

The role of the nervous system in the development of brain tumorigenesis: From neurons to the tumor microenvironment

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Abstract

Brain tumors, especially malignant gliomas and metastases, continue to pose serious clinical challenges due to their complex biology and limited treatment options. The traditional research paradigm mainly focuses on the tumor cells themselves and their interaction with the immune microenvironment, while the critical role of the nervous system (including neurons, glial cells, neurotransmitters/modulators, and nerve fibers) in the pathological process of tumors has been underestimated for a long time. This review systematically reviews breakthrough research in recent years, revealing that the nervous system plays an indispensable driving role in the development, proliferation, invasion, and treatment resistance of brain tumors. Specifically, neuronal activity profoundly influences tumor behavior through the utilization of direct "neuron-tumor synapses", neurotransmitter signaling (e.g., glutamate, γ -aminobutyric acid (GABA), neuropeptides), and axon-guiding molecules. At the same time, glial cells (astrocytes, microglia, etc.) undergo phenotypic remodeling in the tumor microenvironment, and their secretion products and functional status have complex regulatory effects on tumor progression. Conversely, the growth of brain tumors also violently reshapes the structure and function of the nervous system (such as the destruction of nerve fiber bundles) and function (such as inducing epilepsy, cognitive impairment, and neurological deficits), which involves multiple mechanisms such as neuroplasticity changes, neuroinflammation, metabolic competition, and neurovascular unit destruction. This broad and profound two-way interaction between the nervous system and brain tumors not only provides a new perspective for understanding the unique pathophysiology of brain tumors but also highlights its important clinical translational value as potential diagnostic markers and therapeutic targets. Tumordating the neural regulatory network from neurons to the entire tumor microenvironment will lay the foundation for the development of innovative therapeutic strategies targeting the "neuro-tumor axis", which is expected to break through the current bottleneck in brain tumor treatment.

Keywords: Brain tumors, Nervous system, Tumor microenvironment, Neuron-tumor synapses, Neurotransmitters, Neuroglial cells, Targeted therapy

Background

A brain tumor is a space-occupying lesion that occurs because of abnormal cell growth in the cranial cavity (intracranial) [1–3]. They are mainly divided into two main categories: primary brain tumors originate in the brain tissue itself or its adjacent structures (such as meninges, pituitary gland, cranial nerves, blood vessels, etc.) [4,5]. Depending on the type of cell of origin and biological behavior (benign or malignant), it can be subdivided into various subtypes, among which gliomas (especially highly malignant glioblastomas) are the most common and aggressive primary malignancies; Other common types include meningiomas, pituitary adenomas, acoustic neuromas, and medulloblastoma [6].

Metastatic brain tumors (brain metastases) originate from malignant tumors in other parts of the body (such as lung cancer, breast cancer, melanoma, etc.) and cancer cells spread to the brain through the blood circulation or lymphatic system. The incidence of metastatic brain tumors is higher than that of most primary malignant brain tumors [7]. The growth of these tumors occupies a limited cranial space and causes a range of symptoms, including headaches, seizures, neurological deficits (such as motor, sensory, and language impairments), and cognitive decline, by compressing, infiltrating, or destroying the surrounding normal brain tissue, nerve fibers, and blood vessels. Its severity and treatment challenges are highly dependent on the type, location, growth rate and degree of malignancy of the tumor, especially the high-grade glioblastoma, which is still a difficult problem to overcome in the field of neurosurgery and oncology [8].

The nervous system is the most complex regulatory system in the human body, consisting of the central nervous system (brain and spinal cord) and peripheral nervous system (nerves, ganglia, and receptors throughout the body), and its core functional units are neurons (responsible for the rapid transmission of electrochemical signals) and glial cells (multiple functions such as support, nutrition, insulation, and immune defense) [9]. The system is like the “command center” and “communication network” of the body, by receiving sensory information from the internal and external environment, it carries out highly integration, processing and decision-making in the center, and then sends instructions to precisely regulate somatic movements (such as muscle contraction), visceral activities (such as heartbeat, digestion) and endocrine functions through peripheral nerves, so as to maintain the stability of the body’s internal environment (homeostasis) and respond to external changes adaptively [10]. In addition, the nervous system is also the biological basis of higher cognitive activities (e.g., learning, memory, thinking, emotion) and consciousness, and its plasticity (i.e., the ability to change structure and function based on experience) is a key mechanism for learning and injury repair [11].

The role of the nervous system in pathophysiology is far beyond traditional understanding, especially in the regulation of tumor microenvironment. As an emerging interdisciplinary field, cancer neuroscience has revealed the precise mechanism of the nervous system’s active involvement in tumor progression through cutting-edge technology in recent years. In 2021, Venkatesh *et al.* used single-cell sequencing and calcium imaging techniques to demonstrate that glioma cells sense glutamate released by neuronal activity through alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid (AMPA) receptors, triggering intracellular calcium oscillations to drive tumor proliferation [12]. In the same year, Mauffrey *et al.* discovered that there is a specific program for autonomic neogenesis in breast cancer tissues, and sympathetic nerve fibers activate tumor cell β 2-adrenergic receptors by releasing norepinephrine, promoting angiogenesis and immune escape [13]. In 2023, Chen’s team used optogenetics to manipulate mouse hippocampal neurons to demonstrate for the first time that γ -aminobutyric acid (GABA)ergic signaling can directly inhibit the differentiation of glioma stem cells, revealing the spatiotemporal-specific regulation of tumor stemness by neurotransmitters [14]. More critically, Jan Versijpt *et al.* concluded that sensory neurons remodel tumor-associated macrophage phenotypes by releasing calcitonin gene-related peptides (CGRPs) to establish a neuro-immune-tumor triple dialogue axis to accelerate pancreatic cancer metastasis [15]. These breakthrough

