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Neural Influences on Tumor Progression Within the Central Nervous System

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ABSTRACT

For decades, researchers have studied how brain tumors, the immune system, and drugs interact. With the advances in cancer neuroscience, which centers on defining and therapeutically targeting nervous system-cancer interactions, both within the local tumor microenvironment (TME) and on a systemic level, the subtle relationship between neurons and tumors in the central nervous system (CNS) has been deeply studied. Neurons, as the executors of brain functional activities, have been shown to significantly influence the emergence and development of brain tumors, including both primary and metastatic tumors. They engage with tumor cells via chemical or electrical synapses, directly regulating tumors or via intricate coupling networks, and also contribute to the TME through paracrine signaling, secreting proteins that exert regulatory effects. For instance, in a study involving a mouse model of glioblastoma, the authors observed a 42% increase in tumor volume when neuronal activity was stimulated, compared to controls ($p < 0.01$), indicating a direct correlation between neural activity and tumor growth. These thought-provoking results offer promising new strategies for brain tumor therapies, highlighting the potential of neuronal modulation to curb tumor progression. Future strategies may focus on developing drugs to inhibit or neutralize proteins and other bioactive substances secreted by neurons, break synaptic connections and interactions between infiltrating cells and tumor cells, as well as disrupt electrical coupling within glioma cell networks. By harnessing the insights gained from this research, we aspire to usher in a new era of brain tumor therapies that are both more potent and precise.

Abbreviations: ADAM10, A-disintegrin-and-metalloprotease 10; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BDNF, brain-derived neurotrophic factor; CaMK, calmodulin-dependent kinase; CCL2, CC chemokine ligand 2; CCL7, CC chemokine ligand 7; CNS, central nervous system; CPNs, callosum projection neurons; CTCs, circulating tumor cells; DTCs, disseminated tumor cells; EGFR, epidermal growth factor receptor; EPSPs, excitatory postsynaptic potentials; ER, estrogen receptor; ERK, extracellular regulated protein kinases; FGFR, fibroblast growth factor receptor; GBM, glioblastoma multiforme; GDNF, glial cell line-derived neurotrophic factor; GJs, gap junctions; HFC, high functional connectivity; HGF, hepatocyte growth factor; HGGs, high-grade gliomas; ICWs, intercellular calcium waves; IGF-1, insulin-like growth factor-1; LBC, luminal breast cancer; LTP, long-term potentiation; M/T, mitral and tufted; MAPK, mitogen-activated protein kinase; MEK-MAPK, extracellular signal-regulated kinase-mitogen-activated protein kinase; MICs, metastasis-initiating cells; MMPs, matrix metalloproteinases; NBTSC, neuron-to-brain tumor synaptic communication; NF, nuclear factor; NF-κB, nuclear factor kappa-B; NGS, neurogliomal synapses; NLGN3, neuroligin-3; NMDAR, N-methyl-d-aspartate receptor; NRXN, neurexin; NRXN1b, neurexin-1b; OPCs, oligodendrocyte precursor cells; PCs, prohormone convertases; pHGGs, pediatric high-grade gliomas; PI3K-mTOR, phosphoinositide 3-kinase/mammalian target of rapamycin; proBDNF, precursor of BDNF; PSD, postsynaptic density; PSPs, postsynaptic potentials; SCLCs, small-cell lung cancer cells; SDI, social population indices; sNLGN3, secretory NLGN3; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TMs, tumor microtubules; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor

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1 | Introduction

Brain tumors refer to a diverse group of tumors that can originate from different cells in the central nervous system (CNS) or from systemic cancers that metastasize to the CNS [1–5]. Primary brain tumors encompass a range of histological subtypes, with the most prevalent being gliomas, meningiomas, pituitary adenomas, and acoustic neuromas. Among systemic cancers, lung, melanoma, and breast cancers are particularly prone to CNS metastasis [4]. These tumors can manifest symptoms and signs by invading local brain tissue, compressing adjacent structures, and elevating intracranial pressure. Additionally, the clinical presentation of brain tumors is influenced not only by the tumor's histological type but also by the function of the brain area it affects [1–3, 5]. In the United States, the age-adjusted incidence of primary brain and nervous system tumors is about 25 cases per 100,000 individuals, with roughly 30% being malignant [6]. Globally, the incidence of brain cancers is on the rise, especially in countries with lower and moderate social population indices (SDI) [7], emphasizing the urgent need for effective treatment strategies.

The nervous system plays a pivotal role in regulating health. It is composed of a variety of neurons and glial cells with diverse functions and morphologies. While the nervous system facilitates reflexes and nerve conduction, enabling adaptive responses to environmental stimuli, it also orchestrates organ development, maintains homeostasis, and regulates tissue regeneration—all vital processes that underpin the functioning of organ systems, including the immune and endocrine systems [8–16]. Within the CNS, neurons and glial cells engage in intricate, yet complementary roles, with astrocytes nourishing neurons, oligodendrocytes enhancing signal transmission, and microglia acting as the immune sentinels, protecting neurons, and modulating neural plasticity [17–22]. The dynamic interplay between neurons and glial cells is crucial for preserving CNS stability, exerting biological impacts, and enabling a range of functions, including human neural reflexes.

Beyond its physiological roles, the CNS also plays a pivotal regulatory part in pathological states. The emergence of cancer neuroscience has provided a novel perspective for cancer and nervous system research [23, 24]. Cancer neuroscience, as a research field, can be traced back to the 19th century when Young et al. discovered an abundance of nerve fibers in tumors, which became the first evidence of neural involvement in tumor progression [25]. Scherer et al. further contributed by uncovering the “satellite phenomenon,” where glial cells were observed surrounding nerve cells within intracranial gliomas, providing preliminary evidence for the important role of nerves in the occurrence and development of malignant tumors [25]. In 2001, Ayala and colleagues presented in vitro evidence that interaction between nerves and prostate cancer cells can affect cancer growth [26]. These foundational studies laid the groundwork for the evolution of cancer neuroscience and paved the way for future research and clinical explorations. In 2015, a milestone was achieved when a team led by Professor Michelle Monje from Stanford University identified the driver gene Neurolign-3 (NLGN3), establishing a link between cortical neuron activity and the proliferation of high-grade gliomas (HGGs), thereby illustrating the influence of neuronal activity on brain tumor growth [27]. The following years saw a significant breakthrough in 2019, with concurrent publications in *Nature* by Professor Monje's team at Stanford University, Thomas Kuner's at Heidelberg University, and Douglas Hanahan's at the Swiss Federal Institute of Technology in Lausanne. These papers collectively revealed that brain tumor cells can form excitatory synapses with neurons, a mechanism that fosters tumor growth [28–30]. This discovery further elucidated the intricate relationship between excitatory synapses, glial cells, and their role in promoting tumor invasion and proliferation within the tumor microenvironment. Culminating in December 2019, a symposium at the Cold Spring Harbor Banbury Center convened 35 experts from diverse fields including cancer, neuroscience, immunology, and developmental biology. This gathering aimed to chart a course for the burgeoning field of cancer neuroscience. Their collaborative efforts culminated in a comprehensive review published in *Cell* on April 16, 2020, delineating the contours of this emerging discipline and heralding a new era in cancer neuroscience [23]. Nowadays, the focus is not solely on studying neurons or tumor cells in isolation. Instead, there is a growing consensus that the nervous system and tumor can interact at both local and systemic levels. Neurons and glial cells not only directly communicate with tumor cells but also remotely influence immune responses [23, 24, 31–33]. Synaptic communication between neurons and brain tumor cells can regulate tumor growth through neurotransmitters and voltage regulation mechanisms, paracrine substances between neurons and tumor cells facilitate signal transmission between them, substances secreted by neoplastic tissue can affect nervous system function, and tumor treatment also causes neurological toxicity, ranging from peripheral neuropathy to cognitive impairment [23, 24, 31–33].

