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REVIEW

Exploring the Vital Link Between Glioma, Neuron, and Neural Activity in the Context of Invasion

Masafumi Miyai,*†‡ Toru Iwama,‡ Akira Hara,* and Hiroyuki Tomita*

From the Departments of Tumor Pathology and Neurosurgery,‡ Gifu University Graduate School of Medicine, Gifu; and the Department of Neurosurgery,† Hashima City Hospital, Gifu, Japan*

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Address correspondence to Hiroyuki Tomita, M.D., Ph.D., Department of Tumor Pathology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu, 501-1194, Japan. E-mail: h_tomita@gifu-u.ac.jp.

Because of their ability to infiltrate normal brain tissue, gliomas frequently evade microscopic surgical excision. The histologic infiltrative property of human glioma has been previously characterized as Scherer secondary structures, of which the perivascular satellitosis is a prospective target for anti-angiogenic treatment in high-grade gliomas. However, the mechanisms underlying perineuronal satellitosis remain unclear, and therapy remains lacking. Our knowledge of the mechanism underlying Scherer secondary structures has improved over time. New techniques, such as laser capture microdissection and optogenetic stimulation, have advanced our understanding of glioma invasion mechanisms. Although laser capture microdissection is a useful tool for studying gliomas that infiltrate the normal brain microenvironment, optogenetics and mouse xenograft glioma models have been extensively used in studies demonstrating the unique role of synaptogenesis in glioma proliferation and identification of potential therapeutic targets. Moreover, a rare glioma cell line is established that, when transplanted in the mouse brain, can replicate and recapitulate the human diffuse invasion phenotype. This review discusses the primary molecular causes of glioma, its histopathology-based invasive mechanisms, and the importance of neuronal activity and interactions between glioma cells and neurons in the brain microenvironment. It also explores current methods and models of gliomas. *(Am J Pathol 2023, 193: 669–679; https://doi.org/10.1016/j.ajpath.2023.02.018)*

Most primary malignant brain tumors and approximately 30% of all primary brain tumors are gliomas.[1] Glioma growth pattern is characterized by diffuse infiltration into normal brain parenchyma. In 1938, the German pathologist Hans Joachim Scherer (1906 to 1945) characterized four glioma infiltration patterns in humans (namely; perineuronal satellitosis, perivascular satellitosis, infiltration along white matter tracts, and subpial spread), which are currently known as Scherer secondary structures.[2] Infiltration along the white matter tracts and subpial spread are common in patients with late-stage glioma,[3] whereas perineuronal and perivascular satellitosis are seen in early- to late-stage glioma. Although the role of perivascular satellitosis in nutrition and hypoxia has been studied,[4] the effects and mechanisms of perineuronal satellitosis remain largely unknown. Specifically, determining whether gliomas reach the nerve by random stochastic coincidence, the infiltrating glioma cells interact with preexisting neurons, and perineuronal satellitosis contributes to glioma-treatment resistance, remain to determined.

Glial cells perform various functions in the central nervous system (CNS) and aid in the nourishment and metabolism of neurons, which originate from glioma cells.[5] Gliomas with astrocytic-like properties, such as anaplastic gliomas and glioblastomas, are highly malignant, with total resection of the affected area as the most effective available

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treatment strategy.[6] However, most gliomas, independent of malignancy level, exhibit Scherer secondary structures, making total resection impossible. A few invisible, infiltrating glioma cells linger, leading to local relapse.[7] Although resection of the extra parenchyma surrounding the tumor has been performed, it remains controversial, especially in elderly patients.[8]

Alterations in tumor metabolism are a characteristic feature of glioblastoma. Invasive glioma cells can generate the energy required for colonization nearby brain tissue and adapt to novel microenvironments with varying energy and oxygen availability through metabolic reprogramming.[9] The recent Go and Grow hypothesis suggests a phenotypic switching between the go (migration) and grow state (proliferation), depending on the oxygen level and nutrients in the glioma microenvironment.[10,11] This hypothesis suggests that aerobic glycolysis from glucose to lactate serves as the energy source during migration and invasion into the glioma microenvironment, whereas the pentose phosphate pathway is mostly utilized during proliferation.[12] Recent studies using optogenetic techniques and mouse xenograft glioma models have described the unique role of synaptogenesis in the proliferation of gliomas and identified potential targets for therapeutic involvement.[13,14]

Recently, a mouse model that recapitulates the invasion of diffuse gliomas by perineuronal satellitosis has been established.[15] Although a model with a diffuse tumor infiltration into normal brain is reported,[16,17] histopathologic analysis revealed that this model is specifically tailored to perineuronal satellitosis.