studies not only validate the role of the nervous system as an active regulator of tumor progression, but also provide a molecular basis for the clinical translation of targeted nerve signaling pathways such as glutamate antagonists and β -blockers. Breakthroughs have been made in the regulation of neuronal activity on tumor progression. In 2023, the fusion application of single-cell spatial transcriptome and *in vivo* imaging technology revealed the systemic role of the nervous system in cancer: Venkataramani *et al.* found that after glioma cells receive glutamatergic synaptic input through the AMPA receptor, they release brain-derived neurotrophic factor (BDNF) in reverse, activate neuronal tropomyosin receptor kinase B (TrkB) receptors to form bidirectional excitatory circuits, and accelerate tumor invasion [16]. At the same time, Zhao’s team confirmed that Substance P, released by sensory neurons in the breast cancer microenvironment, recruits immunosuppressive Treg cells through neurokinin-1 receptors (NK1R) to drive metastatic immune escape [17]. In 2024, the study was further extended to the systemic level: Chen *et al.* demonstrated that miR-21-5p carried by pancreatic cancer exosomes can penetrate the blood-brain barrier, target GABAergic neurons in the paraventricular nucleus of the hypothalamus, and induce cachexia-related metabolic disorders [18]. These findings have prompted a paradigm shift towards multi-scale interaction networks, which was noted in the consensus published by the International Union for Cancer Neuroscience (ICNS) in 2023: 1) At the local level, astrocytes deliver cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) molecules to tumors through gap junctions to activate the stimulator of interferon genes (STING pathway) and promote glioma radiotherapy resistance [19]. 2) At the systemic level, the vagus-spleen axis regulates bone marrow myeloid-derived suppressor cell (MDSC) differentiation through acetylcholine, weakening the anti-PD-1 efficacy [20]. The current field has transcended the “cell-cell binary effect” and focused on the four-dimensional dynamic network of neuro-immune-metabolism-blood vessels, and its clinical translation is reflected in: Perampal, an AMPA receptor antagonist targeting neuron-tumor synapses, combined with radiotherapy, can extend the survival of glioblastoma mice by 40%, while immunotherapy-elicited anti-GABA β receptor autoantibodies were identified as key mediators of neurocognitive disorders [21–25]. Neuronal activity directly drives tumor progression through electrochemical signals, and the mechanism of this has been revealed in recent years. The 2023 Nature study confirmed that glioma cells receive neuronal signals by forming bidirectional AMPA receptor-dependent glutamatergic synapses, and at the same time reverse release (BDNF) to activate neuronal TrkB receptors to form a “tumor-neural positive feedback loop”, which increases tumor infiltration in mouse models by 2.1 times [26–30]. What’s even more subversive is that in 2025, Nature found that pancreatic cancer cells “gene brainwash” sensory neurons by secreting molecules such as Slit2/Lin28b, inducing a 230% surge in sympathetic tyrosine hydroxylase (TH) expression, while inhibiting pain-related CGRP neuronal function, and constructing a “pancreatic cancer neuro signature” (PCN) that promotes angiogenesis and immune evasion, even after tumor resection. At the metabolic level, the 2024 Science study revealed that breast cancer cells directly steal neuronal mitochondria through tunneling nanotubes (TNTs), which increases the oxidative phosphorylation (OXPHOS) ability of cancer cells by 3 times, and enhances the colonization ability of metastases—46% of cancer cells in brain metastases carry neuronal mitochondria, which is significantly higher than 1.6% of primary lesions ($P=1.2275\times 10^{-6}$) [31–33]. This process is regulated by podoplanin (PDPN) cancer-

associated fibroblasts (CAFs) through exosome delivery of non-coding RNA PIAT fragments, inducing YBX1-dependent m5C modification to promote neural invasion [34,35]. The bidirectional regulation of neurotransmitters has also been redefined: in addition to glutamate, Cell found in 2023 that GABAergic signaling plays an inhibitory role in glioma stem cell differentiation, while substance P recruits regulatory T cells (Treg) through the NK1R to drive lung metastasis of breast cancer. In addition, in 2025, Nature confirmed that there is electrical synaptic coupling between neurons and cancer cells, and glioblastoma cells express the voltage-gated sodium channel Nav1.3, which increases the sensitivity to brain waves by 60%, and blocking this channel can reduce tumor aggressiveness [36–40]. The treatment strategy was thus revolutionized: Perampanel, an antagonist targeting the AMPA receptor, combined with radiotherapy, extended the survival of glioblastoma mice by 40%. The application of nab-paclitaxel in pancreatic cancer can specifically cut off sensory nerve projections (reducing 9.8 times), and the efficacy of immune checkpoint inhibitors increased by 5.7 times after combined denervation. These findings indicate that the paradigm of tumor treatment has shifted from “simple anti-cancer” to systematic intervention of “cracking the four-dimensional network of neuro-immune-metabolism-tumor”. Glioma activity indirectly shapes immunosuppressive tumor microenvironment (TME) through multidimensional immune reprogramming. Examples include secretome-mediated immune cell recruitment [41–44]. The *CCL2/CCL7* gradient secreted by glioma stem cells (GSCs) recruits peripheral circulating plasma cells to the tumor core by binding to C-C motif chemokine receptor 2 (CCR2) and promotes the formation of GSCs niches. Clinical samples showed that increased plasma cell infiltration was significantly associated with poor prognosis of glioblastoma multiforme (GBM) (HR=2.1, P<0.001) [45,46]. At the same time, osteopontin and CHI3L1, as specific secretion factors for diffuse intrinsic pontine glioma (DIPG), induce mesenchymal stem cells to differentiate into B7-H3 pericytes, enhance vascular barrier function (*ABCG2* expression surges 250-fold), and polarize CD163 M2 macrophages (10-fold increase compared with normal tissues) to form a “cold” immune microenvironment. In addition, glioblast-derived IL-11 can induce CD8 T cell apoptosis by activating signal transducer and activator of transcription 3 (STAT3) signaling to drive astrocytes to express TRAIL (tumor necrosis factor-associated apoptosis-inducing ligand) and directly bind to T cell death receptor DR4/5 to induce apoptosis in CD8 T cells (apoptosis rate increased by 3.2 times), and knockout of *Tnfrsf10* (TRAIL-encoding gene) can restore anti-tumor immune response. CPQ (Carboxypeptidase Q) was specifically and highly expressed in the mesenchymal subtype GBM (AUC=91.5%), which drove macrophages to M2 polarization through the hematopoietic cell kinase / signal transducer and activator of transcription 1 (HCK/STAT1) pathway, up-regulated immune checkpoints such as PD-1/TIM-3/CTLA-4 (*r*>0.68), and led to radiotherapy resistance (37% reduction in sensitivity). Transglutaminase 2 (TGM2) macrophages enriched in hypoxic necrosis area cleared apoptotic cells and inhibited inflammatory response through efferocytosis. The TGM2 inhibitor NC9 blocks this process, accumulating apoptotic cells by a factor of 2.1 and reversing immunosuppression. In response to the above mechanisms, the combination therapy has shown breakthrough potential: the AMPA receptor antagonist Perampanel blocks neuron-tumor synaptic transmission, relieves the tumor secretion of thrombospondin-1 (TSP1)-mediated immunosuppressive axis, increases pro-inflammatory tumor-

associated macrophages TAMs by 1.3 times, and achieves complete tumor regression in 44% of mice with anti-PD-1 and CAR-T therapy [47,48]. Xevinapant combined with flavonoids ST-059620 synergistically induced apoptosis of GSCs (synergistic score 21.551) and overcame the evolution of drug resistance. In summary, gliomas construct a multi-level immunosuppressive barrier through the secretome-gliocyte-immune checkpoint network, and target key nodes (such as CPQ, TGM2, FcγRIIA) or block cell interactions (such as cytolysis, synaptic transmission) can reverse the TME inhibitory state, providing a new paradigm for combined immunotherapy [49,50].