The interaction between neurons and tumor cells plays an important role in the development of cancer, especially in the regulation of the tumor microenvironment (TME). The TME is a complex ecosystem comprising not only tumor cells but also non-malignant cells, extracellular matrix, blood vessels, lymphatic vessels, nerve fibers, and various intercellular communication molecules. As interdisciplinary research at the nexus of neuroscience and cancer biology advances, the intricate link between the nervous system and oncogenesis has become increasingly evident. These dynamic relationships can promote the growth, invasion, and evasion of immune surveillance of tumors through diverse mechanisms [3, 24, 25, 32–42]. Neuronal activity can directly affect tumor cells through electrical and chemical signals [28–30, 43–45]. For example, optogenetic stimulation has been shown to trigger tumor proliferation in specific neural circuits, underscoring the significant role of neural activity in the proliferation of HGGs and the occurrence of low-grade gliomas [27, 43]. Additionally, neuronal activity can affect the behavior of tumor cells by releasing proteins such as brain-derived neurotrophic factor (BDNF), NLGN3, and insulin-like growth factor-1 (IGF-1) in the microenvironment. These factors can promote the proliferation, survival, and invasion of tumor cells [44–46]. Synaptic formation between neurons and tumor cells facilitates communication, with glutamatergic synapses, particularly those mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, playing a pivotal role in the TME [29–31, 44].

Furthermore, glioma activity can indirectly shape the TME by modulating the recruitment and activation of immune cells. Secretion of cytokine and chemokine gradients released by GBM, like CC chemokine ligand 2 (CCL2) and CCL7, glial cell line-derived neurotrophic factor (GDNF), hepatocyte growth factor (HGF), and so on [47, 48], induces entry of immune cells to tumor microenvironment, thus influencing glioma-associated microglia/macrophages and fostering tumor maintenance and progression. Glial cells within the glioma microenvironment, including microglia and astrocytes, display notable heterogeneity and can regulate the tumor's immune contexture via multiple pathways, such as cytokines, signaling pathways, immune checkpoints, and chemokines. The glioma microenvironment often exerts a potent immunosuppressive effect, with tumor-associated macrophages (TAMs) and microglia critically involved in sculpting this suppressive milieu. These cells can suppress immune responses through various mechanisms, including inhibiting T cell activation and promoting the infiltration of regulatory T cells (Tregs) [34, 49–58].

On the contrary, tumor cells can reciprocally affect neurons. Glioma cells can release neurotransmitters, such as glutamate, which can disrupt neuronal activity, potentially precipitating conditions like epilepsy [59]. Moreover, gliomas can impair cognitive function and influence patient survival by disrupting the formation of brain functional network circuits [60–62]. GBM can promote its own growth through some molecules, but the transfer of this proliferation signal to neurons can lead to neurodegeneration. For example, miR-26 can drive the GBM cycle progression, and an increase in miR-26 levels can cause abnormal entry of neurons into the cell cycle after mitosis, leading to neuronal cell death. The intercellular transfer of such molecules from glioblastoma to neurons may affect neuronal health, post mitotic status, and overall cell vitality [34, 63–66]. This bidirectional communication between the nervous system and tumor cells underscores the complexity of interactions within the TME and highlights the need for targeted therapeutic strategies that address these multifaceted relationships.

In this review, we delved into the complex dynamics between neurons and CNS tumors—encompassing both primary intracranial growths and those that have metastasized to the brain. We elucidated the role of neurons in the progression of CNS tumors from the perspectives of synaptic structure, paracrine signaling, and the evolution of tumor precursor cells. We also provided a comprehensive overview of the reciprocal effects these entities exert on one another, which can contribute to help developing innovative and effective treatment methods with interdisciplinary collaboration.

2 | Synaptic Connections Between Neurons and Brain Tumor Cells

Synapse refers to the structure in which impulses from one neuron are transmitted to another neuron or another cell through mutual contact [67–69]. In the human brain, synapses are divided into two major categories based on their structure and signal transmission methods: electrical and chemical synapses. Traditionally, people pay more attention to the role of synapses in functional interaction and information transmission among neurons [67–70].

In recent years, mounting studies have uncovered the significant influence synapses exert on the progression and behavior of tumors. Neurons have been observed to form direct synaptic connections with tumor cells and may directly influence them [44, 45]. Of particular interest is the discovery of tripartite synapses, which consist of presynaptic and postsynaptic neurons along with encroaching tumor cells [30, 44, 71]. These tripartite configurations enable neurons to modulate tumor cells through both electrical signaling and the release of neurotransmitters [30, 44].

2.1 | Chemical Synapses

Chemical synapses rely on the release of specific chemicals from the terminals of presynaptic neurons as a medium for transmitting information to affect postsynaptic neurons [72–74]. In the context of CNS tumor, neuron-to-tumor chemical synapses consist of a presynaptic neuron and a postsynaptic tumor cell [28]. As a key structure for neural signal transmission, it is reasonable to hypothesize that tumor cells may “hijack” or “deceive” neurons into forming synaptic or pseudo-synaptic structures and potentially harnessing this ability to trigger neural plasticity to enable gliomas to receive additional neuronal signals and rapidly proliferate [44]. However, not all tumor cells are capable of forming synapses with neurons. For example, in neuroglioma synapses (NGS), these connections occur exclusively between higher-grade gliomas and neurons [28].

This selectivity may stem from the heterogeneity of brain tumors, with tumor cells originating from various brain cell types, including glial cells, precursor cells of glial cells, and metastatic tumors. Incompatibility in molecular and structural profiles between tumor and neuronal cells could preclude synapse formation. Moreover, the gene or protein expression profiles vary among different tumors, and even within the same type, which may affect the interaction between tumor cells and neurons; It was found that a large number of genes involved in neural circuit assembly or remodeling were upregulated in the high functional connectivity (HFC) tumor region [61]. A case in point is thrombospondin-1 (TSP-1), which plays a role in synaptic formation and is predominantly secreted by astrocytes, with its expression elevated seven-fold in HFC areas [61, 75, 76]. Compared with the low functional connectivity (LFC) region, the synaptic markers (Synapsin and PSD-95) in HFC are increased, indicating enhanced synaptic stability and formation in HFC of glioblastoma multiforme (GBM) [61].

In addition, immunoelectron microscopy studies have revealed that the BDNF/TrkB signaling pathway can increase the number of synaptic connections between neurons and glioma cells [44]. Mechanistically, BDNF, upon binding to TrkB, escalates the transport of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPAR) to the glioma cell membrane, increases calcium ion flux, intensifies and prolongs electrical signaling, and subsequently boosts the depolarization amplitude of glioma cell membranes, ultimately promoting glioma cell mitosis [44, 77, 78]. Notably, the synapses between neurons and tumor cells are predominantly glutamatergic [28, 79], with most NGS composed of AMPAR (Figure 1A) [28, 80, 81]. Typically, NGS contain a neurogenic presynaptic membrane, a