This review discusses the state of knowledge on the mechanism of perineuronal satellitosis and the interaction between glioma cells and neurons during tumor development and growth.

Scherer Secondary Structure

Scherer was the first to define perineuronal satellitosis and glioma growth patterns in his influential study titled "Structural Development in Gliomas."[2] His work was based on the microscopic examination of 100 gliomas, including the entire tumor and surrounding structures, from the autopsy specimens of human patients. The term secondary structures is used to indicate all structures formed by glioma cells around preexisting tissue elements.[2] Some of these structural characteristics become more obvious after a complete disruption of the tissue elements by glioma cells.

Scherer described eight categories of secondary structures—perineural and neuronophagic, surface, perivascular, perifascicular, intrafascicular, interfibrillar, white and gray matter growth, and combinations of secondary structures. Perineural infiltration, including perineuronal satellitosis, is observed in perineural and neuronophagic, perifascicular, and interfibrillar growth. Neoplastic cells that spread around neurons and dendrites are known as perineuronal satellitosis. Glioma cells gather to replace the destroyed nerve cells via a process known as neuronophagic proliferation. Presently, perineuronal satellitosis, perivascular satellitosis, subpial spread, and invasion along the white matter tracts are the four basic histologic categories that may be used to categorize the formations (Figure 1).[11]

Scherer secondary structures in the mouse brain can be reproduced and recapitulated using a rare glioma cell line known as IG27 cells,[15] a model of diffuse glioma with H3.3K27M mutation. The IG27-diffuse glioma displays perineuronal and perivascular satellitosis as well as extensive infiltration into normal tissue; IG27-diffuse glioma cells along nerve axons are also seen in the white matter pathways.

Histologic Characterization of Perineuronal Satellitosis in Glioma

Scherer characterized the primary structures of gliomas as morphologic patterns resulting from the intrinsic biology of tumors, which appear independently of previous tissue. Whorls, papillary structures, canaliculi, glandular formations, rosettes, and pseudorosettes are some examples of primary structures.[18] Development of new blood vessels is essential for the growth of glioblastoma tumors, which are highly vascularized. Vascular endothelial cells proliferate, migrate, and differentiate throughout the complicated process of angiogenesis, which is triggered by certain signals.[19]

Scherer secondary structures is the term given to patterns of glioma cell invasion.[2] Scherer secondary structures are histopathologically classified on the basis of glioma distribution, development, and biological potential. The microenvironment significantly influences the migration of glioma cells, as observed via careful examination of histomorphology. Moreover, invasive glioma cells that exhibit Scherer secondary structures imitate crucial intracellular processes of both proliferation and migration in neural stem cells (NSCs) or glial progenitor cells in the CNS.[20]

The term satellitosis refers to both reactive and neoplastic processes and describes an increase in the number of cells around a neuron. Typically associated with diffuse astrocytic neoplasms, neoplastic satellitosis is observed more frequently than reactive satellitosis. Intrafascicular growth occurs when cells preferentially infiltrate along myelinated fibers in white matter tracts, along with subpial, perivascular, and perineuronal accumulation of glioma cells.[21] Reactive satellitosis is characterized by neuronal degeneration, with little changes where the satellite cells are represented by nonneoplastic glial cells.[22]

The structure of perineuronal satellitosis was determined using two-dimensional microscope. A recent study used three-dimensional images obtained using scanning electron microscopy to demonstrate that the histone H3K27M