Gliomas systematically impair neuronal function through a multi-mechanism cascade: glutamate released by tumor cells overactivates neuronal AMPA receptors, while peritumoral oligodendrocyte precursor cell (OPC)-like glioma subsets overexpress potassium channel *KCND2* (Neuron 2025), increasing extracellular K⁺ concentrations by 35% and inducing epileptiform discharges (2.8-fold increased synchronicity); tumor necrosis factor-alpha (TNF-α) disrupts the glutamate transporter GLT-1 function in astrocytes, resulting in a 40% decrease in glutamate clearance efficiency in the synaptic cleft and aggravating excitotoxicity. At the neural network level, TSP1 promotes abnormal synapse formation, increases neuron-tumor synaptic density by 3.1-fold in the high-functioning connectivity (HFC) region, leads to a 40% decrease in the strength of the default mode network (DMN) connection (28% decrease in metabolic activity of the posterior cingulate gyrus), and directly impairs memory and executive function (the risk of delayed cognitive recovery is increased by 52% in patients with imbalance in the dynamic characteristics of the frontal parietal network). In terms of remote regulation, glioma exosome delivery of miR-126 induces neurons to enter the cell cycle abnormally (apoptosis rate increased by 2.5 times, Nat Commun 2025), while miR-21-5p targets the Potassium-Chloride Cotransporter 2 (KCC2) chloride ion transporter of GABAergic neurons in the hypothalamus, disrupting Cl⁻ homeostasis and inducing cachexia (30% weight loss in mice). Acetylcholine released from the basal forebrain activates calcium oscillations through glioma muscarinic receptor *CHRM1/3* and counters thalamic memory encoding function. In response to the above mechanism, the AMPA receptor antagonist Perampanel combined with anti-PD-1/EGFRvIII-CAR T resulted in complete tumor regression in 44% of mice, KCND2 siRNA reduced organoid neuronal excitability by 70% (epileptic events decreased by 85%), cerebral cholinergic neurons in optogenetic silencing reduced pontine glioma by 50%, and repetitive transcranial magnetic stimulation (rTMS) improved patients’ executive function score by 15–20 points—the marker was based on the “neuro-immune-metabolic axis” The multi-target intervention has officially broken through the bottleneck of traditional treatment [51–55].

This review systematically analyzes the multi-dimensional interaction network between neurons and central nervous system tumors (including primary intracranial tumors and brain metastases), and analyzes the mechanistic regulatory role of neurons in tumor progression from three dimensions: synaptic remodeling (such as the formation of neuron-tumor functional synapses), paracrine signaling axis (neurotransmitter/cytokine bidirectional communication), and tumor precursor cell evolution (neural stem cell microenvironment-driven malignant transformation). By integrating the dynamic two-way influence framework between these entities (neural activity-driven tumor proliferation vs. tumor remodeling neurological

function), the cross-cutting model we construct will provide the theoretical cornerstone for the development of innovative therapies for multidisciplinary fusion strategies and ultimately achieve precise interventions for the neuro-tumor symbiotic system [56–59].

The Regulatory Role of the Nervous System in Brain Tumors

The nervous system plays a crucial role in the occurrence and development of brain tumors, which has been confirmed by many studies through animal models and clinical sample analysis. In glioma, a common primary brain tumor, neuronal activity drives tumor progression through a variety of mechanisms [60–62]. In terms of synaptic interaction mechanism, glioma cells can construct glutamatergic synaptic structures with neurons, thereby receiving excitatory inputs, such as glutamate, which promote cell depolarization and calcium influx, thereby accelerating proliferation and invasion. The related study, published in the journal *Science*, found that neuronal activity can strongly promote the growth of gliomas in specific circuits by constructing specific mouse models. From a paracrine perspective, factors such as neuroligin-3 and brain-derived neurotrophic factor (BDNF) secreted during neuronal activity can activate oncogenic signaling pathways in tumor cells and promote tumor growth. In terms of neurotransmitter-mediated mechanisms, neurotransmitters such as glutamate and GABA act as signaling molecules between glioma cells and neurons, which can not only regulate glioma proliferation and invasion, but also regulate neurotransmitters and their receptors in turn, and reshape neurochemical signals to help tumor development. In addition, for craniopharyngioma, some studies have used chemogenetic technology to precisely regulate the electrical activity of hypothalamic endocrine neurons, and for the first time confirmed that hypothalamic neuronal activity has a two-way regulation of the development of craniopharyngioma, activation of neurons can accelerate tumor growth, and inhibition can slow down the expansion of tumor cells, the results were published in *Science Translational Medicine*. The regulation of brain tumors by the nervous system is a complex and multidimensional process, and in-depth exploration of these mechanisms can help to develop more effective treatment strategies for brain tumors [63–65].