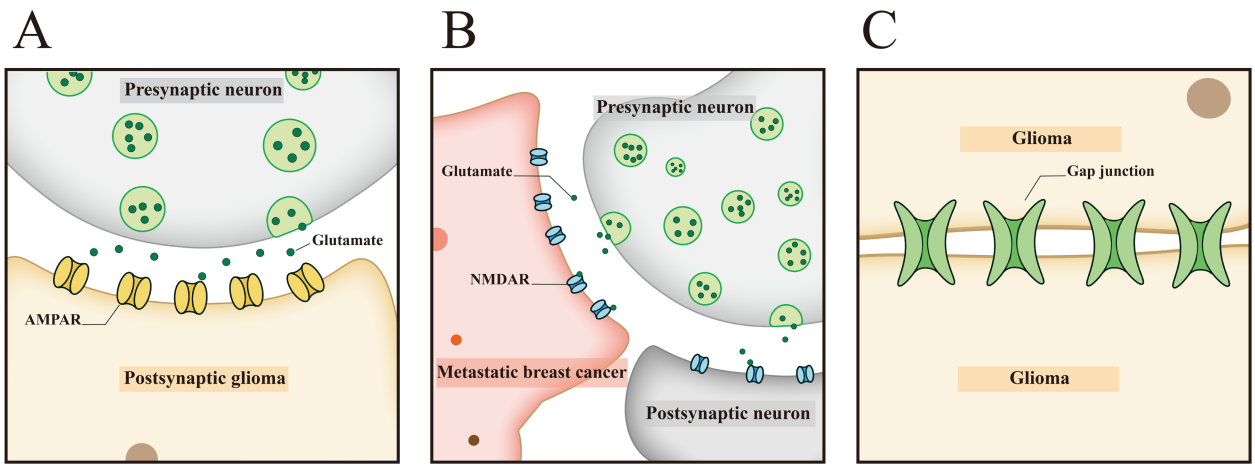

FIGURE 1 | Synaptic connections between neurons and brain tumor cells and their implications in tumor progression. (A) The involvement of AMPA receptors in glioma biology is depicted. Neuronal activity initiates the opening of calcium-permeable AMPA receptors, which are essential for mediating the electrophysiological functions of neurons. The activation of these receptors allows for the transmission of signals to synapses with glioma cells, leading to the depolarization of the glioma cell membranes. This depolarization is a critical event that promotes the proliferation of tumor cells. The diagram illustrates the process where the presynaptic neuron releases glutamate, which then binds to the AMPA receptors on the postsynaptic glioma cell, initiating a series of intracellular signaling events that result in tumor growth. (B) The formation of aberrant synaptic connections between neurons and breast cancer cells in the brain is shown. These "triple synapses" involve presynaptic neurons, postsynaptic tumor cells, and the release of neurotransmitters like glutamate. The interaction between glutamate and NMDA receptors on the cancer cells' membrane triggers a cascade of events that intensify the metastasis and proliferation of breast cancer cells within the brain. The diagram highlights the unique synaptic structure where the breast cancer cells release glutamate, which in turn activates NMDA receptors, fostering continuous synaptic transmission and contributing to tumor progression. (C) The role of gap junctions in the intercellular communication between glioma cells is detailed. Glioma cells establish extensive networks primarily through the formation of gap junctions, which are conduits for the exchange of signaling molecules, including calcium ions, between adjacent glioma cells. This exchange is instrumental in influencing the migration and proliferation of tumor cells, indicating the significance of gap junctions in the collective behavior of glioma cell populations. The diagram illustrates how these gap junctions extend into the surrounding tissues, enhancing the invasiveness and proliferation of brain tumors and facilitating the communication that drives tumor growth. These synaptic connections and networks represent potential therapeutic targets for disrupting the supportive role of neurons in brain tumor progression, offering new avenues for the development of treatments aimed at modulating these interactions to inhibit tumor growth and spread.

synaptic cleft with electron-dense material, a neoplastic postsynaptic membrane zone matrix with docked vesicles, and a postsynaptic density area [28, 82]. The influence of neurons on glioma is multifaceted through NGS [28, 29, 82]. Firstly, NGS can activate glioma networks. Glioma cells within the brain are not isolated entities [83]. They form extensive channels, known as tumor microtubules (TMs), through their cell membranes. These TMs link multiple tumor cells, enabling them to couple and communicate via gap junctions [28, 84, 85]. After the vesicles from presynaptic neurons fuse with the anterior membrane, glutamate is released, crosses the synaptic cleft, and binds to the AMPA receptor on the postsynaptic membrane [80, 81]. After the AMPA receptor is excited, a large amount of ions will flow inward to produce excitatory postsynaptic potentials (EPSPs) [29]. The glioma cell subpopulation stimulated by synapses can transmit calcium waves to the remaining TM connected glioma network, enhancing some inimical attributes of gliomas [28, 29, 83]. Secondly, neural activity can drive glioma invasion and proliferation through NGS [28]. After the activation of AMPA receptor, it will cause transmembrane ion flow, depolarization, and excitation of glioma [28]. Inhibiting AMPA receptors or gap junctions in gliomas could impede their growth, whereas enhancing AMPA receptor signaling could expedite progression [28, 29]. Further exploration is required to uncover the precise mechanisms driving glioma advancement.

The N-methyl-d-aspartate receptor (NMDAR) represents a distinct subtype of glutamatergic synapses, as depicted in Figure 1B [86, 87]. This neuron-to-tumor subtype is identified on the postsynaptic membrane of synapses formed by brain metastatic breast cancer cells and neurons [30]. In a divergence from typical synaptic structures, these breast cancer cells engage in the formation of "pseudo tripartite synapses" with neurons, which are known to release glutamate as a neurotransmitter. Such synapses are pivotal to the metastatic process in the brain and are correlated with a poor prognosis. They are similar to the tripartite synapses formed between two neurons and surrounding non-neuronal supporting cells such as astrocytes [71]. Once these synapses are established, neurons incessantly supply glutamate to the breast cancer cells, facilitating a continuous synaptic transmission [30, 88]. The interaction between glutamate and NMDARs on the cancer cells' membrane triggers depolarization, thereby intensifying the metastasis and proliferation of breast cancer cells within the brain [30, 71, 88]. Studies also have found that breast cancer cells activate NMDARs by the autocrine secretion of glutamate and then promote cell proliferation and migration [30]. Utilizing an immunodeficient mouse model, research has demonstrated that the deletion of these NMDARs markedly reduced the colonization and growth of injected human B2BM breast cancer cells in the brain [30]. The expression of NMDAR seems to be directly related to brain

metastasis of breast cancer, although the precise mechanism for this is yet to be elucidated.

The process of brain metastasis in breast cancer is conceptualized as a two-step phenomenon. Initially, cancer cells must successfully colonize the organ, a process that is considered the primary rate-limiting step in metastatic spread [89–92]. Subsequently, the establishment of tripartite synapses occurs, which is crucial for the progression of metastasis. Research indicates that the NMDAR, along with its downstream signaling effectors MEK-MAPK and CaMK, when activated by self-secreted glutamate, can enhance the invasive capabilities of breast cancer cells [93, 94].

Within the central nervous system, glutamate serves as the predominant excitatory neurotransmitter, being particularly concentrated in the brain. This abundance may account for the propensity of breast cancer cells to metastasize to the brain. NMDARs in neuronal cells are instrumental in synapse formation and function, initiating various signaling pathways like CaMKII and PKC through Ca^{2+} influx [95–100]. Moreover, NMDARs interact with a variety of proteins at the postsynaptic density (PSD), including PSD-95, SynGAP, and Shank. These interactions are essential for receptor stabilization on the postsynaptic membrane and for modulating synaptic maturation and plasticity by creating a complex protein network [101–110].

It is hypothesized that NMDARs in breast cancer cells may exploit glutamate released by neurons to facilitate the formation of their own synaptic structures. Within the tripartite synaptic framework, these cancer cells could secure a steady supply of glutamate, analogous to parasitic relationships. Furthermore, evidence suggests that breast cancer cells which have metastasized to the brain are subject to influences from the brain's microenvironment. This can induce a reprogramming of the cells, mirroring the neurogenesis that occurs during developmental stages [111, 112]. This insight underscores the complexity of the metastatic process and points to potential targets for therapeutic intervention.

It is noteworthy that while normal breast cells typically do not express NMDARs, in instances of breast cancer, particularly when it metastasizes to the brain, the cancer cells may begin to express these receptors. The acquisition of NMDARs by breast cancer cells could involve a range of biological processes, including genetic mutations, genomic amplifications, epigenetic modifications, and body weight sorting. It is particularly intriguing that NMDARs, predominantly expressed in neurons, are also expressed by tumors that have metastasized to the brain from other parts of the body [30, 113]. For example, small-cell lung cancer cells (SCLCs) with brain metastases secrete Reelin, a brain development factor specifically produced by Cajal–Retzius cells in the marginal zones of the cerebral cortex and hippocampus [114, 115]. This secretion attracts astrocytes to the brain metastases [113], which in turn promote the growth of SCLCs by releasing neuronal survival factors, such as SERPINE1 [113].

Recent research has found that the axons of corpus callosum projection neurons (CPNs), namely glutamatergic excitatory neurons, can traverse the cortical hemisphere along the corpus callosum, thereby driving the progression of contralateral GBM [116].