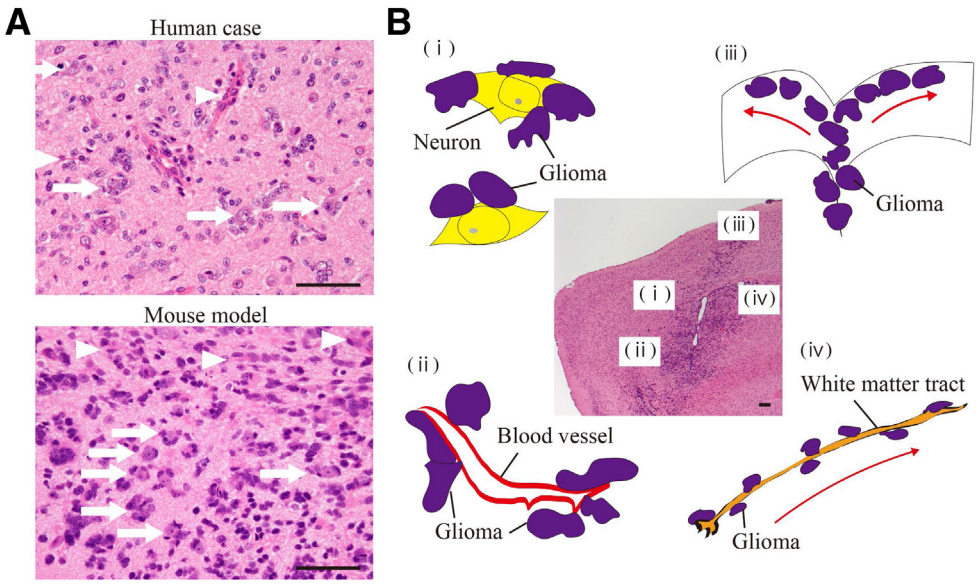

Figure 1 **A: Top panel:** Representative hematoxylin and eosin (H&E)—stained images of human glioblastoma. Perineuronal satellitosis (**arrows**) and perivascular satellitosis (**arrowheads**) are observed. **Bottom panel:** Representative H&E-stained images of IG27-diffuse glioma model. Perineuronal satellitosis (**arrows**) and perivascular satellitosis (**arrowheads**) are observed. **B:** Schematic diagram of the four histologic types of Scherer secondary structure: (i) perineuronal satellitosis, (ii) perivascular satellitosis, (iii) subpial spread, and (iv) invasion along the white matter tracts. Scale bars: 50 μm (**A**); 1 mm (**B**).

mutated IG27 cells are tightly connected to neurons in diffuse gliomas in mouse brain (Figure 2).[15]

The role of neural activity in glioma infiltration and proliferation has been previously elucidated.[13,14,23–25] However, although early research indicated that glioma cells singly infiltrate during neuronal satellitosis and neoplastic glial cell invasion, the precise mechanisms underlying the direct growth-promoting effects of activated neurons on the tumor microenvironment in glioma remain unclear.[26]

Similarities between the Cells of Origin of Gliomas and Neuronal Progenitor/Stem Cells

Although controversy regarding the origin of gliomas persists, accumulating evidence suggests that numerous glioma forms develop from neural stem or oligodendroglial lineage progenitor cells[27–32]; however, this can vary between glioma subtypes.

Neurotransmitters control neural precursor cell proliferation and differentiation during early stages of neurodevelopment by inducing nonsynaptic depolarization.[33] Excitatory amino acid transmitters can also perform neurotrophic functions throughout CNS development, in addition to their role in adult neurotransmission.[34] According to a recent study, transitory glutamatergic synaptic contact between subplate neurons and neuroblasts controls the orderly shift of neocortical neuroblasts from multipolar to bipolar migration.[35] Gibson et al[23] demonstrated that normal neural and oligodendroglial precursor cells in juvenile and adult mammalian brains have a significant mitogenic impact, indicating that neuronal activity may encourage proliferation in high-grade glioma (HGG).

The subgranular zone of the dentate gyrus during hippocampus formation and the subventricular zone (SVZ) of the lateral ventricles are primary neurogenic zones in the adult mammalian brain. Glial fibrillary acidic protein—positive adult NSCs are quiescent cells with unrestricted capacity for self-renewal and multipotency. Proliferative progenitor cells derived from NSCs have a low capacity for self-renewal and are destined to develop into various cell types.[28] New neurons are produced by neuronal progenitor cells, which develop from NSCs in the SVZ and

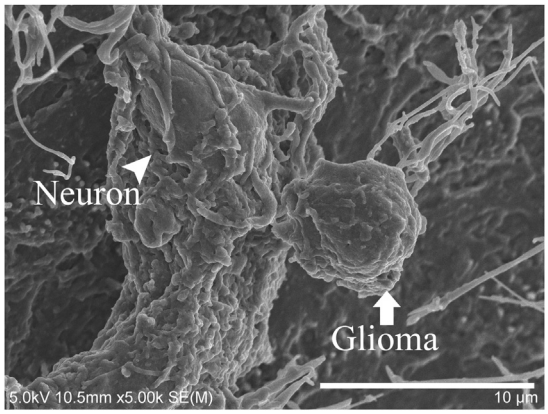

Figure 2 Three-dimensional image of perineuronal satellitosis using scanning electron microscopy. IG27-diffuse glioma cell (**arrow**) and neuron (**arrowhead**) are shown. Scale bar = 10 μm.

