally, Venkataramani *et al* (38) found that connections form between GBM cells and astrocytes via gap junctional coupling.

TMs are morphologically and molecularly heterogeneous. Interconnecting TMs represent a continuation of the membrane of glioma cells, and they extend to other cells while being separated by gap junctions. Meanwhile, non-connecting TMs are ultralong membrane protrusions extended by glioma cells. These TMs hijack numerous characters from neural protrusions. They have blind endings reminiscent of neurite growth cones, and they facilitate the exchange of ions and molecules. More importantly, TMs mediating the functional glioma-glioma networks are predominately resistant to radiotherapy and standard chemotherapy with temozolomide (38).

It was recently revealed that a small population of GBM cells exhibit autonomous oscillatory Ca^{2+} transients (Fig. 4). These cells are highly connected to other glioma cells in glioma-glioma networks, forming a 'hub' within the network. The Ca^{2+}-activated K^+ channel KCa3.1 regulates autonomous and rhythmic oscillatory Ca^{2+} transients in these 'hub cells' that propagate through the connected network of gap junction-coupled tumor cells (62). Furthermore, Hausmann *et al* (62) found that these periodic Ca^{2+} transients are involved in the regulation of mitogen-activated protein kinase 2 and nuclear factor-κB pathways in GBM cells, contributing to their malignant behaviors. KCa3.1 knockdown abrogates these autonomous Ca^{2+} transients, further mitigating glioma growth and prolonging mouse survival in preclinical models of GBM (62).

At present, several molecules related to neurite outgrowth and formation, including growth-associated protein (Gap43), p120 catenin and tweety-homolog 1 (Ttyh1), have been identified as potent drivers of TM outgrowth (63). Similar to the findings in the neurodevelopmental program, Gap43 mainly localizes at the tips of TMs. Gap43 downregulation inhibits TM formation in glioma (64). p120 catenin, an upstream regulator of genes related to neuronal network formation in glioma, affects the formation of TMs, further regulating invasion and network formation by GBM cells (65). Moreover, p120 catenin also modulates Gap43 expression (32). Ttyh1 is a putative calcium-regulated chloride channel related to neurito-genesis in the membranes of axonal growth cones. Ttyh1 downregulation was found to reduce the invasion and proliferation of GBM cells by inducing abnormal TMs, whereas tumor network formation between GBM cells was not affected. These results suggest that molecular functions related to TMs can be divided into invasive and interconnecting subclasses (66). Moreover, Ttyh1 is localized to chromosomal arms 1p and 19q, similarly as the neurotrophic factors nerve growth factor and neurotrophin 4, which upregulates Gap43. These results suggest that 1p/19q intact astrocytoma has significantly more and longer TMs than 1p/19q co-deleted oligodendrogliomas. These data offer a reasonable explanation of the improved prognosis of 1p/19q co-deleted oligodendrogliomas (33).

In addition to the aforementioned molecules, connexin 43 is the most important gap junction protein in TMs. In prior research, connexin 43 downregulation in glioma cells markedly decreased the number of glioma cells entering the glioma-glioma network, reducing communication *via* intercellular calcium waves. These changes led to reduced tumor size *in vivo* (36). In addition, TGF-β was found to participate in TM formation *via* SMAD activation and thrombospondin 1 (67,68).

5. Glioma cells induce neural hyperexcitability

As one of the most common symptoms in patients with gliomas, epilepsy leads to disability and decreases patients'

