Glioma-neuronal interactions in tumor progression: Mechanism, therapeutic strategies and perspectives (Review)

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Abstract. An increasing body of evidence has become available to reveal the synaptic and functional integration of glioma into the brain network, facilitating tumor progression. The novel discovery of glioma-neuronal interactions has fundamentally challenged our understanding of this refractory disease. The present review aimed to provide an overview of how the neuronal activities function through synapses, neurotransmitters, ion channels, gap junctions, tumor microtubes and neuronal molecules to establish communications with glioma, as well as a simplified explanation of the reciprocal effects of crosstalk on neuronal pathophysiology. In addition, the current state of therapeutic avenues targeting critical factors involved in glioma-euronal interactions is discussed and an overview of clinical trial data for further investigation is provided. Finally, newly emerging technologies, including immunomodulation, a neural stem cell-based delivery system, optogenetics techniques and co-culture of neuron organoids and glioma, are proposed, which may pave a way towards gaining deeper insight into both the mechanisms associated with neuron- and glioma-communicating networks and the development of therapeutic strategies to target this currently lethal brain tumor.

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Contents

1. Introduction

Glioma is the most prevalent type of primary brain tumor, accounting for ~75% of malignant central nervous system (CNS) tumors in adults (1). The treatments recommended at present for this aggressive neoplasm include maximal safe surgical resection followed by radiotherapy paired with temozolomide chemotherapy. The addition of tumor treatments from other fields to conventional therapies has also led to improvements in the prognosis of patients (2). However, the intricate biological properties of glioma have restricted the effectiveness of the multiple therapeutic modalities and patients continue to exhibit eventual tumor relapse, with the disease undergoing a dismal course. The median survival rate of glioblastoma multiforme (GBM), the highest grade of glioma (World Health Organization grade IV), which constitutes >50% of the entity, remains at ~16 months, with near-universal lethality (3,4).

Despite the huge efforts that have been made in investigating the intrinsic nature of aggressive tumor behaviors, the processes of rapid proliferation, infiltrative growth and resistance to therapeutics of glioma remain poorly understood. However, emerging evidence has revealed that the tumor microenvironment (TME), where gliomas interact with non-glioma brain cells, provides a substantial basis for glioma progression (5). The complex network consists of multiple non-glioma cell types, including glial cells, immune cells, vascular cells and neurons. These distinct sets of cells may be subverted by gliomas through various mechanisms to form a microenvironment that is conducive to tumor development (6). Preliminary studies have pointed to the possibility that interfering with oncogenic interactions between glioma and non-malignant cells may suppress disease progression (7-9).

Given that glioma infiltrates extensively within the brain and spinal cord and rarely metastasizes outside the CNS, neurons as a crucial component of the glioma milieu potentially confer important microenvironmental dependencies to the pathogenesis of the tumor (10). The crosstalk between glioma and peritumor neurons may be mediated in different ways, which involve electrochemical synapses, secreted factors, tumor microtubes (TMs) and extracellular vesicles (11). The bidirectional interactions provide plentiful scope for malignant cells to develop; henceforth, the tumor-infiltrated brain becomes physiologically disorganized, a process that eventually facilitates glioma growth.

The present review provides an overview of various aspects of the communication between glioma and neurons, and readers will develop further insight into the regulatory mechanisms of glioma-neuronal interactions. Furthermore, potential targets involved in the network are highlighted and novel concepts and technologies are described that may be integrated for the design of novel therapeutic strategies.

2. Neuronal regulation in glioma progression

Neuron-glioma synapses (NGSs), providing a substantial basis for communication between the two entities, are mostly found in the glioma infiltration zone (12). The synaptic contacts may be categorized into three morphological types that have diverse functional properties: i) A single contact on a glioma cell; ii) a multi-synaptic contact to both the neuron and the glioma cell; and iii) a peri-synaptic contact between two neurons accompanied by a glioma cell contact to the synaptic cleft (12). These electrochemical synapses may be regulated by neurotransmitters (Fig. 1), ion channels, TMs and gap junctions, which exert a marked influence on glioma (13).

Neurotransmitters and receptors. γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the adult brain that induces GABAergic signaling mediated via Cl^- influx through activating GABA receptors (GABARs), predominantly $GABA_AR$s (14). A previous study reported on the aberrant expression of chloride extruder K^+-Cl^- cotransporter 2 (KCC2) and Na^+-K^+-Cl^- cotransporter 1 (NKCC1), which was discovered in the peritumoral area following GABAergic signaling (15). The dysregulation of KCC2 and NKCC1 in the adjacent neurons led to an increasing intracellular Cl^- concentration, which resulted in Cl^- efflux. However, it was indicated that a high concentration of glutamate in the TME was able to counteract the inhibitory role of GABA via downregulating KCC2 levels (16). Another study reported that glioma cells expressed $GABA_AR$s when co-cultured with neurons *in vitro*, and activation of $GABA_AR$s resulted in inhibition of glioma-cell proliferation (11). Activation of $GABA_AR$ with the exogenous agonist muscimol, however, failed to elicit further inhibition of glioma-cell proliferation. That study attributed the phenomenon to the fact that GABA seemingly acts on glioma stem cells (GSCs) (17). The overexpression of diazepam-binding inhibitor (DBI) in glioma was reported to inhibit $GABA_AR$s, thereby promoting gliomagenesis. Despite a dearth of $GABA_AR$s, overexpressed DBI facilitated GBM growth through a lipid metabolism pathway mediated by GABA (18). Therefore, employing agonists or antagonists to disrupt the Cl^- current in glioma cells may offer a strategy to inhibit the progress of tumor development.