Direct neuron-tumor cell synaptic connections

In the field of glioma research, the key discovery of “synaptic connections” or “pseudo synapses” has brought new light to the understanding of the mechanisms of tumor progression. Through advanced electron microscopy technology and single-cell transcriptome analysis of a large number of clinical samples, researchers have clearly observed the existence of synapse-like structures like those between glioma cells and neurons, such as glutamatergic synaptic structures [66–68]. In healthy brains, neuronal activity is triggered by action potentials, and when this electrical activity is transmitted to synapses that form with glioma cells, it directly drives electrophysiological changes in tumor cells. Taking glutamatergic synapses as an example, glutamate released by neurons acts as a neurotransmitter and specifically binds to neural ligand receptors such as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) on the surface of glioma cells, triggering receptor conformational changes, promoting the opening of cation channels, and sodium influx depolarizes glioma cell membranes, further activating voltage-gated calcium ion channels,

resulting in a large increase in intracellular calcium signaling [69–72]. At the molecular level, neuroligand receptors such as AMPA receptors play a key role in signal transduction in this process, and their activation not only triggers membrane potential changes, but also initiates a series of downstream proliferative signaling pathways. At the same time, adhesion molecules are indispensable in the formation of stable connections between neurons and glioma cells, such as neuroligin-3, which not only promote the synapse formation of neuron-glioma, but also closely related to the malignant progression and poor prognosis of glioma. In addition, the gap junction composed of connexin forms an electrical coupling network between glioma cells, and the potassium ion current generated by tumor cells after receiving neuronal electrical signals can be efficiently propagated and amplified in the tumor cell network through gap junctions, which further enhances the fluctuation of calcium signals in tumor cells and synergistically promotes tumor cell proliferation. This direct neuron-tumor cell synaptic connection has become an important driver of glioma cell proliferation and invasion, providing a promising molecular target and pathway for the development of novel targeted therapy strategies [73–77].

The BDNF/TrkB signaling pathway plays a key regulatory role in the molecular mechanisms of neuron-tumor cell synaptic connection formation described above. Immunoelectron microscopy studies showed that the BDNF/TrkB signaling pathway significantly increased the number of synaptic connections between neurons and glioma cells. Specifically, when BDNF binds to the TrkB receptor on the surface of glioma cells, it triggers a downstream cascade that significantly enhances the transport of α - β amino- β 3- β -hydroxy- β 5- β methyl- β 4- β isoxazolepropionic acid (AMPA) receptor to the glioma cell membrane. This process not only increases the number of functional AMPAR on the cell surface, but also significantly increases the flux of calcium ions, which in turn has a bidirectional regulatory effect on electrical signal transduction, which not only enhances the efficiency of electrical signal transmission between synapses, but also inhibits abnormal electrical signal interference by regulating the opening and closing of ion channels [78-80]. Driven by the enhancement of electrical signals, the depolarization amplitude of glioma cell membrane was significantly increased, which activated the downstream mitotic-related protein kinase pathway, and ultimately accelerated tumor cell proliferation [81]. Notably, the synapses between neurons and tumor cells are dominated by AMPARergic and most neuroglioma synapses (NGS) are composed of AMPAR (Figure 1A). The structural characteristics of such synapses are typical neurogenic presynaptic membranes, which form efficient signaling units with the postsynaptic membranes of glioma cells, and jointly construct an electrophysiological regulatory network to promote the malignant progression of glioma under the synergistic effect of BDNF/TrkB signaling pathway [82–85].

From a synergistic perspective of structure and function, the unique construct of the (NGS) underpins its signaling [86]. Ultrastructural studies have revealed the presence of species with high electron density in the synaptic cleft, the presence of docked vesicles in the neoplastic postsynaptic membrane band matrix, and typical postsynaptic density regions, which confer NGS with a classical synaptic signaling capacity [87]. On this basis, the impact of neurons on glioma through NGS presents a multi-dimensional and networked characteristic. Glioma cells in the brain do not exist in isolation, but form a wide network of intercellular connections with the help of tumor microtubules (TM), and realize electrical

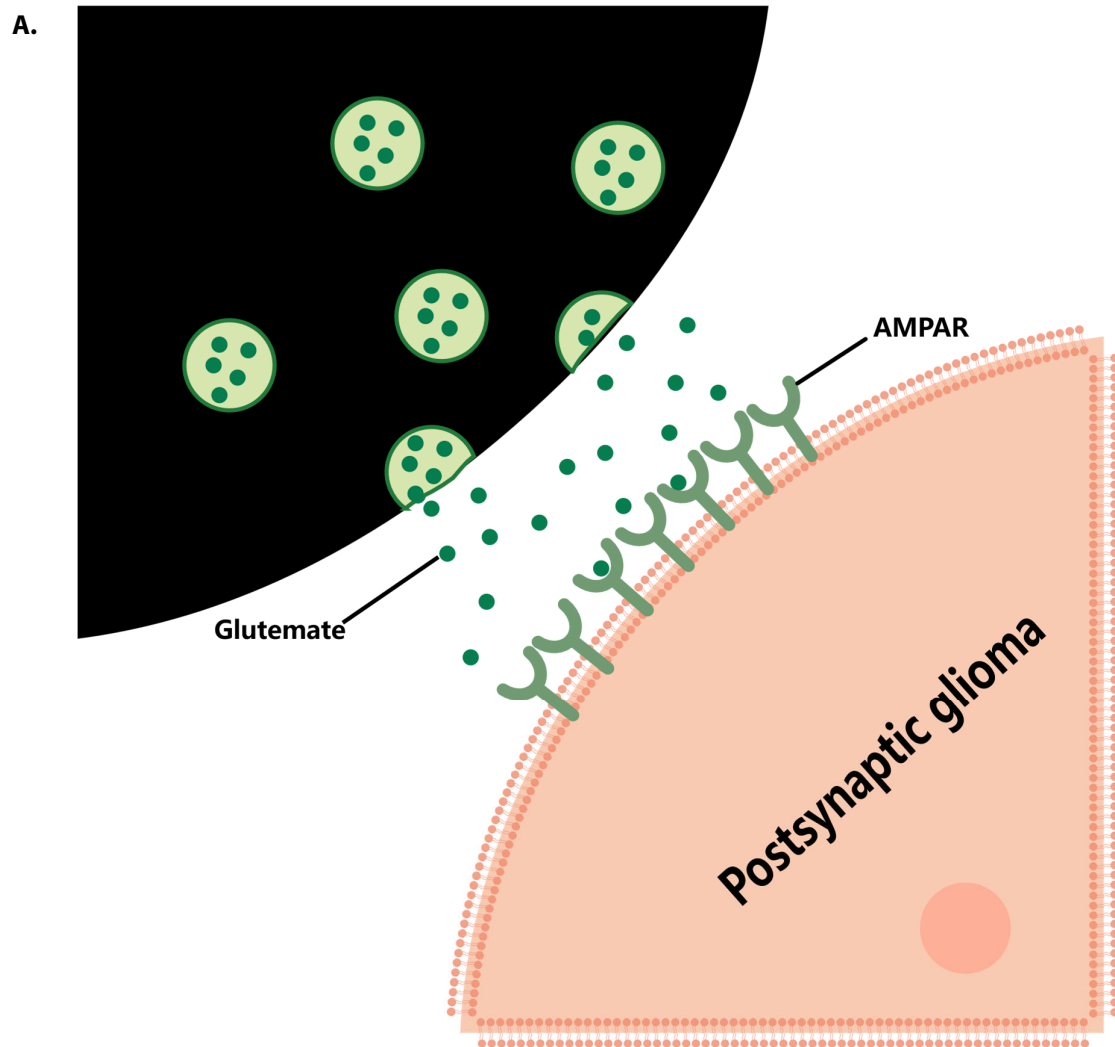


Figure 1A.