2.2 | Gap Junction

Here, we will further discuss the communicated connections formed among tumor cells (Figure 1C) from the perspective of cancer neuroscience and discuss electrical signals mediated by ion flow. Gap junctions (GJs), well-established conduits for direct intercellular communication, are prevalent in the CNS and convey both chemical and electrical messages among neurons [117]. Beyond their recognized roles in processes like metabolic regulation, ion buffering, and energy transfer, GJs also play a part in orchestrating calcium waves, ATP receptor signaling, neural development, and sustaining the nervous system's distinctive functions [84, 117–122]. The primary modality of communication and connection identified between brain tumor cells to date is through GJs, yet the potential molecular signals and additional connecting structures are subjects of ongoing investigation [28–30, 83, 84, 118]. GJs seem to be highly utilized by gliomas as an important component of the glioma network. Studies have revealed that the synapses that bridge neurons and tumors, formed within the TME, possess electrophysiological functions [28–30, 84]. As previously discussed, glioma cells possess exceptionally elongated tubular extensions on their cell membranes, termed “tumor microtubes.” These structures enable the formation of interconnected, multicellular functional networks of glioma cells via GJs [123].

Multiple models of orthotopic xenotransplantation from different patient sources have been used in research [29]. A case in point is the stereotactic injection of GFP-tagged glioma cells into the CA1 region of the mouse hippocampal circuit. Following adequate transplantation and growth, whole-cell patch clamp recordings were conducted on GFP-positive glioma cells within acute hippocampal slices. The results demonstrated that the excitatory postsynaptic currents (EPSCs) of glioma cells depend on neuronal action potentials, with synaptic transmission being carried out via AMPA receptors [29]. Thus, this electrophysiological data corroborate the presence of genuine synapses between neurons and gliomas, capable of inducing electrical excitation in glioma cells through these synaptic connections [29].

Neuron activity enhances glioma excitation by modulating the secretion of paracrine growth factors and facilitating electrochemical communication through synapses between neurons and glioma cells [27, 43, 45, 46]. Concurrently, the influx of calcium ions triggers cell communication within the glioma, propagating activation signals via intercellular calcium waves (ICWs) to other glioma cells through TMs [28, 29, 80]. Currently, a large amount of evidence suggests that neurons and glioma cells, including GBM occurred in both adults and children [29, 44, 84, 124], are directly connected via GJ on the surface of TMs. Here, the AMPA subtype of glutamate receptors relays postsynaptic electrical signals, prompting tumor cells to infiltrate and proliferate autonomously [28–30]. Recent studies have identified that Ca^{2+} specifically activates the MAPK and NF-κB signaling pathways within cellular networks, ultimately driving brain tumor growth [123]. Additionally, neuronal activity also evokes non-synaptic activity-dependent potassium currents that

are amplified through gap junction-mediated tumor interconnections by forming an electrically-coupled network [29, 83, 84]. The elevation of extracellular potassium concentration, a consequence of neuronal action potentials, augments neuronal excitability within the glioma microenvironment. This increase enhances the duration of potassium currents in non-synaptic glioma and intensifies the excitability of synaptic neuron-to-glioma EPSCs [29].

As has been said before, the interconnected network of tumor cells, called "glioma network" and underpinned by this structural framework and the electrical signals conveyed through gap junctions, appears to be pivotal to glioma growth [28, 29, 84, 85, 123, 125–127].

3 | Paracrine Signals From Neurons in the Occurrence and Growth of Brain Tumors

As our understanding of the brain deepens, the pivotal role of the TME in CNS tumors has come into sharper focus [50, 56]. The TME encompasses the internal and external conditions surrounding tumor cells that are intricately linked to tumor occurrence, growth, and metastasis [128]. Within this context, neurons are a crucial component of the TME for malignant brain tumors, exerting biological influences by releasing various factors into the TME [128]. Notably, both brain-derived neurotrophic factor (BDNF) and synaptic protein NLGN3 are instrumental in the proliferation of glioma through paracrine secretion in the TME. Furthermore, insulin-like growth factor-1 (IGF-1) has been identified as a key paracrine regulator of neuronal activity, propelling the growth of olfactory gliomas [27, 43, 45, 46].

3.1 | NLGN3

NLGN3, a vital nerve ligand and cell adhesion protein located on the postsynaptic membrane, is integral to the formation and upkeep of synapses between neurons, thereby sustaining proper neural functions [27, 129]. Historically, NLGN3 has garnered significant attention due to its pivotal role in autism spectrum disorders [130, 131]. A vital mechanism that orchestrates the neural regulation of brain cancer is the activity-dependent cleavage and secretion of NLGN3, which promotes glioma proliferation through multiple signaling pathways (Figure 2A) [27, 45, 132]. NLGN3 connects to presynaptic neurons via Neurexin (NRXN) located on the presynaptic membrane [129, 133]. A-disintegrin-and-metalloprotease 10 (ADAM10), a member of the metzincin metalloproteases crucial for intercellular communication by modulating membrane protein functions, cleaves NLGN3, enabling it to manifest biological effects [134, 135]. This cleavage transforms NLGN3 into its secretory form (sNLGN3), which subsequently acts on glioma cells within the TME to promote tumor progression [27, 45, 136].

The most classical downstream pathway of NLGN3 is the phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K-mTOR) pathway [27, 45, 136]. Emerging studies have

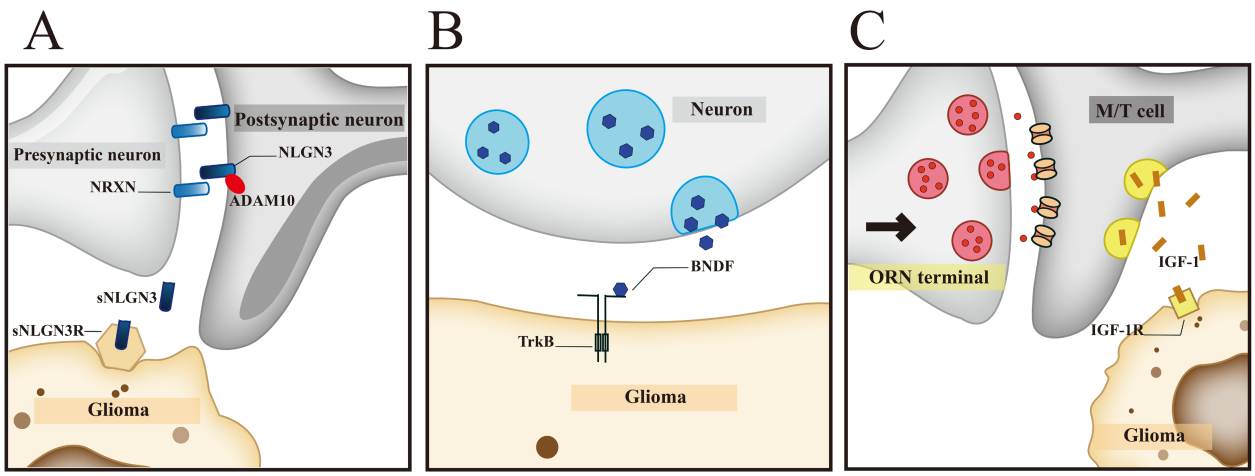

FIGURE 2 | Paracrine signals from neurons in the occurrence and growth of brain tumors. (A) The role of the synaptic protein neuroligin-3 (NLGN3) in the tumor microenvironment (TME) is illustrated. The secretory form of NLGN3, generated by the action of the protease ADAM10, is depicted as a key factor that stimulates the proliferation of glioma cells. This process underscores the contribution of synaptic proteins to the complex interactions within the TME that can promote glioma growth. The diagram shows how NLGN3, once cleaved and released, can bind to its receptors on glioma cells, initiating downstream signaling pathways that enhance cell survival and proliferation. (B) The BDNF/TrkB signaling pathway and its implications for synaptic plasticity and tumor malignancy are detailed. When dysregulated, this pathway can augment the complexity and strength of the tumor's synaptic network, thus fostering further tumor progression. The diagram illustrates the mechanism by which BDNF, secreted by neurons, interacts with the TrkB receptor on tumor cells, initiating a cascade of intracellular signaling events that can lead to increased tumor cell survival, growth, and potentially the formation of stronger synaptic connections with neurons. (C) The influence of olfactory neurons on the proliferation of oligodendrocyte precursor cells (OPCs) through the release of insulin-like growth factor 1 (IGF1) is shown. Specifically, the mitral and tufted (M/T) cells in the olfactory bulb are highlighted as the primary source of IGF1, which can accelerate the proliferation of OPCs that have undergone pro-oncogenic mutations. The diagram depicts the process where sensory input, such as the presence of certain gases, stimulates olfactory neurons, leading to the release of IGF1 and the subsequent promotion of gliomagenesis in the olfactory bulb. These paracrine signals represent critical mechanisms by which neurons can modulate the behavior of tumor cells in the brain. Understanding these pathways is essential for developing targeted therapies that may disrupt the supportive role of the neuronal environment in brain tumor growth and spread.