Glutamate is the predominant excitatory neurotransmitter, which is synthesized and secreted by neurons (19). The association between glutamate receptors and glutamate-induced Ca^{2+} signaling was demonstrated through the upregulation of the Ca^{2+} permeable-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) in glioma, which increased the rate of Ca^{2+} influx. The elevated Ca^{2+} concentration serves to activate the pro-oncogenic Akt and ERK/MAPK signaling pathways (20). It was reported that glutamatergic synapses were formed between neurons and glioma cells (termed neurogliomal synapses), and AMPARs are expressed on post-synapses. AMPAR-mediated neuronal activity has been indicated to induce tumor invasion and growth (12). AMPARs comprise four different types of subunits: GluA1, GluA2, GluA3 and GluA4 (21). Blockade of GluA1 and GluA2 overexpression reduced the proliferation rate of glioma cells by inducing apoptosis and decreasing cell invasiveness and migration (22). A study has demonstrated the role of auxiliary subunits (of the transmembrane AMPAR regulatory protein, cystine-knot AMPAR modulating protein and cornichon homolog families) of AMPARs in promoting gliomagenesis (23).

Activation of N-methyl-D-aspartate receptors (NMDARs) in GBM by extracellular glutamate may potentially boost tumor expansion *in vivo* (24). However, the expression of NMDARs on neurogliomal synapses and the further impacts on glioma development remain elusive. Previously published studies, however, have confirmed the inhibitory effects on glioma growth via NMDARs (25,26). Metabotropic glutamate receptors (mGluRs) consist of three groups of G-proteins: Groups I (mGluR1 and -5), II (mGluR2 and -3) and III (mGluR4 and -6-8). The group III receptor antagonists were observed to exert their anti-tumor effects in various types of tumor, including hepatoma, melanoma and non-small-cell lung cancer (26). Riluzole has been reported to promote apoptosis in glioma cells via antagonizing mGlu3, which results in the suppression of ERK activation (27). At present, evidence is lacking; however, in terms of whether mGluRs are expressed on neurogliomal synapses, although mGluRs are closely associated with glioma progression, may suggest the involvement of other neuron-glioma interactions.

Serotonin and dopamine are predominant neurotransmitters in the CNS. Of note, a previous study suggested a correlation between depression and gliomagenesis, probably due to the shared molecular pathways and gene networks (28). Dopamine receptor D4 is a receptor that is involved in autophagy and apoptosis, which interferes with glioma-cell proliferation (29). Serotonin exerts an impact on the glutamatergic system through influencing AMPARs and NMDARs (30). Selective serotonin reuptake inhibitor (SSRI) has been indicated to impair glioma cell growth via inducing autophagy and apoptosis (31), although such effects were also observed in patients with a history of long-term drug therapy using tricyclic antidepressants (32). In those patients, the morbidity rate of glioma was reduced. As serotonin receptors are also expressed in glioma cells, it is tempting to hypothesize that SSRI may also exert an influence through impacting neuron-glioma synapses (33).