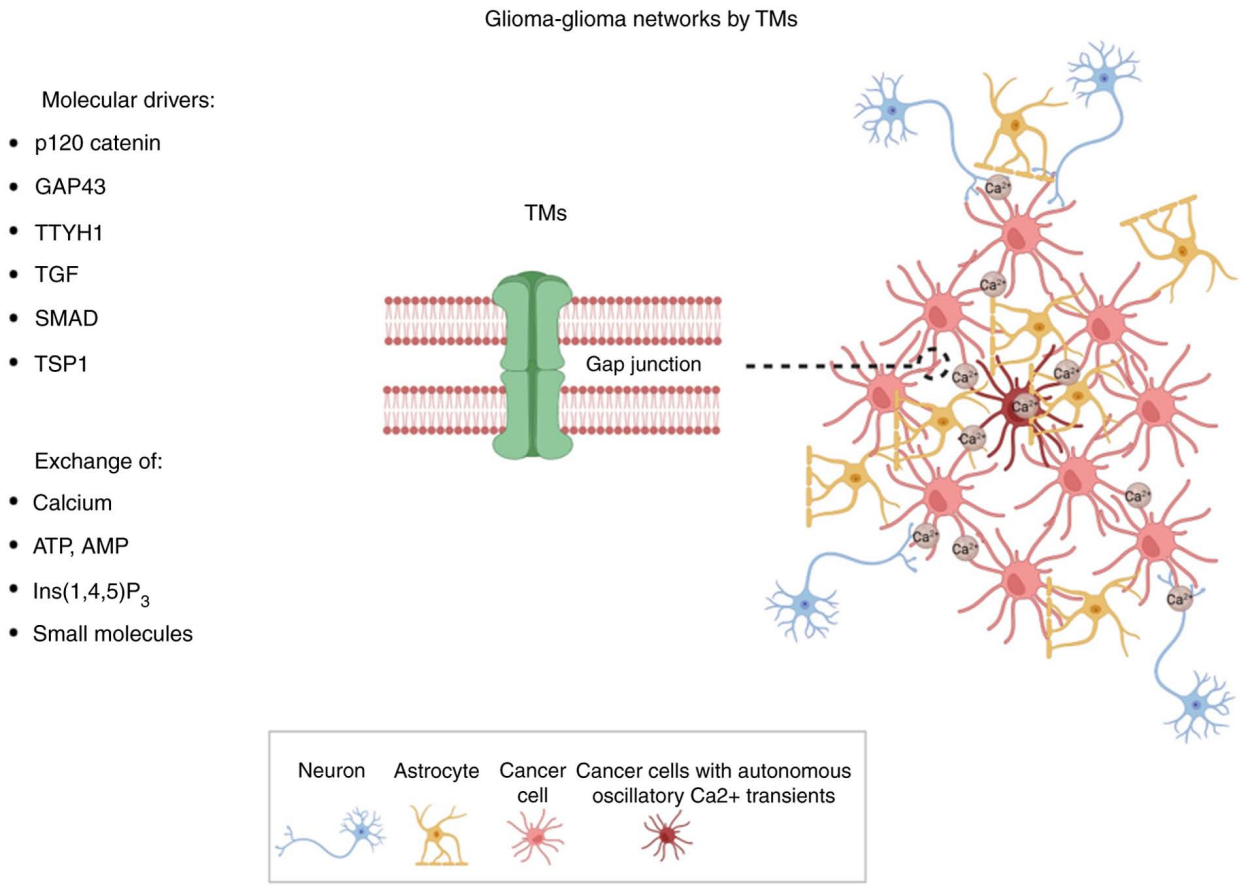

Figure 4. Glioma cells are interconnected with each other by tumor microtubes, thereby constructing glioma-glioma networks.

quality of life. This is closely related to increased neural activity induced by glioma cells. The involved mechanisms include the secretion of glutamine by GBM cells via the glutamate-cysteine exchanger system X_C (69), loss of inhibitory GABA interneurons in the microenvironment (70), change in the neural response to GABA (70), and glioma cell secretion of synaptogenic factors such as glypican (71) and TSP-1 (25). Of course, the diversity of somatic mutations in glioma cells definitely contributes to peritumoral hyperexcitability and seizures over the course of the disease. Tobochnik *et al* (72) discovered that glioma genetic profiling can reveal diverse somatic mutations of oncogenes relevant to peritumoral hyperexcitability that contribute to glioma-related epilepsy. Meanwhile, neural hyperexcitability and glioma growth engage in a vicious cycle of mutual promotion. This cycle is a plausible therapeutic target to manage glioma.