illuminated that NLGN3 acts on glioma cells accompanied by activation of the extracellular regulated protein kinases (ERK) pathway and nuclear factor kappa-B (NF-κB) pathway [45, 136]. In previous studies, activation of the PI3K-mTOR pathway can inhibit apoptosis induced by various stimuli, promote cell cycle progression, and thus enhance cell proliferation and survival [137, 138]. It also contributes to the formation of tumor vasculature and plays a cardinal role in tumor metastasis and development [27, 139, 140]. Within the ERK pathway, through the three-stage kinase cascade reaction of mitogen-activated protein kinase (MAPK) signal transduction, phosphorylated ERK1/2 is translocated from the cytoplasm to the nucleus. There, it mediates the transcriptional activation of *Elk-1*, *ATF*, *Ap-1*, *c-fos*, and *c-Jun*, and results in cell proliferation and differentiation [45, 136, 141, 142].

Recent experimental evidence indicates that the dual knockout of Gαi1/3 significantly represses the expression of NLGN3, subsequently inhibiting mTORC1 and Erk activation, which are downstream of NLGN3. This inhibition effectively curbs the proliferation and migration of glioma cells [136]. Additionally, NLGN3 is crucial for the establishment of NGS through the PI3K-mTOR signaling pathway [27, 45]. When neurons are activated, they secrete considerable levels of NLGN3 into the TME, where it interacts with presynaptic membrane proteins, facilitating synaptic maturation and preserving neuronal function. Furthermore, NLGN3 has been shown to phosphorylate key receptors on tumor cells, including VEGF, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and integrins, thus exerting their biological effects [27, 45, 143].

Interestingly, the NF-κB signaling pathway is activated in both NLGN3-mediated effects and within the glioma network [45, 123]. The activation of this pathway has been extensively validated in glioma research, highlighting its pivotal role in tumorigenesis. The growth of tumor cells and tissue invasion require continuous neovascularization, of which proteins are affected by NF-κB adjustment [144]. Among them, vascular endothelial growth factor (VEGF), the most important member of the angiogenic factor family, and nuclear factor (NF), which is continuously activated by NF-κB, can enhance the transcription of *VEGF* [145]. Furthermore, NF-κB can significantly inhibit the transcription of apoptosis-related genes, such as *c-IAP1/c-IAP2* [146], tumor necrosis factor receptor binding factor *TRAF1/TRAF2* [147], and zinc finger protein *A20* [144, 148, 149]. The two characteristic stages of malignancy development are tissue invasion and metastasis, which can also be caused by the regulation of NF-κB-dependent genes, including matrix metalloproteinases (MMPs), urokinase plasminogen activator, interleukin-8, and so on [144, 148, 149]. Currently, research is scarce, and concrete evidence is lacking regarding the specific effects of the interaction between NLGN3 and glioma by the NF -κB pathway, further research is warranted to elucidate these mechanisms.

Previous research has firmly established that higher levels of *NLGN3* mRNA and protein, derived from tumors, are inversely linked to the survival rates of adult glioblastoma patients [150]. The latest findings further suggest a correlation between neuronal secretion of NLGN3 and the severity of gliomas. Specifically, in high-grade gliomas such as adult glioblastoma, anaplastic oligodendroglioma, pediatric glioblastoma, and diffuse intrinsic pontine glioblastoma (DIPG), increased NLGN3 expression is associated with increased tumor aggressiveness and poorer patient survival [45, 151, 152]. Therefore, understanding the expression patterns of NLGN3 is crucial for improving clinical diagnosis, treatment strategies, and prognostic evaluations.

3.2 | BDNF

Brain-derived neurotrophic factor (BDNF) is a crucial protein that facilitates brain plasticity, enabling the strengthening of synaptic connections and the reinforcement of neural circuits formed during learning [153–157]. In the context of gliomas, these tumors exploit BDNF's mechanisms to their advantage, mimicking the healthy brain's developmental pathways [44]. BDNF, secreted by neurons, moves to tumor cells and initiates intracellular signaling cascades that support tumor growth, ultimately helping the tumor to form more and stronger synapses with neurons [44]. When the cellular mechanisms triggered by BDNF are more strongly activated, tumor cells will respond with stronger currents, which in turn fosters their growth [44]. In other words, tumor utilizes the learning mechanisms of the brain to grow.

BDNF exists in two distinct forms: precursor of BDNF (proBDNF) and mature BDNF [158–160]. Their distinct functions are carried out through two separate transmembrane receptor signaling systems: p75NTR and TrkB [44, 154, 156, 161]. The roles of the BDNF/TrkB signaling system in tumor cell proliferation and survival have been deeply demonstrated [154, 156, 161]. proBDNF, synthesized by neurons, is then cleaved by prohormone convertases (PCs) and/or furin, or extracellularly by plasmin and MMPs to release the mature homodimeric protein (mature BDNF) outside cells. Mature BDNF activates TrkB receptor with high affinity on glioma surface, thereby promoting cell survival [154, 156, 161]. The activation of the JNK pathway, mediated by BDNF/TrkB signaling, has been implicated in the progression of CNS malignancies [161]. Investigations have substantiated that BDNF serves as a potent activator of signaling cascades such as BDNF/TrkB/PI3K/Akt and TrkB/ATF4, effectively counteracting the inhibitory and apoptotic impacts of BDNF inhibitors on C6 glioma cells [162, 163]. It has been noted in several studies that pediatric gliomas frequently exhibit elevated TrkB expression, a key BDNF receptor, within their malignant cell populations [44, 164]. Further research has demonstrated that genetically or pharmacologically inhibiting TrkB not only negates BDNF's influence on glioma synaptic activity but also significantly enhances the survival rates in xenograft models of pediatric glioblastoma and diffuse pontine glioma [44]. Furthermore, the presence of BDNF and TrkB has also been noted in human gangliogliomas, underscoring their role in glioma biology [165].

While NLGN3 also possesses the capability to stimulate synapse formation between neurons and gliomas [29], its proliferative effect on pediatric cortical high-grade gliomas (pHGGs) is relatively less pronounced compared to BDNF [45]. This highlights the nuanced roles of various paracrine factors in modulating glioma behavior.

3.3 | IGF1

In recent years, researchers have made compelling progress in understanding the importance of insulin-like growth factor (IGF) in the regulation of CNS function. Studies focusing on the pituitary glands of neonatal mice have revealed that IGF-1 not only bolsters cell survival, growth, and differentiation but also amplifies the neurons' resistance to apoptosis, thereby exerting a neuroprotective influence [166–169]. In addition, the N-terminal glycine fragment produced by the hydrolysis of IGF-1 protein into des-N-(1–3) IGF-1, which is likely the predominant form of IGF-1 in the brain, has been shown to facilitate neuroprotective effects both in vitro and in vivo [170].

Olfactory gliomas, originating in the olfactory system, predominantly affect the olfactory bulb—the nexus for communication between the primary and secondary neurons of the olfactory circuit [171–173]. Utilizing a mouse model of primary gliomas that originate from adult oligodendrocyte precursor cells (OPCs) with conditional knockout of the tumor suppressor genes Trp53 and Nf1 (referred to as the CKO model), researchers have observed a high incidence of gliomas in the olfactory bulb, the initial site of olfactory sensory neuron transmission. Additionally, a heightened likelihood of glioma development in other olfactory-related centers, such as the anterior olfactory nucleus, olfactory nodule, pyriform cortex, and amygdala, has been noted, albeit with a later onset compared to the olfactory bulb.