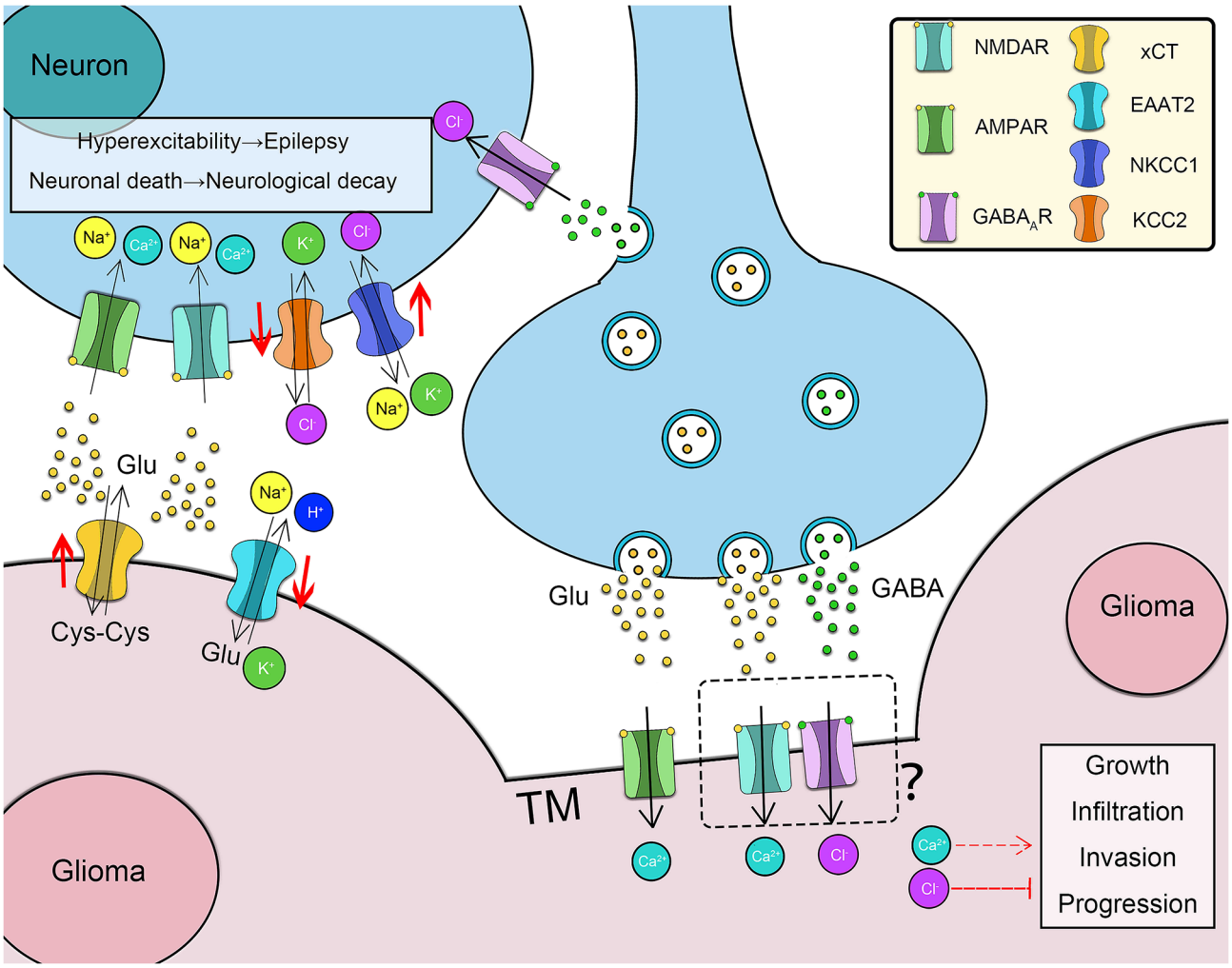

Figure 1. Roles of neurotransmitters in neuron-glioma interactions. The enrichment of Glu in the glioma microenvironment is regulated via xCT overexpression and EAAT2 inhibition. Glu activates adjacent neurons by binding to AMPARs and NMDARs. The high concentration of Glu leads to hyperexcitability and cell death of adjacent neurons, resulting in neurological decay and tumor-associated epilepsy. The expression of NKCC1 and KCC2 in para-tumoral neurons is downregulated and upregulated, respectively. The intracellular concentration of Cl^- in neurons is consequently high. GABA may depolarize the para-tumoral neurons and cause epilepsy. Neurons form synapses with the TMs of glioblastoma multiforme. Upon binding to AMPARs/NMDARs, Glu promotes glioma progression via influx of Ca^{2+}, whereas GABA inhibits glioma development via influx of Cl-. xCT, cystine/glutamate antiporter; EAAT2, excitatory amino acid transporter 2; Glu, glutamate; Cys, cystine; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor; GABAAR, GABAA receptor; NKCC1, Na^+-K^+-Cl- cotransporter 1; KCC2, K^+-Cl- cotransporter 2; GABA, γ-aminobutyric acid; TM, tumor microtube.

Ion channels. As mentioned above, ion currents are involved in neuron-glioma crosstalk. Ion channels exist in the CNS, primarily Na^+, K^+, Ca^{2+} and Cl^- channels, which regulate cell migration, invasion, proliferation and apoptosis (34). Specifically, the K^+ channel members include voltage-gated K^+ channels (VGKC or Kv), calcium-activated K^+ channels (KCa) and ATP-sensitive K^+ channels (KATP). Voltage-gated calcium channels (VGCCs) are the most important members of the Ca^{2+} channel group, consisting of the L-, T-, N- and P/Q-types.

The migration of neural progenitor cells and stem cells is influenced by the electric current generated by the local field potential (35). It was recently indicated that the electric current directs the migration and invasion of glioma cells (36). The electrotaxis processes of GBM cell lines are regulated by voltage-gated channels. For instance, in T98G cells, electrotaxis was demonstrated to be mediated via R-type VGCCs, whereas in U251 cells, it was mediated via P/Q-type VGCCs. By contrast, in both T98G and U251 cells, electrotaxis was regulated via A-type VGKCs and acid-sensing ion channels (ASICs) (37). Inhibition of ASICs by benzamil significantly impaired the directedness of the electrotaxis of U251 and T98G cells (37). Of note, P/Q- and N-type VGCC inhibitors derived from spider venom were indicated to markedly inhibit tumor growth *in vivo* (38). Collectively, these data suggest that electric fields exert important effects on glioma-cell invasion and migration. Therefore, targeting ion channels may be a potential therapeutic strategy for glioma.

Ion channels are employed by cells to regulate their volumes for the purpose of cell migration. Glioma cells accumulate Cl^- intracellularly via NKCC1, whereas Cl^- channel protein 3 (CLC3) serves to regulate the Cl^- efflux (39). To balance the Cl^- efflux, glioma cells express KCa1.1 and KCa3.1 channels, which regulate K^+ influx via Ca^{2+} activation (39). Chlorotoxin, a small neurotoxin of 36 amino acids, causes the internalization of CLC family members, thereby impeding glioma-cell

invasion (40). A previous study suggested that specific inhibition of KCa3.1 by TRAM-34 leads to a reduction in the migration and infiltration rates of U87, GL261 and U251 GBM cells (41). Furthermore, blockade of KCa1.1 inhibited the radiation- and hypoxia-induced migration of GBM cells (42).

Apart from cell migration and invasion, ion channels are also involved in regulating the cell cycle, proliferation and apoptosis (39). A previous study revealed that glioma-cell proliferation was inhibited following the blockade of Kv channels by 4-aminopyridine (43). Inhibition of Kv1.1 by KAaH2, a homologous Kv1 blocker from scorpion venom, impaired U87-cell proliferation (44). Ca^{2+}-activated K^+ channels (BK channels) have also been indicated to be involved in regulating proliferation (45). However, the association between neuronal activity and ion channels in terms of how they influence glioma proliferation remains inadequately understood. Hypothetically speaking, neuronal hyperexcitability may promote glioma proliferation, since the activation of ion channels by electric signals is essential for downstream pathway signaling. Considering all of this evidence, ion channels have been indicated to act as an important bridge between neuronal activity and glioma progression, although their role still requires to be confirmed and fully elucidated in further studies.

TMs and gap junctions. TMs are a type of tumor protrusion consisting of F-actin and microtubules formed by gliomas, which permit cell-to-cell material transportation (46). Targeted patch-clamp recordings have suggested that a spontaneous excitatory post-synaptic potential arises in glioma cells cocultured with neurons, which induces further Ca^{2+} influx (12). Importantly, TM connectivity is responsible for the distribution of Ca^{2+} ions, which serve as crucial messengers of glioma activity throughout the glioma syncytium (12). Furthermore, NGSs significantly promote glioma invasion through Ca^{2+} signaling, and potentiate glioma proliferation through AMPAR activation (12). In a *Drosophila* glioma model, Frizzled 1 receptors were indicated to be highly expressed within TMs, where glioma cells were able to vampirize Wingless-related integration site (WNT) ligands from neurons (47) (the process 'vampirization' is defined in that article). The depletion of WNT from neurons led to glioma proliferation and expansion through the JNK/matrix metalloproteinase (MMP) pathway, conversely resulting in a reduction of neuronal synapse activity (47). TM-associated gap junctions have also been indicated to amplify the extracellular K^+ current and to promote tumor proliferation (48), suggesting that the TM network potentiates the pro-tumoral effects of NGSs.