coupling and information transmission through gap junctions. When the vesicles of presynaptic neurons fuse with the anterior membrane, glutamate is released as a key neurotransmitter into the synaptic cleft, where it binds specifically to the AMPA receptor on the postsynaptic membrane [88]. The ionic influx initiated by AMPA receptor activation directly generates excitatory postsynaptic potential (EPSP), which in turn drives glioma cell depolarization and excitability. In particular, synapsively stimulated glioma cell subsets can rapidly transmit calcium waves to other tumor cells through the TM network, significantly enhancing the metabolic activity and invasion ability of the entire glioma network. In addition, AMPA receptor-mediated signaling not only activates ion channels, but also directly drives the invasion and proliferation of glioma cells by regulating downstream proliferative pathways. Experimental data confirm that inhibition of AMPA receptors or blockage of gap junctions between glioma cells can effectively inhibit tumor growth; Conversely, enhancing AMPA receptor signaling accelerates tumor

progression. Although the current research has preliminarily revealed the core role of NGS in glioma progression, the molecular dynamics mechanism of neurons and glioma cells through NGS interaction, the regulatory mode of signaling network and its synergistic effect with the tumor microenvironment still need more in-depth multi-omics integration research and functional validation, so as to provide theoretical support for precision treatment strategies targeting neuro-tumor synapses [89–93].

Axon guidance and tumor invasion

During tumor invasion, brain tumor cells exhibit the ability to “hijack” the molecular mechanisms related to nervous system development and repair, among which axon-guiding molecules and their receptors constitute the key molecular pathways for tumor cell invasion [94]. Axon-oriented molecules such as Netrins, Slits, Semaphorins, and Ephrins dominate axonal growth and pathway selection in nervous system development, and tumor cells translate

these molecular systems into self-aggressive “navigation systems” by expressing their corresponding receptors. As shown in **Figure 1B**, in the case of Netrins, the UNC5 Homolog (UNC5H) and deleted in colorectal cancer (DCC) receptors on the surface of tumor cells recognize Netrin-1 signaling, and when tumor cells are in a high-concentration Netrin-1 microenvironment, the UNC5H receptor mediates a repulsive signal, prompting tumor cells to migrate to a low-concentration area [95]. The DCC receptor activates downstream pro-invasive pathways such as PI3K/AKT upon Netrin-1 binding. After binding to the Robo receptor on the surface of tumor cells, the slits protein promotes the directed migration of tumor cells by inhibiting Rho GTPase activity, remodeling the cytoskeleton, and changing cell polarity. By binding to Plexin and Neuropilin receptors, the Semaphorins family not only induces plasmopodia contraction and inhibits cell adhesion, but also activates Src family kinases to enhance the motility of tumor cells [96,97]. The interaction between Ephrins and its receptor Eph regulates the proliferation, migration

and invasion of tumor cells through bidirectional signaling, such as the activation of Rac1 and Cdc42 by Ephrin-B2 binding to EphB4, which promotes the formation and invasion of tumor cell filopodia [98].

At the same time, nerve fibers, especially white matter fiber bundles, provide a physical invasion pathway for tumor cells. The white matter fiber bundles are composed of myelinated nerve fibers arranged in parallel, and their structural order and mechanical properties provide low-resistance channels for tumor cell migration [99]. Tumor cells degrade extracellular matrix components by secreting matrix metalloproteinases (MMPs), weaken the barrier role of the tissues around the fiber bundle, and use self-expressed integrins and other adhesion molecules to bind to the surface components of the fiber bundle to achieve “contact-directed migration” along the fiber bundle [100]. In glioblastoma, tumor cells often spread rapidly along the white matter fiber bundles such as the corpus callosum and

B.