Detailed anatomical examination of the olfactory bulb's substructures has uncovered that the majority of tumors are confined to the synaptic glomerular layer, the critical site of information exchange between the first-level neurons (olfactory sensory neurons, ORNs) and the second-level neurons (mitral and tufted cells, M/T cells) within the olfactory circuit. Notably, IGF1 is predominantly expressed in the mitral and tufted (M/T) cells of the olfactory bulb, but not neurons and glial cells, thereby identifying M/T cells as the principal source of IGF1. Targeted ablation of IGF1 in M/T cells has been demonstrated to effectively curtail the proliferation of mutated oligodendrocytes and to impede tumor progression, emphasizing the critical role of IGF-1 in glioma development [46].

Previous studies have shown that the function of IGF1 relies on the activation of its receptor, IGF1R. Chronic activation of olfactory receptor neurons in the olfactory bulb after knocking out IGF1R did not promote glioma growth, indicating that olfaction regulates glioma development through the IGF1-IGF1R signaling pathway (Figure 2C) [46].

This intricate interplay between neurons and glioma cells, mediated by paracrine signals such as BDNF, NLGN3, and IGF-1, underscores the complexity of the TME in brain tumors and highlights potential therapeutic targets for future interventions.

4 | The Role of Neurons in Tumor Precursor Cells Should Not Be Underestimated

Within the nervous system, a diverse array of precursor cells possesses the remarkable capacity to differentiate into various cellular constituents, including neurons, astrocytes, and oligodendrocytes, thereby contributing significantly to brain tissue formation. These cells are categorized into several subtypes, such as neural precursor cells, radial glial cells, intermediate progenitor cells, oligodendrocyte precursor cells, retinal precursor cells, and so on [174–180]. Oligodendrocytes are produced by OPCs [181]. In various types of cancers, the cell sources may be multifunctional neural stem cells, lineage-restricted neuronal precursor cells, or lineage-restricted glial precursor cells, each playing a distinct yet complementary role in neural development and function [29, 182–185].

Primary brain tumors are believed to originate from the neural precursor cell population. HGGs, with their diverse molecular and clinical subtypes, are believed to stem from these precursors, progressing along a differentiation spectrum from less differentiated neural stem cells to more lineage-restricted OPCs [29, 182–185].

The connection between neurons and OPCs involves paracrine mechanisms, such as the numerous roles of BDNF in neural development and plasticity, IGF signaling in gliomagenesis, and in addition to promoting tumor proliferation mentioned earlier, also facilitating myelin development [46, 186–188]. Alternatively, glutamatergic and GABAergic neurons can communicate directly with OPCs through synapses (Figure 3) [43, 79, 189, 190]. Future perspective could involve the dysregulation of myelin plasticity potentially promoting malignant cell proliferation within the primary brain cancer group, or still providing positive feedback on neuronal effects.

Using optogenetic technology to regulate the activity of neurons in the brain, research has found that the activated neurons in cerebral cortex and optic nerve are helpful in promoting the proliferation of OPCs and adapting to myelin sheath changes. The malignant counterparts of these activity-responsive neural precursor cells may exploit mechanisms of myelin development and plasticity to foster growth [27, 43].

The exploration of primary brain cancer's origins from the neural precursor cell population underscores the profound influence of neuronal interactions and developmental pathways on tumorigenesis. The intricate paracrine and synaptic communications between neurons and OPCs, along with the potential of optogenetic technology to modulate neuronal activity, reveal the critical role of neuronal regulation in both normal brain development and the aberrant proliferation seen in cancer. This understanding not only deepens our insight into the cellular dialogues that drive tumor growth but also opens avenues for innovative therapeutic strategies that target the neuronal mechanisms underlying cancer progression.

5 | Prospect

5.1 | Potential Targets and Therapeutic Sites

Elucidating the dynamics of neuron-brain tumor interactions, particularly the mechanisms by which neurons contribute to tumor progression, opens up new avenues for therapeutic intervention. Existing therapies for CNS tumors encompass a range of treatments, including surgery, radiation therapy, chemotherapy,

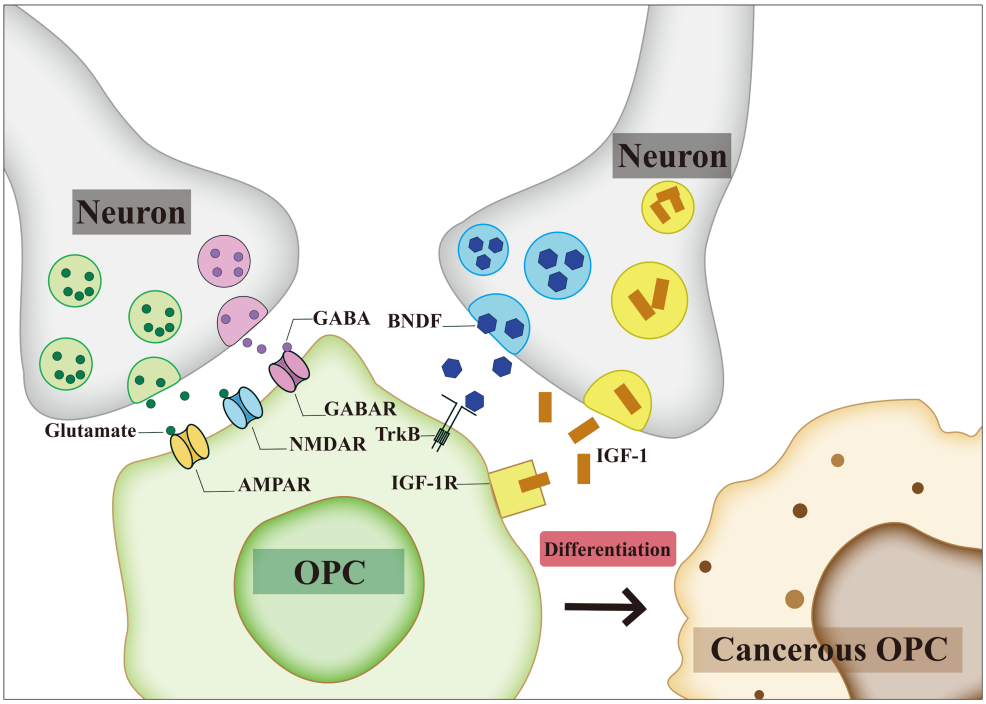

FIGURE 3 | The role of neurons in the transformation of oligodendrocyte precursor cells (OPCs) into tumorigenic cells. The pivotal role of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1) in the transformation of OPCs into glioma cells is highlighted. These factors exert their influence through paracrine signaling pathways, which allow for the modulation of neighboring cells, including OPCs, in a manner that promotes their differentiation into tumorigenic cells. The diagram illustrates how BDNF and IGF-1, secreted by neurons, bind to their respective receptors on OPCs, triggering intracellular signaling cascades that enhance the survival, proliferation, and potentially the malignant transformation of these cells. The direct synaptic communication between glutamatergic and GABAergic neurons and OPCs is detailed as a crucial aspect of this process. These synaptic interactions facilitate the transmission of electrical and chemical signals that promote the differentiation of OPCs into glioma cells, thereby contributing to the complex interplay between the nervous system and the development of brain tumors. The diagram shows the synaptic connections between neurons and OPCs, indicating the flow of signals that can drive the transformation of OPCs. The potential dysregulation of myelin plasticity that may promote the proliferation of malignant cells within the primary brain cancer group is suggested as an area of future investigation. The diagram represents the hypothesis that the mechanisms involved in myelin development and plasticity could be exploited by malignant counterparts of activity-responsive neural precursor cells to foster growth. This figure emphasizes the multifaceted communication between neurons and OPCs and how these interactions can lead to the initiation and progression of brain tumors. Understanding these neuronal influences on OPCs is essential for uncovering new therapeutic targets and developing strategies to prevent or treat gliomagenesis.

and targeted therapies [3, 5, 191–198]. However, due to the unique challenges posed by the blood–brain barrier, the sanctuary of the CNS from immune surveillance, and the heterogeneity of tumor types, traditional therapies have limitations: Surgery, the primary treatment for many CNS tumors, aims to remove as much of the tumor as possible while preserving neurological function, but complete resection is not always feasible, especially for tumors deeply infiltrating critical brain areas [199–203]; radiation therapy utilizes high-energy particles or waves to destroy tumor cells which can be delivered in focused doses to the tumor site using techniques like stereotactic radiosurgery, but it can also damage healthy brain tissue [191, 204–206]; although chemotherapy and targeted therapies can specifically inhibit rapidly dividing cells, the blood–brain barrier often limits the penetration of chemotherapeutic agents into the CNS [3, 5, 193, 194, 197, 198, 207, 208]. Future strategies may focus on two primary approaches: the development of pharmaceuticals to inhibit or neutralize proteins and other bioactive substances secreted by neurons, and the direct delivery of interventional drugs to the synapses formed between neurons and neoplastic cells, or to their downstream targets. Key targets include the inhibition of synaptic and presynaptic signal transmission, the disruption of glutamatergic neuron-to-brain tumor synaptic communication (NBTSC), the electrical coupling within glioma cell networks, the synaptogenesis between neurons and glioma, and the hyperexcitability of neurons that stimulates brain tumor growth [24, 209].