In cell-cell communication, gap junctions, which consist of connexin (Cx) proteins, form conductive pores in the plasma membranes between adjacent cells that allow the transportation of cellular material (49). Cx43-based gap junctions and neuronal growth-associated protein-43 (GAP-43) have been indicated to be essential for TM formation (50). Depletion of GAP-43 and Cx43 led to both an impairment of the ability of TMs to form connections and tumor-cell volume reduction *in vivo* (51). In a subsequent study, suppressing Cx43 with a peptide, TAT-Cx43266-283, inhibited glioma-cell invasiveness, reduced the stemness properties of GSCs and prolonged the survival rate of mice bearing GSC-derived gliomas (52). IMM, a small molecule that is able to induce F-actin polymerization, was demonstrated to hinder TM formation and to prevent glioma invasiveness (53). It is noteworthy that the role of Cx43, a tumor suppressor, appears to be somewhat paradoxical in terms of the overall picture (54). According to a previously published meta-analysis, Cx43 expression was reported to improve the overall survival rate in patients with glioma (55). Hence, the function of Cx43 in glioma should be interpreted with caution in further studies. TM formation was also indicated to be dependent on the EGFR/PI3K signaling pathway, which induces actin cytoskeleton remodeling and initiates TM expansion. The microtubule-targeted agent BAL101553 has entered into clinical trials (Table I). Therefore, targeting TM-associated gap junctions or other pathways may prove to be useful in terms of treating glioma.

Neuronal secretion. The activity of cortical projection neurons promotes glioma growth and progression through neuronal secretion. Neurotrophins (NTs), neuroligins (NLGNs), neurotransmitters and mitogens have all been demonstrated to have participatory roles in neuron-glioma communication (56). In addition to direct (or synaptic) neuronal secretion, glioma cells have also been indicated to be regulated by indirect (or non-synaptic) paracrine and autocrine signaling pathways (57).

NTs. NTs are growth factors that are expressed in the nervous system and have an impact on neural growth, survival and biological function. The four types of NTs comprise nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). NGF has a preferential affinity for tyrosine kinase receptor (Trk)A, whereas BDNF and NT4 have a preference towards TrkB and NT3 has an affinity for TrkC (58).

In the CNS, NGF is secreted predominantly in the cortex, hippocampus and pituitary gland (59). The specific NGF receptors TrkA and $p75^{NTR}$ have been indicated to be expressed in gliomas (60). The effects of NGF on glioma cells, however, appear to be somewhat paradoxical. Ectopic treatment of the pediatric low-grade glioma cell (PLGG) line Res259 with NGF led to inhibition of cell growth, whereas NGF treatment promoted the growth of another PLGG cell line, Res186 (61). A different study suggested that NGF stimulated U87-cell proliferation through the NOTCH1 receptor signaling pathway (62). The underlying impact of NGF on glioma development, however, requires to be further clarified.

Barreda Tomás *et al* (63) observed that both progenitor BDNF (pro-BDNF) and BDNF were expressed in glutamatergic and GABAergic neurons of the mouse cortex. Another study demonstrated through an immunocytochemical analysis that BDNF and its receptor, TrkB, are extrasynaptic, whereas BDNF is preferentially located at the glutamatergic synapse (64). It was suggested that BDNF may exert its effects on glioma through NGSs and the paracrine signaling pathway. Targeting BDNF by specific microRNAs inhibited glioma invasion, migration and proliferation (65), indicating the promoting role of BDNF in glioma malignancy. BDNF also induced the synthesis of GluA1 subunits and the synaptic incorporation of CP-AMPARs in primary hippocampal neurons (66). As mentioned above, a high concentration of glutamate in the glioma microenvironment confers neuron hyperexcitability, leading to epilepsy (67). Although AMPARs have been

Table I. Pivotal clinical trials concerning the treatment of gliomas with neural influence.

ClinicalTrials gov Identifier	Country	Conditions	Phase	Estimated enrollment	Allocation/masking	Intervention model	Intervention	Status/results
NCT00064363	US	Brain and central nervous system tumors	II	30	Open label	-	Drug: Talampanel	Talampanel was well-tolerated as single agent. The PFS6 was 4.6 and 0% for the initial 22 GBM patients and 8 AG patients, respectively The median PFS was 5.9 weeks for GBM and 8.9 weeks for AG patients. The median OS was 13 weeks for GBM patients and 14 months for AG patients
NCT00267592	US	GBM	II	72	N/A/Open label	Single group assignment	Drug: Talampanel Radiation: RT 5 days a week+ Drug: TMZ 75 mg Drug: Adjuvant TMZ 200 mg	Talampanel was well-tolerated in combination with RT plus TMZ The mOS was 18.3 months
NCT03295396	US	Glioma	II	95	Non-randomized/ open label	Single group assignment	Drug: ONC201	ONC201 was safe The best response to RANO-HGG or RANO-LGG was 30% Duration of response to RANO-HGG was median 52.7 weeks
NCT00040573	US	Glioma brain neoplasm	I	18	Non-randomized	Single group assignment	Drug: 131I-TM-601	A single dose of 10 mCi I^{131}-TM-601 was well tolerated for 0.25 to 1.0 mg

Table I. Continued.

ClinicalTrials gov Identifier	Country	Conditions	Phase	Estimated enrollment	Allocation/masking	Intervention model	Intervention	Status/results
								TM-601. Median survival time was 25.7 weeks for patients in panel 1 (0.25-mg dose), 77.6 weeks in panel 2 (0.50-mg dose), 23.6 weeks in panel 3 (1.00-mg dose) and 27.0 weeks in all three dosing groups
NCT01753713	US	Adult giant cell glioblastoma, adult glioblastoma, adult gliosarcoma, recurrent adult brain tumor	II	33	Non-randomized/ Open label	Parallel assignment	Drug: Dovitinib, Other: Laboratory biomarker analysis	PFS6 in Arm 1 was 12±6%; Time to progression in Arm 2 was 0.7-1.8 months
NCT04295759	US	GBM anaplastic astrocytoma, anaplastic oligodendroglioma, DIPG, high-grade astrocytoma, NOS, CNS primary tumor, NOS (malignant glioma)	I	28	N/A/Open label	Single group assignment	Drug: INCB7839	Recruiting
NCT03250299	US	Glioblastoma, MGMT-unmethylated glioblastoma	I	30	Non-randomized/ Open label	Sequential assignment	Drug: Microtubule-targeted agent BAL101553; Radiation: Radiation therapy; Other: Laboratory biomarker analysis; Other:	Recruiting

Table I. Continued.