Table 1 Articles with a Focus on Glioma Cell Infiltration Using Laser Capture Microdissection

Article no.	Study	Samples	Genes/pathway related to glioma infiltration	Implications of the genes/pathway
1	Prabhu et al (2017)[42]	Human glioma tissue 37 case	Autophagy. Fatty acid metabolism unique to early stages of gliomagenesis. Neuronal receptor signaling.	Comparison of central tumor and infiltrating tumor in glioma. Infiltrating tumor showed amplification of genes regulating neuronal receptor signaling and autophagy involved in the regulation of neurotransmitter release.
2	Civita et al (2019)[43]	Human glioblastoma tissue 3 case Formalin-fixed, paraffin-embedded tissue	CDC42 signaling and activity. Epithelial-mesenchymal transition. Integrin family cell surface interactions. The citric acid cycle and respiratory electron transport. Transmembrane transport of small molecules.	Comparison of the gene expression of astrocytes in perineuronal satellitosis to that of astrocytes in the tumor core. Top five biological pathways up-regulated in perineuronal satellitosis.
3	Daubon et al (2019)[44]	Patient-derived xenografts Snap-frozen samples	DNM1. PLP1.	PLP1 and DNM1 were significantly overexpressed in tumor cells in the invasive region.
4	Mariani et al (2001)[45]	Human glioblastoma tissue 7 case Cryopreserved glioblastoma specimens	P311.	The invading cells had higher levels of the protein P311 compared with the tumor core cells.
5	Nakada et al (2004)[46] Nakada et al (2010)[47]	Human glioblastoma tissue 7 case Cryosectioned glioblastoma specimens Human glioblastoma tissue 19 case Cryopreserved glioblastoma specimens	EphB2 receptor. Ephrin-B2 ligand.	The EphB receptor/ephrin-B expression in invasive glioma cells was higher than in normal brain, and activation of EphB2 promotes glioma migration and invasion.
6	Hoelzinger et al (2005)[48]	Human glioblastoma tissue 4 case Flash-frozen tissues	ATX. BCLW.	Comparison of tumor cores and white matter infiltrating cells. Infiltrating tumor cells of various grades showed amplification of ATX and BCLW.

ATX, autotaxin; BCLW, B-cell lymphoma-w; CDC42, cell division control protein 42 homolog; DNM1, dynamin-1; EphB, erythropoietin producing hepatocellular B; PLP1, proteolipid protein 1.

move along the rostral migratory stream and into the olfactory bulb, whereas migration of neurons into the granular cell layer occurs in the subgranular zone.[28]

The activity of cholinergic neurons that branch out into the postnatal SVZ controls neurogenesis in that region.[36] Similarities between glioma stem cells and NSCs of the SVZ include high cell migration, variability of genetic material, strong proliferative potential, affiliation with blood vessels, and bilateral interaction with niche components, such as endothelial cells, pericytes, astrocytes, or extracellular matrix.[37]

In addition, recent studies have shown that the SVZ may potentially be a source of brain tumor stem cells, which resemble neurons, astrocytes, and oligodendrocytes that produce NSCs in terms of morphology and physiology.[37–40]

Overall, NSC migration and glioma cell infiltration are likely to be similar in the SVZ region or niche. Therefore, investigating the processes underlying the formation of oligodendroglial precursor cells and normal neural progenitor cells in the postnatal brain will provide insights into the microenvironmental factors influencing HGG development.

Histopathology-Based Invasive Mechanisms of Glioma

The Ivy Glioblastoma Atlas, published by Puchalski et al[41] in 2018, is an anatomy-based transcriptional atlas of human glioblastoma. It correlates individual histologic characteristics with genomic and gene expression patterns, considering the most significant morphologic hallmarks of glioblastoma a molecular significance. Its database contains information regarding the expression of genes associated with several structural characteristics frequently observed in glioblastoma tumors that have undergone laser capture microdissection (LCM) (Table 1).[42–48] Only tumor cells are extracted via LCM from the diverse tumor microenvironment, which includes immune cells, fibers, neurons, and glial cells. To identify the gene sets with enhanced expression in each anatomic characteristic, LCM has been utilized

to separate RNA from infiltrating and cellular malignancies, pseudopalisading cells surrounding necrosis, and microvascular proliferation.[41] Prabhu et al[42] observed that glioblastoma subtype heterogeneity and its distinct tumor microenvironment are related, as are invading cells with a proneural hallmark.[41]