The research of cancer neuroscience opens the door to a new avenue of treatment: repurposing neuromodulatory drugs for oncology. Neurotransmitter modulators that affect neurotransmitter release, reuptake, or receptor binding could influence the synaptic connections between neurons and tumor cells. For example, glutamate receptor antagonists might disrupt the excitatory synaptic transmission that promotes tumor growth [28–30]. Neurotrophic factor inhibitors like BDNF and other neurotrophic factors are implicated in tumor growth, inhibiting their signaling pathways (e.g., Trk inhibitors) could be explored for their anti-tumor effects [29, 154]. Neuronal activity modulators drugs that alter neuronal activity, such as sodium channel blockers and GABA analogs used in epilepsy, might affect the hyperexcitability of neurons that contributes to tumor progression [61, 210–215]. Synaptic plasticity modulators affect synaptic plasticity, such as those influencing long-term potentiation

(LTP) and long-term depression (LTD), which could potentially alter the adaptive changes in the neural circuitry that support tumor growth [216–221]. Paracrine signaling inhibitors, targeting paracrine factors like NLGN3, IGF-1, and their downstream signaling pathways could disrupt the supportive TME for tumor cells [29, 45, 46].

Current practices involve the suppression of proteins and other substances secreted by neurons which can enhance tumor activity. For instance, NLGN3, a synaptic adhesion molecule, is targeted using its inhibitor Neurexin-1b (NRXN1b), which binds specifically to NLGN3, depleting it [27]. ADAM10 inhibitors, such as INCB7839 and GI254023X, also intervene in the NLGN3 production pathway (NCT04295759). In addition, the NLGN3 knockout mice can also achieve tumor suppression effects in combination with the aforementioned treatments [31]. Given that TSP-1 can serve as a regulatory factor for neuronal activity to drive glioma growth, researchers introduced gabapentin, a TSP-1 receptor blocker, into the co-culture medium of neurons and glioma cells. After 24–48 h of exposure, both the nerve pulses and the proliferation of HFC glioma cells co-cultured with neurons were significantly decreased. Genetic shRNA targeting of TSP-1 or pharmacological inhibition can similarly reduce GBM cell proliferation in the TME, laying the foundation for the development of therapeutic strategies that can improve cognition and survival [61]. Furthermore, genetic or pharmacological blockade of TrkB has been shown to impede the growth of pediatric gliomas, as evidenced by increased survival rates in mice with brainstem NTRK2-KO invasive pediatric glioblastoma or frontal cortex NTRK2-KO pediatric cortical glioblastoma, compared to controls to wild-type controls [44].

It is crucial to acknowledge that while inhibiting these molecules can yield tumor-suppressive effects in laboratory settings and mice, the broader implications of such interventions on brain function have not been fully explored. Researchers should consider the potential impact of inhibiting or knocking out proteins and synaptic structures on cognitive functions, and further studies involving animal models should assess effects on behavior, including cognitive and anxiety-related responses. For example, the role of NLGN3 in the maturation of excitatory synapses and its broader impact on brain function during tumor intervention needs further investigation [129, 131, 222]. Additionally, BDNF's role in neuronal survival, synaptic plasticity, and neurogenesis, particularly its influence on LTP, which underpins learning and memory processes, must be evaluated to understand the full scope of potential cognitive effects on humans [44, 100, 223–225].

A complementary strategy involves disrupting the glioma network. Since traditional chemotherapy and radiation may not always be effective as aforementioned [226–229], addressing glioma network resistance and the potential for calcium waves to worsen biological effects on tumor cells is vital [226–229]. The molecular underpinnings that drive the formation, progression, and maintenance of TMs and their GJs present viable targets for pharmaceutical innovation. Upstream regulatory factors, such as GAP43 and TTYH1, are integral to the genesis and functionality of TMs and could emerge as promising candidates for therapeutic intervention [124, 125, 230–235]. Currently, several clinical trials targeting the glioma network are in progress. For instance, in the treatment of recurrent adult glioblastoma, a combination therapy involving temozolomide chemotherapy is being tested to disrupt the glioma tumor network (MecMet/NOA-24; EudraCT 2021-000708-39). Additionally, pirenzepine, an antiepileptic drug functioning as a non-competitive AMPA receptor inhibitor, is being investigated for its potential to target glutamatergic neuronal-glial synapses, thereby inhibiting the glioma network at the excitatory synapse level (EudraCT 2023–503,938-52).

Given the crucial role of various secreted proteins and synaptic structures in the brain, it is our conviction that in treating intracranial tumors, interventions should be carefully targeted at the points of interaction between neurons and tumor cells, with a paramount focus on preserving the integrity of the surrounding neural tissue. Employing frameless stereotactic technology or image-guided neurosurgery allows for the precise delivery of therapeutic agents to tumor tissues, thereby minimizing collateral damage to other brain regions [230, 236–242]. Concurrently, the administration of neuroprotective agents, which do not contribute to tumor progression, is imperative for safeguarding healthy brain tissues [243, 244]. Protecting neurons from damage, such as oxidative stress or inflammation, might also protect against the neurotoxic effects of tumors and support the health of the CNS microenvironment [245–250]. With the advancement of fundamental research and the ongoing refinement of clinical trial methodologies, it is hopeful that we will soon develop efficacious treatments for intracranial tumors that spare brain function.

5.2 | A New Perspective on Brain Tumors

Brain tumors are not isolated entities but are interconnected with neurons, glial cells, and proteins in their environment. The role of neurons provides an expanded perspective for investigating the mechanisms behind brain tumor emergence and progression.

Initially, innovative interactions among tumor cells, neurons, and other tumor cells have been discovered. The interaction between neurons and tumors has not been extensively studied, and the communication among tumor cells seems to have been similarly overlooked in previous research. However, the communication among immune cells within the TME is likely to be more frequent and intimate, involving a complex array of chemokine receptor signals and interleukins [251–255]. The field of cancer neuroscience, which explores the relationship between tumors and neurons, provides us with fresh insights into the microtubules and networks of brain tumors. Some cells within GBM are interconnected through TMs, forming a network that may be responsible for the resistance of tumors to various treatment modalities [84]. The formation of synapses between neurons and tumor cells may exploit these tumor networks to facilitate the proliferation and invasion of GBM [28, 84]. Notably, the intriguing observation that neurons and tumor cells can form synaptic structures indeed opens up a plethora of questions regarding the nature of these interactions and the functional capabilities of tumor cells within such an arrangement. In classical synapses, the postsynaptic density is a complex structure enriched with various proteins that are crucial for synaptic function, including

receptors, scaffolding proteins, and enzymes [256–259]. It would be valuable to investigate whether tumor cells forming synapses also develop a similar postsynaptic density (PSD), which is very common in classic synapses [260–262]. Identifying the specific proteins present and their organization could provide insights into the functional state of these atypical synapses. In addition, whether tumor cells undergoing synaptic integration will exhibit morphological changes similar to neurons is something we need to focus on in future research. Investigating these changes under microscopic examination could offer clues about the structural adaptations that enable synaptic communication. Furthermore, it would be essential to examine their electrophysiological properties to determine if tumor cells can truly function as postsynaptic elements, which have already been reported [28–31, 85]. This includes assessing whether they can generate postsynaptic potentials (PSPs) in response to neurotransmitter release and whether they exhibit changes in membrane potential or ion channel activity. Finally, it is also important to consider whether these tumor-associated synapses exhibit plasticity, similar to that seen in the nervous system, potentially manifesting as alterations in synaptic strength or structure in response to activity [28, 44, 84, 124].