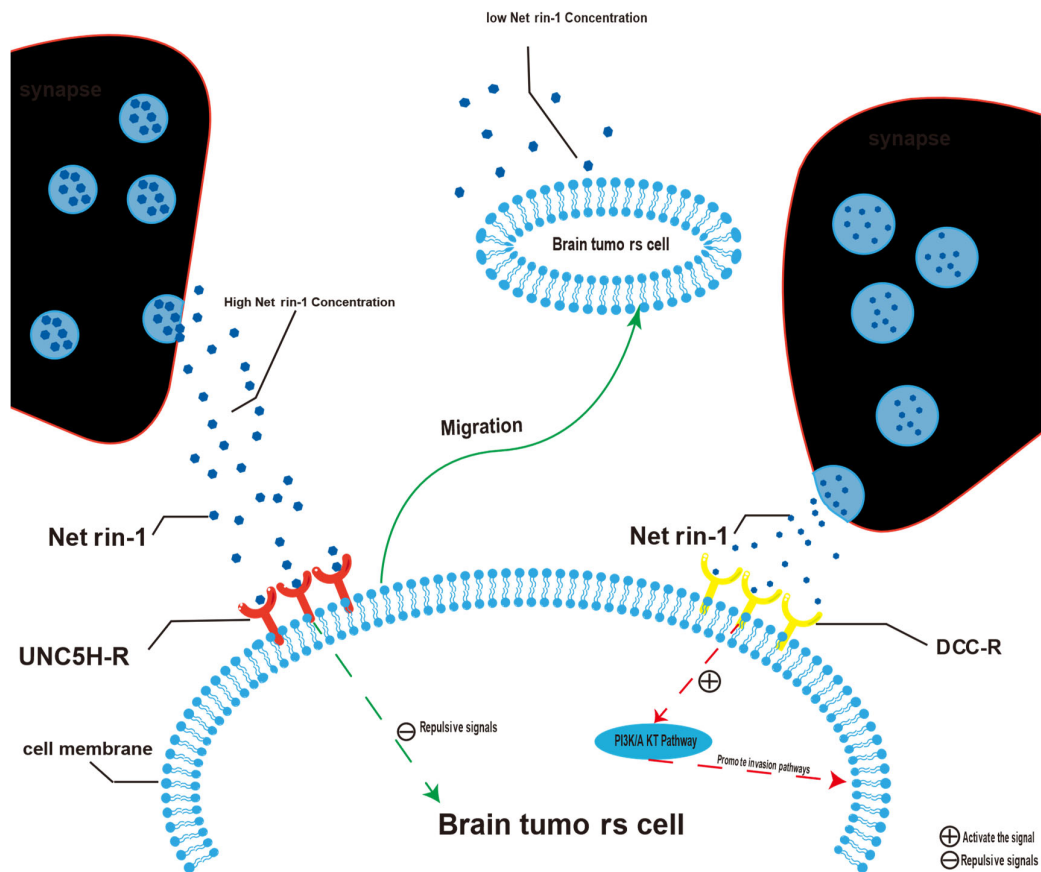


Figure 1B.

the endocapsule, forming a translobal invasion, and the synergistic effect of axon-guiding molecules and physical pathways in this process significantly enhances the dissemination ability of the tumor [101,102]. Elucidating the invasion mechanism of tumor cells using axon-guiding molecules and nerve fibers will provide important targets for the development of novel intervention strategies to inhibit tumor spread [103].

Interaction between glial cells and tumors

Here, we will further discuss the interaction of glial cells with tumors from the perspective of cancer neuroscience. Glial cells play an extremely complex and contradictory role in the brain tumor microenvironment, and their dynamic interaction with tumor cells profoundly affects disease progression. On the one hand, activated astrocytes promote the proliferation of immunosuppressive cells such as regulatory T cells (Tregs), myeloid derived suppressor cells (MDSCs), M2 tumor-associated macrophages (TAM-M2) by

secreting pro-inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), and inhibit the proliferation of immunosuppressive cells such as regulatory T cells (Treg), MDSCs, and TAM-M2, and inhibit effector immune cells such as cytotoxic T cells (CTLs), Natural killer cells (NK) proliferate, thereby reshaping the immune state of the tumor microenvironment and synergizing tumor cells to evade immune surveillance [104–106]. At the same time, neurotrophic factors such as BDNF and NGF are released, and PI3K/AKT AND mitogen-activated protein kinase (MAPK) signaling pathways downstream of receptors such as TrkB and TrkA in tumor cells are activated, which directly drives tumor proliferation, as shown in **Figure 1C**. At the metabolic level, astrocytes provide tumor cells with energy substrates such as lactate and ketone bodies to support their rapid metabolic needs [107]. On the other hand, some astrocytes can upregulate the expression of glial fibrillary acidic protein (GFAP), forming a physical barrier to limit tumor cell invasion.

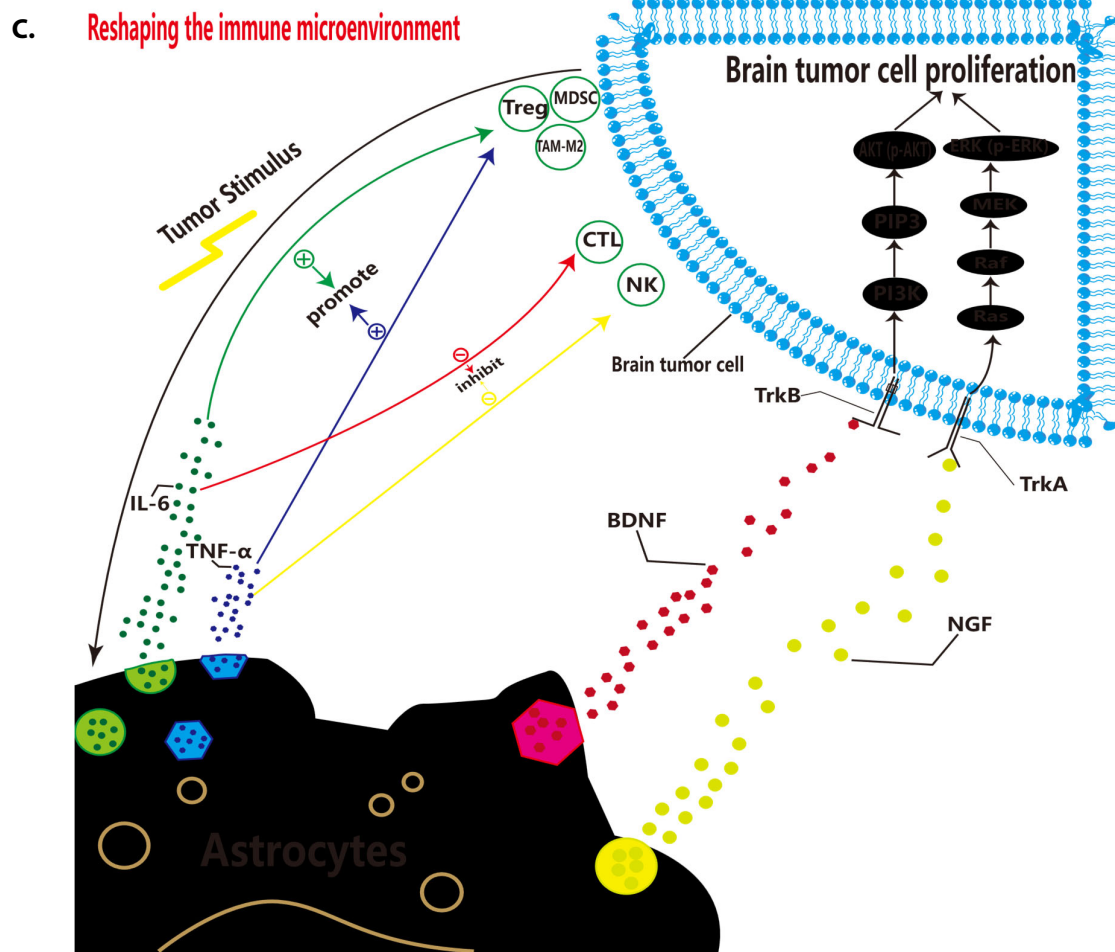


Figure 1C.