Civita et al[43] generated single-cell LCM RNA sequences of six different histologic contexts within the primary human glioblastoma samples without R132 isocitrate dehydrogenase 1 (IDH1) or R172 IDH2 mutations and 1p/19q codeletions. The authors analyzed the histologic significance of perineuronal astrocytes in satellitosis and neurons with satellitosis in human glioblastoma tissues. Perineuronal astrocytes overexpress particular aquaporins (AQP1 and AQP4)[49,50] and matrix metalloproteinases (MMP9 and MMP28),[51] which are essential for cell migration in the satellitosis compartment. In addition, perineuronal astrocytes in satellitosis cells overexpress secreted protein acidic and cysteine-rich like protein 1[52] and breast cancer susceptibility gene 1 (BRCA1),[53] both of which increase glioma cell viability, invasion, and migration, and are associated with a poor prognosis. A proteomics investigation of LCM in glioblastoma-invasive regions of patient-derived xenografts, which identified proteolipid protein 1[54,55] and dynamin-1[56,57] as novel markers of glioma invasion, was conducted by Daubon et al.[44] Overall, LCM is a useful tool for studying gliomas that infiltrate the normal brain microenvironment.

In addition, single-cell RNA and DNA sequencing have recently been widely applied in a variety of biological domains, including cancer research. Although single-cell RNA sequencing is used primarily for gene expression analysis, single-cell DNA sequencing is employed in investigating cancer mutations and tumor evolution heterogeneity. Because of their significance in cancer biology, both techniques have received significant attention.[58]

Molecular Signaling and Pathways in Glioma Invasion Related to Perineuronal Satellitosis

Cell Division Control Protein 42 Homolog

Integrin binding to extracellular matrix ligands activates a complex network of intracellular signaling pathways that control cell migration. The pathway involves activation of focal adhesion kinase, which triggers the activation of multiple signaling proteins, including rat sarcoma viral oncogene (RAS), SRC proto-oncogene, and SHC adaptor protein, thereby leading to the activation of other signaling molecules, such as phosphatidylinositol 3-kinase, Raf proto-oncogene, Rac family small GTPase, p21-activated kinase, and extracellular signal-regulated kinase. To control a variety of biochemical pathways, including the p21-activated kinase pathway, activated RAC and cell division control protein 42 homolog work together. These activated signaling pathways influence numerous biochemical pathways, including transcriptional activity and changes in the cytoskeleton, which lead to the migratory phenotype of the cell.[59]

Isolated astrocytes with neuronal satellitosis have extremely active integrin family cell surface contact pathways, which regulate the interaction between endothelial and tumor cells and the extracellular matrix.[60–63] The signaling and activity pathways of the cell division control protein 42 homolog are additional mechanisms that are active in astrocytes during satellitosis.

Previous studies have shown a connection between malignant glioma aggressiveness and invasiveness and cell division control protein 42 homolog activation.[64–66]

Chemokine Receptor Type 4

In glioblastoma, chemokine signaling is essential for carcinogenesis, growth, angiogenesis, tumor infiltration, and metastasis.[67] Indeed, the chemokine receptor type 4 (CXCR4) signaling pathway plays multiple roles in glioma cell invasion, angiogenesis, proliferation, and tumor progression.[68–70]

Zagzag et al[68] proposed a mechanism to determine Scherer secondary structures at glioma border involving differential expression of stromal cell–derived factor (SDF)-1α (also known as CXCL12) and CXCR4, a receptor for the SDF-1. In human glioma tissue and xenograft mice models, SDF-1α is significantly expressed in neuronal cells, blood vessels, white matter tracts, and subpial areas that provide structural foundation for Scherer secondary structures. In contrast, the invading glioma cells growing near blood vessels and neurons in subpial areas and along white matter tracts have high levels of CXCR4. In addition, Goffart et al[69] demonstrated the function of CXCR4–SDF-1α signaling in glioma infiltration along corpus callosum and SVZ environment. CXCR4–SDF-1α has also been linked to glioblastoma cell motility, self-renewal, and invasion in several studies. Overall, chemokine signaling is extremely important in glioma progression and leads to the generation of a more invasive and robust phenotype.[67,71–74]