Secondly, from the perspective of cancer neuroscience, it is imperative to re-evaluate the underlying mechanisms that drive tumor metastasis. For example, breast cancer is the most common malignant tumor among women, with its metastasis mechanism being a multifaceted process [263, 264]. Historically, researchers have delved into a plethora of molecular mechanisms. Breast cancer metastasis typically unfolds through a series of sequential steps: local invasion by tumor cells, entry into the bloodstream or lymphatic system to become circulating tumor cells (CTCs), escape from circulation and colonization in distant tissues as disseminated tumor cells (DTCs), and ultimately transformation into metastasis-initiating cells (MICs) that establish metastatic foci [35, 265–267]. Recent studies have uncovered novel molecular mechanisms linked to bone metastasis in breast cancer, such as ULK1 protein, FAM20C kinase, CENPF protein, and CTGF secreted by tumor cells [268–276]. These factors significantly contribute to the bone metastasis of breast cancer. Breast cancer metastasis exhibits a distinct organ preference, particularly for bone metastasis, which predominantly occurs in estrogen receptor (ER)-positive luminal breast cancer (LBC) [277, 278]. It has been discovered that SCUBE2, secreted by tumors, is a pivotal factor in mediating the bone metastasis propensity in LBC [278]. The intriguing phenomenon previously mentioned, where tumors that metastasize to the brain from peripheral sites tend to express proteins typically found in the nervous system, appears to be relevant in these contexts as well. For instance, the FAM20C enzymes, implicated in the bone metastasis of breast cancer, are not commonly expressed in breast cells but are significant in bone tissue [274, 279]. Notably, as a secreted kinase, it is essential for osteoblast differentiation and function during bone development and the mineralization process [279–281]. The elevated expression of specific or key proteins within metastatic tissue before the onset of metastasis merits further exploration. The unique tripartite synaptic structure and its interaction with neurons have been elucidated for the first time. Based on electrophysiological studies and interventions on synapses and neurotransmitters, this structure may play a crucial role in inhibiting brain metastasis of breast cancer or directly suppressing breast cancer in the brain. However, there is a regrettable gap in our understanding of how this tripartite synapse is formed and the specific mechanisms of structural modification that promote brain metastasis of breast cancer, which warrants further exploration.

Thirdly, we have proposed new insights into the occurrence of tumors. Previous research has firmly established that neural precursor cells (NPCs) serve as a significant source of tumor cells, with their transformation into malignancy being a key pathway for the development of intracranial tumors [45, 46, 282–285]. The conversion of NPCs into tumor cells is a multifaceted process that entails intricate molecular and cellular interactions. Genetically, mutations in crucial tumor suppressor genes—including TP53, NF1, and PTEN—and the activation of oncogenes like EGFR and PDGFRA can initiate cell proliferation, impede apoptosis, and foster tumorigenesis [185, 286–294].

Additionally, the tumor microenvironment's influence, characterized by the presence of oncogenic factors, the disruption of cellular signaling cascades, and alterations in cellular components—encompassing immune cells, endothelial cells, and astrocytes—as well as changes in the extracellular matrix (ECM), can collectively facilitate the malignant transformation of NPCs [286, 295–306]. The role of neurons, as integral and central elements of the nervous system, in the initiation of cancer from precursor cells represents a novel and unanticipated dimension in our understanding of neuro-oncogenesis. Within the framework of cancer neuroscience, research has illuminated that the secretion of BDNF and IGF-1, coupled with direct synaptic interactions between glutamatergic and GABAergic neurons and OPCs, plays a crucial role in the malignant transformation of OPCs into glioma cells [43, 46, 79, 186–190]. However, there are numerous considerations that merit attention. For instance, while it is commonly believed that the sense of smell does not precipitate the development of glioma—a tumor originating from the neuroepithelium and potentially linked to factors such as ionizing radiation and viral infections—Liu's research presents compelling evidence that environmental stimuli can interact with our senses and potentially trigger cancer. In his study, gases were found to stimulate olfactory neurons, prompting other cells in the olfactory bulb to release IGF1, which in turn can stimulate the division of OPCs harboring pro-cancer mutations [46, 307]. This suggests a significant interaction between our environment and senses that could lead to cancer. However, there is no evidence to suggest that analogous mechanisms are at play in humans. The mice used in Liu's experiments were genetically engineered to develop gliomas. If olfactory stimulation is to be considered a key factor in the genesis of human gliomas, a stronger genetic predisposition association may be necessary. Moreover, our comprehension of olfactory gliomas is in its infancy with this study. Currently, investigations into the carcinogenesis of neural precursor cells through neuronal intervention are primarily confined to OPCs. It is essential to expand research to encompass a broader spectrum of precursor cell types to gain a more comprehensive understanding of neuro-oncogenesis.

Lastly, from the perspective of cancer neuroscience, we explore some differences between central primary tumors, such as

gliomas, and brain metastases. The first point is that the origins and developments of them are different: primary CNS tumors, such as gliomas, meningiomas, and pituitary adenomas, arise from the cells native to the CNS and their neural regulation of their TME is influenced by the direct interactions between resident neurons and glial cells, which can contribute to tumor growth through paracrine signaling and the formation of synaptic connections [5, 36, 56, 308–318]. In contrast, metastatic tumors, such as those from lung, melanoma, and breast cancers, have already undergone the process of invasion and intravasation in their primary sites, and once in the CNS, these cells may adapt to the neural environment by altering their gene expression and protein production profiles to engage with neurons and other CNS cells [30, 113, 319, 320]. The second point is that the neural-tumor interaction mechanisms differ markedly: primary CNS tumors can form direct synaptic connections with neurons, influencing their behavior through neurotransmitters and electrical signaling [24, 27–29, 45, 128]. Metastatic cells within the CNS may engage in unique synaptic interactions not typically seen with primary tumors, such as "pseudo tripartite synapses" between breast cancer cells and neurons, which can release glutamate and promote tumor growth and metastasis within the brain [30]. While both primary and metastatic tumors within the CNS are subject to neural regulation, the specific mechanisms and implications of these interactions can vary greatly. Primary tumors may have a more direct and continuous interaction with the CNS microenvironment, whereas metastatic tumors must adapt to a new environment that is distinct from their origin, potentially involving unique adaptations and signaling pathways. Gaining insight into these differences is crucial for developing targeted therapies that can effectively combat both types of CNS tumors.

6 | Conclusions

Neurons significantly influence the development and growth of both primary and metastatic brain tumors. They are capable of establishing functional connections with tumor cells via chemical or electrical synapses, thereby directly or indirectly modulating the behavior of the tumor through intercellular coupling networks. Furthermore, neurons contribute to the TME by secreting proteins that can foster tumor growth and facilitate the establishment of synaptic connections with tumor cells. Neurons also transform OPCs into cancerous cells through synaptic and paracrine signaling. Targeting and interrupting these neuron-to-tumor pathways could potentially lead to the amelioration or halting of tumor advancement. Emerging therapeutic strategies are likely to concentrate on the development of pharmaceuticals designed to inhibit or neutralize the proteins and bioactive substances released by neurons. These drugs aim to sever synaptic links and interactions between infiltrating cells and tumor cells, as well as to disrupt the electrical coupling within glioma cell networks. Nonetheless, it is imperative to confront the unique challenges associated with the central nervous system, including the blood–brain barrier's impermeability to many drugs and the complexities inherent in brain tumor treatment, alongside the potential side effects of neuroactive medications. We hold a strong conviction that, with ongoing advancements in foundational research and the refinement of clinical trial methodologies, it is within our reach to devise more potent treatment approaches for intracranial tumors that concurrently safeguard vital brain functions.

Author Contributions

W.L. wrote the main part of the article. Y.W. guided writing, offering suggestions to revise, and reviewed and agreed upon the final version of the manuscript. All authors read and approved the final manuscript.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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