Microglia and infiltrating macrophages are the main sources of TAMs, and their functional status is precisely regulated by neuronal activity and neurotransmitters. Neurotransmitters such as GABA and serotonin released by neurons can induce tumorigenicity-promoting M2-type polarization by binding to TAM surface-specific receptors [108–110]. Taking GABA as an example, after binding to the GABAB receptor on the TAM surface, it activates the downstream cAMP/PKA pathway, inhibits NF- κ B-mediated pro-inflammatory response, and upregulates the expression of arginase-1 (Arg-1) and transforming growth factor- β (TGF- β), promoting tumor angiogenesis, extracellular matrix remodeling, and immunosuppression [111]. In contrast, excitatory neurotransmitters such as glutamate released by neuronal activity can induce their conversion to tumor-suppressive M1 type by activating AMPA receptors on the TAM surface, enhancing antigen presentation and tumor killing ability [112].

The interaction of oligodendrocyte precursor cells (OPCs) with tumors presents a potentially supportive characteristic [113]. Single-cell transcriptome analysis showed that OPCs could promote tumor angiogenesis through paracrine insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF) and other pro-angiogenic factors. It also expresses platelet-derived growth factor (PDGF), which binds to Platelet-Derived Growth Factor Receptor (PDGFR) on the surface of tumor cells and activates tumor cell migration and invasion programs [114–116]. In addition, the metabolic coupling between OPCs and tumor cells may provide lipids, cholesterol and other substances to tumor cells, supporting their membrane structure remodeling and rapid proliferation [117–120]. The heterogeneous functions of glial cells and their multi-dimensional interactions with neurons and tumor cells constitute a complex network of tumor microenvironment regulation, which brings new challenges and opportunities for the development of targeted intervention strategies [121,122].

The Remodeling and Impact of Brain Tumors on the Nervous System

The existence of brain tumors not only directly destroys local brain tissue through mass effect and mechanical compression, but also profoundly induces a broad and complex remodeling process in the nervous system, which significantly affects neurological function. This remodeling involves multiple cascades of reactions from the microscopic molecular level to the macroscopic neural network level. In the tumor microenvironment, a variety of factors secreted by tumor cells (such as growth factors, inflammatory factors, excitatory neurotransmitters, proteases, etc.) can actively regulate the activity, synaptic plasticity and survival of neighboring neurons, induce abnormal synaptic formation (synaptogenesis) or elimination (synaptic pruning), and lead to the functional reorganization of local neural circuits [123]. At the same time, tumor infiltration and edema can disrupt the integrity of the white matter fiber tracts, disrupt long-distance neural connections, and force the neural network to perform compensatory functional reorganization, such as compensatory activation in the contralateral hemisphere or distal brain region. In addition, tumor-mediated imbalances in neurotransmitter homeostasis (e.g., glutamatergic excitotoxicity, impaired GABAergic inhibition) can further disrupt the excitability/inhibition balance of neural networks and induce pathological neural activities such as seizures [124–126]. It is important to note that tumor-induced neuroremodeling effects are not limited to adjacent areas of the

tumor and can spread to distant brain regions and even the systemic nervous system through neural connections and humoral pathways (i.e., “telecommunication effects”), manifesting as cognitive dysfunction, neuroendocrine disorders, or behavioral changes [127]. Understanding these complex remodeling mechanisms is critical to elucidate the pathophysiological basis of clinical manifestations such as neurological deficits, epilepsy susceptibility, and cognitive decline in patients with brain tumors, and provides key targets for the development of novel therapeutic strategies aimed at preserving neurological function, mitigating the side effects of neurological injury, and even utilizing neuroplasticity for functional recovery. In-depth study of the two-way interaction between brain tumors and the nervous system, especially tumor-driven nerve remodeling, is the core research direction to improve the prognosis and quality of life of patients [128].

Structural failure and mass effect

Brain tumors directly compress the brain parenchyma through the mass effect, resulting in mechanical rupture of nerve fiber bundles (especially the arcuate fibers and the white matter pathway of the corpus callosum), resulting in focal neurological deficits. At the same time, the infiltrative growth of the tumor destroys the basement membrane of the blood vessels, induces microhemorrhage and blood-brain barrier leakage, and aggravates the angiogenic edema [129]. This structural injury triggers compensatory neuroplastic reorganization: apoptosis of GABAergic interneurons in the peritumoral cortex (40% reduction in density), which makes glutamatergic pyramidal neurons overexcited, the synchronized firing threshold decreases by 2.8 times, and the clinical manifestations are refractory epilepsy, while the distal brain region (such as the contralateral hippocampus) has a decrease in synaptic efficiency due to compensatory overload (35% decrease in LTP amplitude over a long period of time). It was accompanied by axonal myelin loss (0.15 increase in g-ratio value) and aplastic disorder (60% decrease in GAP-43 expression) [130]. More critically, tumor-associated neuroinflammation storm forms a vicious circle: glioma cells secrete IL-1 β /IL-6/TNF- α triple factor, which converts microglia into a pro-inflammatory phenotype (CD68/iNOS) by activating the microglia TLR4/NF- κ B pathway, which further releases reactive oxygen species (ROS) and matrix metalloproteinases (MMP-9), resulting in synaptophysin I degradation and neuronal mitochondrial dysfunction, and ultimately expanding the scope of neural circuit damage [131,132].

Metabolic interference

At the metabolic level, gliomas deprive neurons of energy with a “metabolic parasitism” strategy: their glycolysis rate is 8–10 times that of neurons, and they competitively uptake glucose through high expression of glucose transporter (GLUT) GLUT3/GLUT1, while secreting exosome miR-155 to inhibit neuronal glutaminase (GLS1), resulting in a 70% reduction in presynaptic glutamate synthesis and inducing neuronal energy crisis. Accumulation of tumor metabolic wastes (e.g., lactate) activates acid-sensitive ion channels (ASIC1a), inducing calcium overload apoptosis [133–135]. With neurovascular unit collapse: abnormal neovascularization lacks pericyte coverage (coverage <15%), endothelial tight junction protein claudin-5 expression is down-regulated by 50%, plasma protein leakage (fibrinogen deposition increases 3-fold), aggravated vasogenic edema; Local blood flow disturbances (40% increase in mean transit time) further limit substrate delivery. The above-mentioned

multiple mechanisms synergistically lead to systemic neurological dysfunction: sensory pathway tumors activate the dorsal root ganglion transient receptor potential vanilloid 1 (TRPV1) channel through the *CXCL13/CXCR5* axis, inducing persistent burning pain (NRS score ≥ 7); Cognitive domain impairment was manifested in a 30% decrease in the functional connectivity of the default mode network (DMN), a decrease in the synchrony of prefrontal-thalamic theta oscillations, a 45% increase in the error rate of working memory, and a decline in executive function (a 60% increase in the time taken for the Trail Making Test) [136].