Neuroligin-3

Neuroligins, transmembrane cell adhesion proteins found in the postsynaptic membrane, maintain synapses via attachment to presynaptic neurexin proteins.[75] A previous study has shown that neuroligin-3 (NLGN3) is produced in both excitatory and inhibitory synapses in juvenile rodents.[76] NLGN3, which binds to presynaptic neurexin proteins, is involved in the development and operation of synapses.[77,78]

Venkatesh et al[24] have reported that activated neurons stimulate HGG proliferation and development in mice with human glioma xenografts. The growth of patient-derived HGG cells is aided by conditioned media from optogenetically triggered cortical slices, demonstrating that the NLGN3 protein is the primary potential mitogen. Soluble

Table 2 Molecular Signaling and Pathways with Invasion and Cell-Neuron Interaction of Gliomas

Article no.	Molecular signaling and pathways	Model	Methods	Summary
1	CDC42[64,65]	Vitro. Vivo: orthotopic xenograft mouse model (U251)[64,65] and rat model (C6).[65] Human tissue specimens.[64]	Immunohistochemistry.[64,65] Matrigel invasion assay.[64,65] Migration assay.[64] mRNA expression.[64] RT-PCR.[65] Three-dimensional spheroid invasion assay.[64] Two-photon excitation microscopy.[65]	The activity levels of Cdc42 are higher in glioma cells invading the brain parenchyma compared with the perivascular region. Activated Cdc42 in glioma cells is responsible for the migratory and invasive phenotype.
2	TRPV4[66]	Vitro. Vivo: orthotopic xenograft mouse model (U87MG). Human tissue specimens.	Cell migration and invasion assay. Immunohistochemistry. mRNA expression. Pull-down assay.	TRPV4 is expressed in the cell membrane and cellular protrusions and regulates the development of invadopodia and filopodia in glioma cells, thereby promoting glioma cell migration and invasion.
3	Chemokine receptor type 4[68,69]	Vitro.[68,69] Vivo: orthotopic allograft mouse model (GL261)[68]: 1. Patient-derived orthotopic xenograft.[69] 2. Orthotopic xenograft mouse model (U87MG).[69] Human tissue specimens.[68]	Bioluminescense imaging.[69] Chemotaxis cell migration assay.[69] Enzyme-linked immunosorbent assay analysis.[69] Flow cytometry.[68] Immunohistochemistry.[68,69] *In situ* hybridization.[68] Migration assay.[68] Real-time PCR.[68,69] Time-lapse analysis.[69]	SDF-1α expression in gliomas and its secretion from the neurons may entice CXCR4-positive glioma cells to migrate into the brain in the vicinity of tumors.
4	Neuroligin-3[24,25]	Vitro.[24,25] Vivo: patient-derived orthotopic xenograft.[25] Analysis of data from The Cancer Genome Atlas.[25]	CellTiter-Glo assay.[24,25] Click-iT EdU visualization.[25] EdU incorporation assay.[24] Generation of conditioned medium from acute cortical slices.[24,25] Immunohistochemistry.[24,25] *In vivo* optogenetic stimulation.[25] Neurosphere formation assay.[24] Phosphorylated antibody array.[24] Proteomic analysis.[25] RT-PCR.[24,25]	Neuroligin-3 secreted through neuronal activity promotes proliferation via the PI3K/mTOR pathway in high-grade glioma.
5	Glutamate[89]	Vitro. Vivo: orthotopic xenograft mouse model (D54-MG). Human tissue specimens.	Glutamate release assays. Immunohistochemistry. Migration assays. Ratiometric $[Ca^{2+}]_i$ measurements. RT-PCR.	The glutamate released by gliomas and neurons acts as an important autocrine/paracrine signal to promote the glioma cell invasion.
6	AMPA receptor[13,14]	Vitro.[13,14] Vivo: patient-derived orthotopic xenograft.[13,14] Human tissue specimens.[13,14]	Calcium imaging. Analysis.[13,14] CellTiter-Glo assay.[13,14] Electron microscopy.[13,14] Electron tomography.[14] Fluorescence-activated cell sorting.[13,14] Immunohistochemistry.[13,14] *In vivo* multiphoton laser scanning microscopy.[14] *In vivo* optogenetic stimulation.[13,14] Neuron-glioma co-culture.[13,14] Quantitative PCR.[13] RNA sequence.[13,14] Single-cell sequencing analysis.[13] Three-dimensional invasion and migration assays.[13]	Peritumoral neurons and glioma cells directly interact through the post-synaptic AMPA receptor and increase the glioma proliferation and infiltration.
7	Neurotrophins[114]	Vitro. Vivo: orthotopic xenograft mouse model (U87). Human tissue specimens.	Circular monolayer migration assay. Enzyme-linked immunosorbent assay. Flow cytometric analysis. RT-PCR. Transwell motility assay.	Neurotrophin secretion in glioma and neurons may regulate the glioma invasion through p75NTR in glioma.