ClinicalTrials gov Identifier	Country	Conditions	Phase	Estimated enrollment	Allocation/masking	Intervention model	Intervention	Status/results
NCT02880371	US	Advanced solid tumors	II	19	Non-randomized/ Open label	Single group assignment	Pharmacological study drug: ARRY-382; Drug: Pembrolizumab ARRY-382 plus pembrolizumab	The recommended phase 2 dose of ARRY-382 in combination with Pembrolizumab was 300 mg QD were safe. Stable disease was the best response observed for patients in the PD-1/PD-L1 IR, prOVCA and PDA cohorts: 8 (42.1%), 4 (36.4%), and 5 (18.5%) patients, respectively. Median PFS (95% CI) was 1.4, 1.6 and 2.1 months in the PDA, PD1/PD-L1 IR and prOVCA cohorts, respectively
NCT01349036	US	Recurrent glioblastoma	II	38	Non-randomized/ Open label	Single group assignment	Drug: PLX3397	PLX3397 was well-tolerated. No significant improvement in PFS was observed

GBM, glioblastoma multiforme; TMZ, temozolomide; PFS, progression-free survival; PFS6, progression-free survival at 6 months; CNS, central nervous system; RT, radiation therapy; mOS, median overall survival; N/A, not applicable; AG, anaplastic gliomas; DIPG, diffuse intrinsic pontine glioma; NOS, not otherwise specified; PDA, pancreatic ductal adenocarcinoma; PD-1/PD-L1 IR, advanced solid tumors that were refractory to PD-1 or PD-L1 inhibitor therapy; prOVCA, platinum-resistant ovarian cancer.

indicated to participate in glutamate-induced epilepsy, BDNF may promote glioma-associated epilepsy due to its capability of regulating the synthesis and incorporation of AMPARs. In addition, glutamate was indicated to stimulate the production of BDNF in neurons (68), which may, in turn, facilitate glioma progression. Of note, pro-BDNF has been observed to exert an inhibitory effect on glioma. A previous study reported that the ratio of pro-BDNF to BDNF was decreased in high-grade glioma, whereas the expression of pro-BDNF was increased. Pro-BDNF was also found to inhibit the growth and invasion of glioma cells via $p75^{NTR}$ (69).

NT-3/TrkC signaling has also been indicated to be necessary for the induction of glioma-cell death through the inhibition of autophagy under hypoxic conditions (70), suggesting a life-supporting role of NT-3/TrkC signaling in GBM in the state of hypoxia. The effect of NT-4/5 on glioma cells, however, remains elusive, and this requires further investigation.

NLGN3. NLGN3 exerts an important role in synaptic function and maturation by binding presynaptic neurexin (71). Venkatesh *et al* (71) suggested that spontaneous neuronal activity in the cortex induces NLGN3 secretion and promotes glioma-cell proliferation (71). Potentiated neuronal activity also led to an increase in NLGN3 cleavage mediated by MMPs, which may contribute towards mGluR activation (72). In the clinic, NLGN3 expression was observed to be positively correlated with oscillatory brain activity and this was negatively associated with progression-free survival of patients with glioma (73). NLGN3 not only caused an increase in its own expression, but it also led to an upregulation of the sheddase A disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) in glioma cells (74). Abundant evidence has indicated the pivotal role of NLGN3 in supporting glioma malignancy. In an NLGN3-deficient brain model, human glioma xenografts were indicated to both survive longer and not exhibit any clear signs of glioma-cell infiltration (75), indicating that glioma malignancy may depend on the presence of NLGN3.

NLGN3 activates several oncogenic signaling pathways, including the PI3K/mTOR pathway, and induces transcriptional changes, including the upregulation of numerous synapse-associated genes (76). NLGN3 has also been indicated to induce the expression of Tweety homologue-1, which has a role in the construction of the glioma microtube network in high-grade glioma (77). In addition, protein kinase C (PKC)-induced NLGN3 cleavage is dependent on MMPs, particularly MMP3 and MMP9. MMP3/9 blockade led to inhibition of PKC-induced NLGN3 (78). Collectively, these results suggested that MMP3/9 inhibition may be effective in terms of glioma suppression. Patients with GBM were also indicated to harbor high levels of NLGN3 in the deep regions of the brain, which may partly explain the high recurrence rate of GBM (73).

NLGN3 is cleaved from both cortical neurons and oligodendrocyte precursor cells via ADAM10, the release of which from neurons is dependent on neuronal activity (75). ADAM10 inhibitors have been reported to prevent the release of NLGN3 and to block glioma growth *in vivo* (75). These data indicate that targeting NLGN3 for gliomas may be a putative therapeutic strategy. Generally speaking, preventing the release of NLGN3 into the glioma microenvironment through the use of ADAM10 inhibitors, blocking certain targets in oncogenic signaling pathways and silencing NLGN3-associated genes are three transformative methods for the treatment of glioma (Fig. 2).

Extracellular vesicles (EVs) in neuron-glioma interactions. EVs have an indispensable role in cell-cell interaction in the brain microenvironment. A previous study observed how the development of rat cortical neurons led to the secretion of exosomes containing GluA2/3 subunits of AMPARs (79). Similar patterns of exosome secretion were also observed in the differentiated neurons (80). A previous study indicated that exosomes derived from cortical neurons only bind to neurons and not to glial cells (81), suggesting that neuron-derived EVs (NEVs) mediate neuron-to-glioma communication indirectly. This indicated that the secretion of exosomes is activity-dependent and is specifically mediated by glutamatergic activity involving AMPAR and NMDAR (79,80). The glioma microenvironment renders neurons hyperexcitable due to the high glutamate concentration (67). The hyperexcitable neurons are able to promote the secretion of NEVs, which is chiefly regulated by glutamatergic activity. In a previously published study on human neural cultures where MECP2 was knocked down (termed MECP2LOF neural cultures), NEVs were observed to increase neuron proliferation and cell numbers (82). These results suggested that NEVs contain neuroprotective proteins that fulfill an important role in regulating neural circuits and neurogenesis. The impact of NEVs on gliomagenesis, however, remains elusive. It is possible that neurogenesis may increase the formation of NGSs and potentiate neuronal activity to promote glioma growth.