6. Neurons affect the immune microenvironment of glioma

Although multiple cancer types respond to immunotherapy (73-76), the pivotal phase 3 clinical trial in GBM ended in failure (77). The failure of immunotherapy for GBM was attributed to the immunosuppressive microenvironment (78). The nervous and immune systems are both crucial for brain function and health. Consequently, immune cells and neurons within gliomas are inevitably involved in tumor growth and immunotherapy failure. Recently, Nejo *et al* (79) found that regions with elevated connectivity were typified by regional immunosuppression in GBM. In an intracerebral syngeneic GBM model, TSP-1 knockdown in GBM cells inhibited synaptogenesis and glutamatergic hyperexcitability and synchronously restored antigen presentation and pro-inflammatory responses. Moreover, TSP-1 knockdown prolonged the survival of immunocompetent mice harboring intracerebral syngeneic GBM, but it had no effect in immunocompromised mice. Simultaneously, TSP-1 knockdown promoted the infiltration of pro-inflammatory TAMs and $CD8^+$ T-cells in the TME (79). However, the molecular mechanism by which neural-glioma circuits induce regional immunosuppression by TSP-1 remains unknown. TSP-1 is involved in synaptogenesis has been extensively studied (80), while Liu *et al* (81) identified that TSP1 upregulated PD-L1 by activating the STAT3 pathway. These may be the molecular mechanisms underlying TSP-1-induced immune suppression relationships to synaptogenesis. In addition, Guo *et al* (82) defined the axis through which neurons, T-cells and microglia interact to regulate neurofibromatosis-1 (NF1)-mutant LGG growth. It was found that NF1-mutant human and mouse brain neurons induce midkine to activate $CD8^+$ T-cells. Then, the activated $CD8^+$ T-cells produce Ccl4 to induce the production of the LGG growth factor Ccl5 by microglia. Ccl5 is a critical factor for LGG stem cell survival. Ccl5 upregulation is associated with lowered survival in patients with LGG (82). In the future, more detailed principles of neuron-immune cell-glioma cell crosstalk are likely to be elucidated.

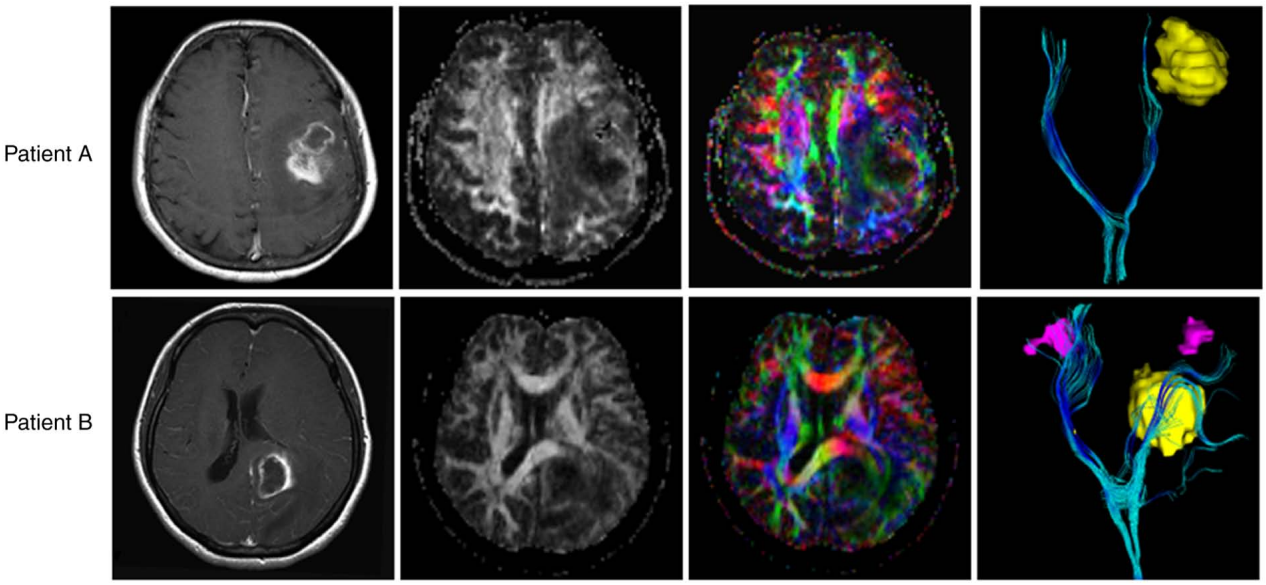

Figure 5. Two typical diffusion-weighted images of patients with glioblastoma multiforme.