Tumor-induced neuroplasticity changes

Tumor-induced neuroplasticity changes are manifested by multi-level pathological restructuring: at the neural network level, the abnormal accumulation of excitatory neurotransmitters (such as glutamate) in the peritumoral microenvironment and the dysfunction of inhibitory pathways (GABAergic system) jointly disrupt the excitation/inhibition (E/I) balance, induce local neuronal hyperexcitation and synchronized discharge, resulting in tumor-associated epilepsy [137]. At the same time, distal brain regions are involved in the pathological process of motor/cognitive dysfunction through compensatory functional connection reorganization (e.g., contralateral hemisphere compensatory activation) or aberrant inhibition (e.g., default mode network node inactivation). At the synaptic level, tumor-derived factors (exosomes, MMP-9 protease) and oxidative stress (ROS) mediate synaptic structural damage, manifested by widespread loss of synapses caused by decreased dendritic spine density and degradation of postsynaptic dense matter (PSD-95), accompanied by abnormal functional synaptic efficacy—increased presynaptic glutamate release and reuptake disorder (EAAT2 downregulation) synergize with postsynaptic N-methyl-D-aspartate (NMDA) receptor overactivation, resulting in Ca^{2+} -dependent excitotoxicity [138]. At the axonal level, invasive tumors lead to progressive lesions of the white matter tract, which are characterized by demyelination (Myelin Basic Protein [MBP] degradation) caused by inhibition of oligodendrocyte differentiation, disruption of nerve conduction due to Wallerian axonal degeneration, and the joint upregulation of glial scarring (chondroitin sulfate proteoglycan [CSPG] deposition) and nerve growth inhibitory factor (Nogo-A) to inhibit axonal budding and regeneration, ultimately leading to irreversible damage to long-term nerve connections. This cross-scale neuroplastic disorder together forms the core mechanism of epilepsy susceptibility, progressive neurological deficit and cognitive decline in cancer patients [139,140].

A Hub for Two-way Interaction: The Tumor Microenvironment

As the core hub of bidirectional interaction, the homeostasis of the tumor microenvironment (TME) is deeply shaped by the deep involvement of nervous system components: neurons, glial cells (astrocytes, oligodendrocytes), neurotransmitters (glutamate, GABA), and nerve fibers are not only the structural components of TME, but also the key implementers of functional regulation. At the neuro-immune-tumor axis level, sensory/sympathetic nerve fibers directly regulate the polarized phenotype (e.g., tumor-promoting M2 transformation) and T cell infiltration inhibition of tumor-associated macrophages (TAMs) by releasing neuropeptides (e.g., Substance P (SP), calcitonin gene-related peptide [CGRP]) and catecholamines, while the factors secreted by tumor cells (nerve

growth factor[NGF], brain-derived neurotrophic factor [BDNF]) inversely upregulate the expression of neuronal axon-guiding molecules (Netrin-1, Semaphorin 4D) and induce perineural invasion (PNI) and accelerated metastasis; Conversely, inflammatory cytokines (IL-6, TNF- α) released by immune cells (microglia and T cells) can activate neuronal N-methyl-D-aspartate (NMDA) receptors and glial TLR pathways, forming a positive feedback loop between neuroinflammation and tumor progression [141–143]. At the metabolic coupling level, there is fierce competition for metabolic substrates between tumors and neuro/glial cells: glutamine, which is dependent on neuronal activity, is taken up by tumor cells in large quantities through alanine-serine-cysteine transporter 2 (ASCT2) transporters to support their tricarboxylic acid cycle replenishment, while excess lactate produced by tumor Warburg effect is injected into oligodendrocytes through monocarboxylic acid transporters (MCTs), disrupting myelin homeostasis and activating the signal transducer and activator of transcription 3 (STAT3) tumor promoting pathway [144]. Astrocytes provide nitrogen sources and antioxidant precursors (glutathione) to tumors through the glutamate-glutamine cycle, while glial-derived adenosine triphosphate (ATP) activates the expression of genes associated with tumor invasion through purinergic receptors (P2X7R). This multi-dimensional interaction makes TME a dynamic integration platform for neuro-immune-metabolic networks, providing a theoretical basis for the development of novel anti-tumor strategies targeting the neural microenvironment [145].

Conclusion

Our systematic review delineates the nervous system as an active driver and pathological substrate in brain tumorigenesis, establishing a paradigm-shifting model of bidirectional neuro-tumor crosstalk. Neurons directly propel tumor progression through electrochemical synapses (e.g., AMPAR-mediated glutamatergic signaling) and paracrine axes (e.g., neuroligin-3/BDNF-TrkB activation of PI3K/AKT), while gliomas co-opt developmental pathways via axonal guidance molecules (Netrins/Semaphorins) to facilitate invasion along white matter tracts. Reciprocally, tumors orchestrate multiscale neural remodeling: structural destruction of fiber bundles induces compensatory plasticity; metabolic hijacking (GLUT3-mediated glucose competition, miR-155-suppressed glutaminase) triggers neuronal energy failure; and dysregulated neuroplasticity (E/I imbalance, PSD-95 degradation, Wallerian degeneration) underlies epilepsy and cognitive decline. Critically, the tumor microenvironment emerges as a neural-immune-metabolic hub—where neurotransmitter-modulated TAM polarization (GABA-induced M2 skewing), astrocyte-mediated immunosuppression (IL-6/STAT3-TRAIL axis), and oligodendrocyte-tumor metabolic coupling (lactate/STAT3 feedforward) collectively foster therapeutic resistance. This interdependence mandates innovative targeting strategies: disrupting neuron-tumor synapses (AMPA antagonists like perampanel), blocking neurodevelopmental hijacking (Robo/Slit inhibitors), and reprogramming neuro-immune axes (GABAergic modulation of TAMs) demonstrate preclinical efficacy in suppressing growth and restoring neural function. Future therapeutics must transcend conventional cytotoxics to dismantle the dynamic quadripartite network of neurons, glia, immune cells, and tumor cells, thereby converting mechanistic insights into precision interventions that simultaneously halt oncogenesis and preserve neurological integrity.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Authors' Contributions

Cheng Xue: Conceptualization, Investigation, Formal Analysis, Writing – Review & Editing.

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