(*table continues*)

Table 2 (*continued*)

Article no.	Molecular signaling and pathways	Model	Methods	Summary
8	Glut1[15]	Vitro. Vivo: orthotopic allograft mouse model (IG27 glioma cell). Human tissue specimens.	Chip-qPCR. DNP-MRI imaging. Glucose uptake assay. Metabolome analysis. Microarray analysis. Scanning electron microscopy. Seahorse XF glycolysis stress test. Time-lapse imaging lactate assay.	Glut1 in the glioma cells controls attachment to and interaction with surrounding neurons via lactate release.

AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CDC42, cell division control protein 42 homolog; Chip, chromatin immunoprecipitation; CXCR4, chemokine receptor type 4; EdU, 5-ethynyl-2′-deoxyuridine; Glut1, glucose transporter 1; mTOR, mechanistic target of rapamycin; p75NTR, p75 neurotrophin receptor; PI3K, phosphatidylinositol 3-kinase; qPCR, real-time quantitative PCR; SDF-1α, stromal cell–derived factor-1α; TRPV4, transient receptor potential vanilloid 4.

NLGN3 enhances glioma cell feed-forward expression of NLGN3 by activating the phosphatidylinositol 3-kinase and mechanistic target of rapamycin signaling pathway. These results support the critical function of activated neurons in the microenvironment of brain tumors.

NLGN3 is highly expressed in oligodendroglial precursor cells and neurons,[79] both of which influence the activity-regulated NLGN3 production and glioma formation via a disintegrin and metalloproteinase 10 (ADAM10) sheddase.[25] Proteins from the ADAM family are membrane-anchored proteases that shred the extracellular domains of membrane-bound protein.[80] The functional roles of ADAM10 sheddase include the regulation of wound healing, neurogenesis, and skin homeostasis via shedding of various transmembrane proteins.[81] Furthermore, ADAM10 inhibitors suppress the proliferation of HGG xenografts. A potential method to alter the levels of NLGN3 in the tumor microenvironment for HGG treatment is to target ADAM10 sheddase.[25,82]

Glutamate

Glutamate, an essential component of energy metabolism, functions as an excitatory neurotransmitter in the CNS.[83] Glutamate is often synthesized from glutamine[84] and is released from neurons as a neurotransmitter,[85] where it is taken up by astrocytes and transformed into glutamine and released once more.[86] In the cytoplasm, the enzyme glutaminase converts glutamine into glutamate.[87] In addition, as a consequence of glutathione production, glioma cells produce and release glutamate[88] as a key autocrine/paracrine signal that encourages cell invasion,[89,90] triggers tumor formation,[91,92] and induces excitotoxic activity.[93,94]

Studies have shown that glioma and glial progenitor cells express glutamate receptors.[95,96] The primary excitatory network of the CNS is the glutamate receptor system, which is composed of three subfamilies. The N-methyl-D-aspartate and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors are ligand-gated ion channels, whereas the metabotropic glutamate receptor (mGluR) is a metabotropic receptor.[97,98] AMPA receptors are tetrameric ion channel receptors consisting of the glutamate receptor 1 (GluR1), GluR2, GluR3, and GluR4 distinct subunits. AMPA receptors are expressed in both normal glial cells and gliomas.[96,99] In addition, glutamate promotes glioblastoma cell survival, expansion, and migration by activating phosphatidylinositol 3-kinase/Akt signaling via the AMPA receptor in response to calcium influx.[91,96,100] The release of glutamate by glioma cells is associated with an autocrine/paracrine effect on the development, survival, and infiltration of gliomas.