In addition to NEVs, glioma also influences neuronal functions via glioma-derived EVs (GEVs). A previous study suggested that GEVs enhanced the frequency of neuronal spontaneous synaptic responses (83). This indicated that GEV-induced neuron hyperexcitability may promote NLGN3 levels, leading to glioma progression.

3. Retroaction of glioma cells on neurons

As mentioned above, neuron-glioma interaction is a bidirectional process. Neuronal activity facilitates glioma formation through the regulation of precursors, electrochemical signaling pathways and neuronal secretion. Reciprocally, neuronal activity is activated by gliomas in various ways, i.e., through the release of neurotransmitters, promotion of synaptogenesis and remodeling of neurons in the microenvironment, as well as other possible mechanisms (77).

Clinical symptoms of glioma-associated neuronal excitability include cortical hyperexcitability and seizure activity (84). The cystine/glutamate antiporter is the key protein involved in glutamate secretion and this is significantly upregulated in GBM cells. At the same time, excitatory amino acid transporter 2, which is responsible for the re-uptake of glutamate, is downregulated in gliomas (67). The high concentration of glutamate within the peritumoral microenvironment leads to hyperexcitability in adjacent neurons and glioma-associated epilepsy (67). A previous study also reported that the firing of

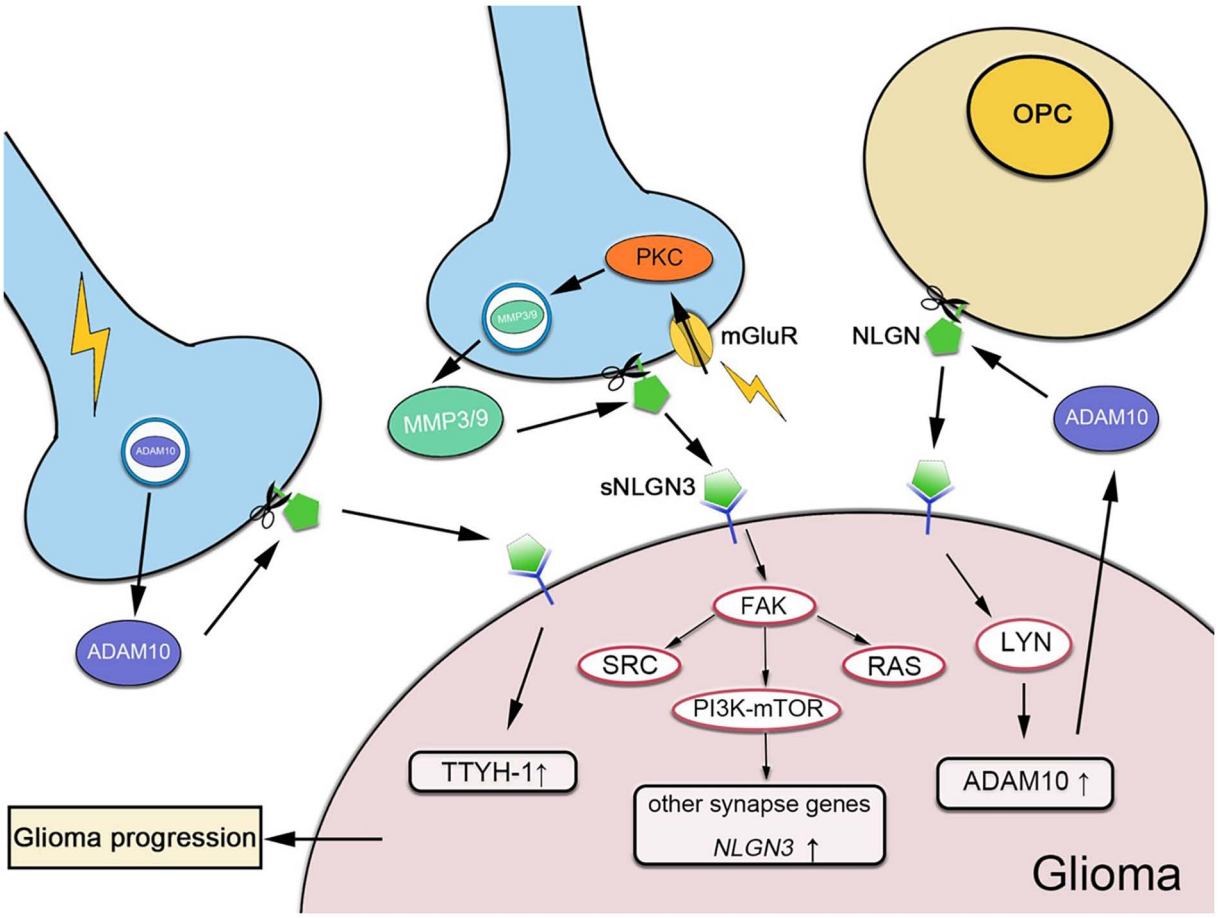

Figure 2. Mechanism of NLGN3 in neuron-glioma interactions. Neurons and OPCs release sNLGN3 through ADAM10 and/or MMP cleavage. In neurons, the release of NLGN3 depends on neuronal activity. The expression of ADAM10 is mediated by neuronal activity. mGluR activation induces the expression of MMP3/9 through PKC. sNLGN3 is able to activate NLGN3 and other synapse genes through the PI3K-mTOR pathway, whereas ADAM10 expression is upregulated through the Lyn kinase signaling pathway, which increases TTYH-1 expression. NLGN3, neuroligin-3; OPCs, oligodendrocyte precursor cells; sNLGN3, soluble NLGN3; ADAM10, A disintegrin and metalloproteinase domain 10; mGluRs, metabotropic glutamate receptors; MMP3/9, matrix metalloproteinase 3/9; PKC, protein kinase C; TTYH-1, Tweety homologue-1; Proto-oncogene tyrosine-protein kinase SRC, SRC; Focal adhesion kinase, FAK.