7. Clinical translation of glioma neuroscience

Predictive value of glioma neuroscience. Although numerous studies have confirmed that bidirectional interactions between glioma cells and neurons represent a major tumor-promoting factor (83-85), these related theories have not yet been translated into clinical applications. Recently, Drexler *et al* (86) identified an epigenetically defined neural signature that independently predicts the survival of patients with GBM. Using the reference signatures of neural cells, they classified GBM samples into low- or high-neural tumors. High-neural GBM features hypomethylated CpG sites and increased expression of genes relevant to synaptic integration. Via single-cell transcriptomic analysis, they found a high abundance of malignant stem cell-like cells, primarily of the neural lineage, in high-neural GBM. Furthermore, these cells are classified as neural progenitor cell-like, astrocyte-like and oligodendrocyte progenitor-like, alongside oligodendrocytes and excitatory neurons. Via survival analysis, researchers revealed a significant survival benefit of gross total resection (GTR, 100% resection) and near GTR (≥90% resection) compared with partial resection (<90% contrast enhancement resection) in low-neural glioblastoma. However, no survival benefit of near GTR was observed in high-neural GBM. This suggests that more extensive resection might be necessary to confer a survival benefit in high-neural GBM. Furthermore, it was also revealed that BDNF could aid in stratifying patients with GBM based on their neural subtype (86). The other study have identified peripheral and CNS BDNF levels as s a promising biomarker in patients with glioma (87). In order to be clinically applicable, large-scale multicenter clinical studies is required.

White matter tracts (WMTs) represent one of the main pathways by which GMB spreads, and these tracts contribute to treatment failure (88). Using diffusion-weighted imaging (DWI), Wei *et al* (89) characterized WMT disruption in a study of more than 100 patients with GBM. It was found that the most likely disrupted tracts were associated with fiber pathways connecting distant cortical brain regions, providing a pathway for the long-range migration of GBM cells. GBM-induced interruption of WMTs was linked to distant recurrence and lower overall survival (89). Salvalaggio *et al* (90) investigated whether the local properties of WMTs at the sites of GBM lesions were predictive of overall survival, revealing that GBM lesions within regions that contain a higher density of WMTs are related to lower survival, and vice versa. The correlation between local WMT characteristics and the survival of patients with GBM. Our result was similar to that of Salvalaggio *et al* (90). Two typical DWI of patients with GBM are presented in Fig. 5. Patient A had more severe WMT damage than patient B, resulting in shorter survival for patient A despite the greater possibility of complete resection in this patient. Consequently, this information from DWI can improve assistance of surgeons in achieving maximum tumor resection with minimal impact on patient neurological function. Moreover, DWI findings can also be used to better predict the prognosis of patients with GBM. As early as 2015, Abhinav *et al* (91) had found that DWI contributed to surgical planning for patients with glioma (91).

Therapeutic potential of glioma neuroscience. Abnormal molecules identified in glioma neuroscience can also be used as therapeutic targets to treat gliomas. Targeting the molecules involved in information communication between neurons and glioma cells could become a new approach for glioma treatment. First, inhibiting neuron-glioma synapses has great therapeutic potential. Venkatesh *at al* (51) identified soluble neurexins and ADAM10 inhibitors as favorable treatments for reducing malignant synaptogenesis. Likewise, by antagonizing the binding of TSP with its receptor, namely calcium channel auxiliary protein α2δ, gabapentin and pregabalin suppress excitatory synaptogenesis (92,93). Recently, Bernstock *et al* (94) demonstrated a survival benefit

associated with gabapentin following surgical resection of newly diagnosed glioblastoma in retrospective research. In addition, inhibition of synaptic and perisynaptic signal transmission, such as AMPAR or NMDAR inhibition, is another therapeutic strategy (95). The interruption of electric coupling in glioma-glioma networks has therapeutic potential. Ion channels in neuron-glioma malignant circuits and neural circuits supplying nutrients could emerge as treatment targets (95). Finally, suppressing neural hyperexcitability by anti-epileptics possesses therapeutic potential in GBM (96). Although there are numerous targets for neuron-glioma networks, no target associated with significant inhibition of tumor growth has been identified. Large numbers of preclinical and clinical trials are needed in the future to identify effective therapeutic targets.