AMPA receptor-dependent neuron-glioma synapses that promote glioma growth were first reported by Venkatesh et al[13] and Venkataramani et al.[14] Venkatesh et al[13] evaluated single-cell transcriptomic data sets using pretreatment biopsy samples of the main types of adult and pediatric HGG and observed synaptic gene enrichment in glioma cells similar to oligodendroglial precursor cells.[82] Meanwhile, Venkataramani et al[14] observed the presence of glutamatergic AMPA receptors in neuron-glia synapses and that AMPA receptor blockade suppresses glioma proliferation in xenograft models.[82,101]

Fluoxetine not only acts as a selective serotonin reuptake inhibitor but also selectively inhibits N-methyl-D-aspartate receptors and blocks AMPA receptors. Fluoxetine may therefore inhibit the glutamatergic synaptic communication between neurons and glioma cells, thereby inhibiting the proliferation of glioma cells.[102,103]

Neurotrophins

Neurotrophins regulate different aspects of the growth, survival, and functionality of neurons in both the peripheral nervous system and CNS.[104] One of the most studied and thoroughly described neurotrophic factors in the CNS is the neurotrophin brain-derived neurotrophic factor (BDNF).[105] Cleavage of pro-BDNF inside and outside the cell produces mature BDNF.[106] Tropomyosin receptor kinase B (TrkB) and p75 neurotrophin receptor (p75NTR) are two kinds of neurotrophin receptors via which BDNF

communicates. TrkB and p75NTR mediate various biological functions alone or in combination.[107] NF-κB, several enzymes (phosphatidylinositol 3-kinase), mitogen-activated protein kinase, phospholipase C (PLC)-γ, and guanosine triphosphate hydrolases of the RAS homologous protein family are activated via the binding of the mature domain of BDNF to TrkB and p75NTR.[108] BDNF-signaling pathways control several physiological functions, including the survival and apoptosis of neurons,[109] dendritic development,[110] and synaptic plasticity.[111,112]

Glioma cell lines and patient-derived HGG tissues can produce neurotrophins and their receptors (TrkB and p75NTR) and are correlated with glioma tumor progression. Moreover, neurotrophins can stimulate several processes, including invasion, migration, tumor cell proliferation, survival, and angiogenesis.[113−116] The significance of neurotrophins in the development of glioma cells has been previously demonstrated via BDNF involvement in NLGN3 activity-dependent glioma proliferation.[24]

Johnston et al[114] have reported that invading glioma cells up-regulate the p75NTR gene both *in vitro* and *in vivo* and that p75NTR migrates and invades genetically distinct glioma. In addition, p75NTR-positive cells have been shown to migrate more infiltratively than p75NTR-negative glioma cells within samples from patients with glioma.[114] Neurotrophins are also required for p75NTR-mediated invasion, which decreases RAS homologous A activity.[114]

Several studies have elucidated the function of BDNF-TrkB signaling in the tumor microenvironment.[115,117] Wang et al[118] found that glioblastoma cell invasion, migration, and proliferation are promoted by NSCs in nude mice. TrkB is produced in HGG cells and glioma stem cells/brain tumor−initiating cells isolated from fresh human tumor.[117] In addition, Roesler[119] has suggested that the release of neurotrophin by NSCs may facilitate interactions between glioblastoma cells and neural stem cells.

Although evidence for the glioma progression-related downstream signaling pathways of neurotrophin receptors (p75NTR, TrkA, TrkB, and TrkC) is lacking, targeting neurotrophin signaling pathways may offer a novel therapeutic approach for treatment-resistant and recurrent glioblastoma.[116] Table 2 summarizes molecular signaling and pathways in glioma invasion related to perineuronal satellitosis.

Conclusion and Perspectives

This review discussed neuron and glioma cell interactions, neural activity, and changes in the metabolic pathways of glioma cells in perineural satellitosis in glioma.

In the past, electronic stimulation or functional magnetic resonance imaging were the common methods of examining glioma-neuron interaction and neural activity. However, these methods are unable to fully elucidate the relationship between neural responses and functions and the way neural activity affects glioma microenvironment. Recently, several mouse glioma models have been developed,[120−122] which will provide insights into the biological basis of gliomas and the development of effective treatment. Not only changes in genome but also histopathologic morphology will aid in developing therapeutics. However, further research is warranted to clarify the function of neural activity in the tumor microenvironment and the mechanism underlying perineuronal satellitosis (Scherer secondary structure of glioma).

Author Contributions

All authors wrote and revised the manuscript.

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