peritumoral GABAergic interneurons initiated interictal-like activity, which is a characteristic of pre-operative seizures in patients with glioma. This may result from a low expression of KCC2 and a high expression of NKCC1 (85). Another study demonstrated that KCC2 expression was downregulated by glioma via increasing the intracellular Zn^{2+} concentration in neurons, eliciting GABA-dependent depolarization of co-cultured neurons (86). These data implied that glioma may contribute towards epilepsy by influencing both glutamatergic and GABAergic signaling in neurons.

Subsequently, a study conducted using a xenograft model demonstrated a positive correlation between synaptogenic properties and glioma progression (33). A high concentration of glutamate contributes towards neuronal death, which frees up space in which tumors may grow (67). Furthermore, glioma cells were indicated to disrupt normal neuron-glial communication, leading to neuronal degeneration and neurological decay. This pathophysiological process has been indicated to be more rapid and aggressive in GBM (87).

Gliomas are able to influence the surrounding neurons by expressing and releasing trophic factors. The expression of NGF was positively correlated with the glioma grade and negatively correlated with the median survival time (88). A different study indicated that the exogenous application of NGF promoted glutamatergic synapse activity via binding to Trk receptors. This promotion of glutamatergic synapse activity was regulated by potentiating the pre-synaptic release of glutamate (89). These data suggested that NGF released by glioma cells may enhance the glutamatergic NGSs and promote glioma growth. BDNF was deemed to be an important trophic factor involved in synaptogenesis, synaptic plasticity and neuroprotection (90). It has been reported that depression is a concomitant syndrome of glioma (28) and is associated with decreased levels of BDNF (91). It was hypothesized that glioma may downregulate BDNF, thereby supporting its own survival and influencing neuronal function (28). In a *Drosophila* model, GBM cells were indicated to produce ImpL2, an antagonist of the insulin signaling pathway, leading to mitochondrial damage and the loss of synapses in adjacent neurons. The progression of GBM has also been observed to be associated with attenuation of the insulin signaling pathway in neurons (37).

Glioma retroaction on neurons accounts for several neurological disorders, including epilepsy, depression and neurodegenerative diseases. The present review has provided several suggestions of potential therapeutic targets that may

be used to prevent neuronal aberrations and in anti-glioma strategies.

4. Perspectives and future directions

Immunoregulation. In the glioma microenvironment, microglia and tumor-associated macrophages (TAMs) are the dominant immune cells assisting neuronal regulation in glioma cells. Microglia/microphages exert their immune-modulating effects through mediating the neurotransmitter functioning processes, as well as via releasing regulatory EVs. Novel immunotherapies may be devised based on neuron-microglia/macrophage-glioma interactions.

Microglia regulate synapse formation by forming direct contacts with glioma cells and secreting growth factors, such as BDNF and interleukin-10 (IL-10) (92). On the other hand, GSCs were observed to regulate the secretion of IL-10 from microglia, suggesting the possible presence of a bidirectional communicative process. Through this bilateral talk, the secretion of IL-10 by microglia was altered, which may interfere with normal synapse formation (93). It was reported that activated microglia were able to increase glutamatergic synapses on neurons with perineuronal 'nets' (94), possibly via microglial chemokine C-X-X-X-C motif ligand 1 (CX3CL1) signaling (95), promoting glioma growth and invasion. It was indicated that depletion of GluA2 on the microglial membrane resulted in an increase in the expression of tumor necrosis factor-α (TNF-α), which, in turn, may enhance AMPAR levels on the neuronal membrane (96). An increased expression of AMPARs on neurons promoted neuron hyperexcitability and death in an environment containing a high concentration of glutamate. As the overexpression of GluA2 inhibits GBM proliferation (97), this treatment was able to both ameliorate the TME and protect the neurons simultaneously. In addition, IL-β and TNF-α secreted by microglia were indicated to decrease the levels of mGlu5 in astrocytes, which impaired glutamate uptake and led to a further increase in the extracellular glutamate concentration (98). GABA was also indicated to exert anti-tumor effects via GABA-$GABA_AR$ in the neuron-microglia-tumor axis (11). Microglia-released IL-1β and TNF-α inhibited GABAergic synaptic activities in neurons, which supported glioma growth (99). Taken together, TAMs act as a bridge in neuron-glioma interactions via pro-inflammatory cytokines acting as mediators. Targeting microglia/macrophages therefore offers a promising strategy for the treatment of glioma.

Colony-stimulating factor 1 (CSF-1) is produced by glioma cells and is highly expressed in TAMs (100). CSF-1 inhibition was observed to significantly reduce both the number of TAMs and glioma progression *in vivo* (101), whereas administration of PLX3397, a CSF-1 inhibitor, had no efficacy in recurrent GBM according to a phase II clinical trial (101).

EVs fulfill an important role as secondary messengers within microglia-glioma communication networks. GEVs under hypoxic conditions skew macrophages towards the M2-type, which was subsequently indicated to support the proliferation and migration of U87 cells *in vitro* and *in vivo* (102). Microglia have a critical role in the 'tripartite synapse', which is formed by an astrocyte and two neurons. The normal functions of the astrocyte-neuron crosstalk are supported by microglia and neurons in turn, which regulates the activation and motility of the microglia (95). Neurons maintain the homeostatic phenotype of microglia via CX3CL1-CX3CR signaling (95,103), which may have an important role in glioma progression by regulating the function of microglia. Reciprocally, microglia-derived EVs (MEVs) also mediate neuronal growth and activity by increasing the miniature excitatory postsynaptic current via the membrane components of MEVs. In addition, MEVs have been demonstrated to exert roles in neuritogenesis and neuroprotection, which may potentiate the neuron-glioma circuit. In addition, inhibition of neutral sphingomyelinase 2 successfully impeded the release of EVs from the brain and aggravated the symptoms in a Parkinson's disease mouse model, suggesting that the crosstalk between neurons, microglia and glioma cells based on EVs may be a possible option for therapeutic intervention (104).