8. Conclusions and future perspectives

The brain features a network of interleaved neural circuits. Brain connectivity characteristically acts as a network of nodes and edges, abstracting away the rich biological information of local neurons (17). Glioma involves the malignant transformation of a certain node in the brain network. Consequently, communication between neurons and glioma cells is inevitable during the initiation and progression of glioma. Numerous studies have confirmed that glioma and neural activity mutually regulate each other (97-101).

Although some progress in glioma neuroscience has been made, knowledge of the specific cellular and molecular interactions of neurons and glioma cells and the extent of neuron- and glial cell-specific molecular alterations remains scarce. Whether there are differences of neuron-glioma synapses at different grades of glioma or not need to identify. Furthermore, owing of GBM's heterogeneity, whether neuron-glioma interactions vary across transcriptional subtypes or not also need to identify. Guo *et al* (83) identified that neuronal activity supported glioblastoma progression through proneural-to-mesenchymal transition of glioma stem cells. In terms of the underlying mechanisms of the interactions between neurons and glioma cells, the identified synaptic inputs onto glioma cells mainly involve local glutamatergic projections. The role of other types of neurons in the occurrence and development of gliomas have been overlooked. In addition, in *in vitro* glioma neuroscience studies, neurons are often co-cultured with glioma cells without other cells of the TME. Organoids are histologically and functionally similar to human organs, maintaining the characteristics of glioma and the TME, and organoids have high sensitivity and high specificity in forecasting the efficacy of anticancer drugs, thereby improving the accuracy of preclinical studies (88). Organoids are also used to study the role of neurons in glioblastoma, as it highly preserves high fidelity of tumor and the TME. Consequently, organoids will inevitably become advantageous tools for glioma neuroscience in future. Conversely, mouse models of glioma do not always fully recapitulate the human disease. The development of mouse models that emulate human glioma more faithfully should be a priority for this field in the future Furthermore, research on the neuroscience of glioma requires multi-omics research of glioma relevant to neuroscience, more sophisticated imaging techniques, and other components. Additionally, some other questions relevant to clinical translation remain incompletely answered. First, it has to be investigated which appropriate therapeutic targets can be successfully targeted with sufficient specificity for clinical benefit. How can treatment targeting the connections between neurons and gliomas be synergistically integrated into existing treatment regimens? Can histopathological or other molecular biomarkers, which include neural markers (such as NLGN3, BDNF and Gap43), specify patients who are most likely to benefit from these therapeutic strategies? Beyond developing novel treatments, the possibility of repurposing existing drugs that modulate the nervous system and typically have a tolerable adverse effect profile in glioma should be investigated.

The nascent field of glioma neuroscience is increasing rapidly, with parallel efforts aiming to uncover the mechanistic underpinnings of neuron-glioma interactions and develop novel therapies. Data obtained from TME studies suggest that disrupting neuron-glioma crosstalk could eventually become an important therapeutic strategy of clinical oncology akin to anti-angiogenic and immunomodulatory therapies.

Acknowledgements

The authors would like to thank Dr Joe Barber Jr., PhD, ELS, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Funding

The present study was supported by the Natural Science Foundation of Tianjin Municipal Science and Technology Commission (grant no. 23JCYBJC01610) and College Students' Innovation and Entrepreneurship Training Program Project (grant no. 202513661003).

Availability of data and materials

Not applicable.

Authors' contributions

CZ and HZ wrote and formatting the manuscript. JC was responsible for bioinformatic analysis (analysis of sequencing data from all cited literature). ML provided suggestions on content related to MRI and participated in writing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

No applicable.

Competing interests

The authors declare that they have no competing interests.

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