It is theoretically feasible that viro-immunotherapy may be utilized to reverse the immunosuppressive environment by introducing oncolytic viruses (OVs). OVs exert antitumor effects through polarizing TAMs towards the M1 phenotype, which has the effect of upregulating the pro-inflammatory response (105). A pro-inflammatory TME leads to inhibition of glioma growth. It is also possible that engineered MEVs are used to manipulate the neuron-glioma circuit for better tumor suppression and neuroprotection.

Neural stem cell (NSC)-based delivery systems. NSCs have the property of tropism towards glioma and these are dependent on interactions between growth factors and receptors (106). This property of NSCs paves the way towards a novel approach of developing NSC-based drug delivery systems. On this basis, murine NSCs transfected with adenoviral vector containing TNF-related apoptosis-inducing ligand (TRAIL) genes were able to successfully migrate towards glioma cells and express TRAIL *in vivo*, thereby significantly increasing the rate of tumor apoptosis (107). Furthermore, IL-23-expressing NSCs derived from bone marrow stem cells have been utilized to treat glioma in an animal model, where the survival time of mice was significantly prolonged; these effects were attributed to the potentiated activity of CD8+ T cells, CD4+ T cells and natural killer cells (108). Recently, researchers have loaded NSCs with oncolytic viruses to obtain more effective therapeutic effects on gliomas. Batalla-Covello *et al* (109) observed that the virus-loaded NSCs successfully migrated towards glioma and exerted anti-glioma effects *in vivo*. These findings demonstrated the feasibility and efficacy of using an NSC-based delivery system. It is noteworthy that researchers have observed a close contact (possibly physical) between NSCs and glioma cells through the use of immunohistochemistry and fluorescence immunohistochemistry (107-111). More importantly, Benmelouka *et al* (108) observed that the transplanted NSCs were capable of differentiating into neurons, astrocytes and oligodendrocytes *in vivo*. Therefore, NSCs may incorporate into the neuron-glioma circuit or neuron-glial network and form NGSs between neurons and gliomas. To use NSCs as a vehicle to deliver drugs, including small-molecule inhibitors, nucleotides such as miRNAs and oligonucleotides to target receptors and channels with both precision and efficiency

may prove to be beneficial in the treatment of glioma, and this approach warrants further investigation.

Optogenetic modulation. The application of emergent optogenetic tools with their great precision and high safety provides the possibility of treating gliomas by neuronal manipulation. Optogenetic tools are able to modulate the activation of receptors on the neuronal membrane, which affects the tumor behavior via neuron-glioma activities (15). In a recent exploratory study, Trks were engineered with a photosensory core module of DrBphP, named Dr-Trk opto-kinase, which was successfully suppressed by far-red (FR) light and reactivated by near-infrared light (112). It is notable that the optical modulation may be limited to a single molecule of Dr-Trk, whereas, by contrast, even selective chemical receptor tyrosine kinase inhibitors usually suppress several targets simultaneously. Furthermore, the inhibitory effects of FR light were similar to pharmacological inhibition (112). In addition to the effects of modulation on membrane receptors, optogenetic technology may also be used to regulate neuronal activity. It was demonstrated that optical stimulation on GABAergic interneurons resulted in impaired glioma proliferation. The sensory stimulation promoted glioma cell growth, whereas this effect was limited to glioma cells in the visual cortex (15). Based on the insight gained on neuron-glioma interaction, optogenetic technology harbors great therapeutic potential for the future due to its non-invasiveness and accuracy.

Co-ulture of neuron organoid and glioma. The neuron organoids, mostly derived from embryonic stem cells or induced pluripotent cells, recapitulate multiple structures and functions similar to those found in the human brain (113). The co-culture system provided a suitable microenvironment for glioma development and interplay with other TME determinants, including astrocytes, oligodendrocytes, microglia and neurons (114). Brain organoids and GSCs constitute an *ad hoc* three-dimensional system, which may be used to further verify the functions of above-mentioned neuronal interacting factors, including neurotransmitters and transsynaptic proteins (including NLGN3 and its modifying enzyme, ADAM10). The super-resolution imaging technique revealed that GSCs develop an enhanced tropism for mature neurons by forming direct hemi-synapses containing pre-synaptic vesicles, for which a complete explanation of the internal structure awaits further investigation (115). Of note, the co-culture system provides an 'off-the-wall' methodology for advanced studies on glioma invasion and screening anti-invasive compounds. Single-cell transcriptomics combined with neural organoids have provided a novel perspective in terms of studying glioma heterogeneity and invasion, as well as the transcriptomic characterization of surrounding organoid cells upon glioma interaction. Therefore, specific transcriptional changes underlying therapeutic targets were denoted to enable effective drugs to be screened in a patient-specific manner (116). An up-to-date study has accumulated evidence of cognitive and electrophysiological neural responses in patients with glioma to analyze the impacts of functional integration on clinical outcomes. The results obtained suggested that gliomas with increased functional connectivity are correlated with higher aggressiveness through remodeling functional neural circuits in certain cortex areas (117). It is theoretically feasible that the co-culture of neuron organoids and glioma, as a more characteristic and accessible tool, may be applied to study the integration of glioma with neural networks and this technology may give rise to a therapeutic strategy that affords cognitive outcomes and survival.

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Availability of data and materials

Publicly available datasets were analyzed in this study. The summary table of clinical trials included data from https://clinicaltrials.gov/.

Authors' contributions

TH, HS, JC and HW conceptualized this study. TH, HS, MZ, CC, QH, YS, SW and XZ performed the literature search and drafted the manuscript. TH and HS completed the visualization. All authors participated in reviewing the paper and HW and QH mainly performed revision of the manuscript. JC and HW conducted project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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