

## An active role for neurons in glioma progression: making sense of Scherer's structures

Shawn Gillespie and Michelle Monje

*Cancer Biology Graduate Program (S.G.) and Department of Neurology and Neurological Sciences (S.G., M.M.), Stanford University, Stanford, California*

**Corresponding Author:** Michelle Monje, MD PhD, Stanford University, Lorry I. Lokey Stem Cell Research Building, 265 Campus Drive, Room G3035, Stanford, CA 94305 ([mmonje@stanford.edu](mailto:mmonje@stanford.edu)).

### Abstract

Perineuronal satellitosis, the microanatomical clustering of glioma cells around neurons in the tumor microenvironment, has been recognized as a histopathological hallmark of high-grade gliomas since the seminal observations of Scherer in the 1930s. In this review, we explore the emerging understanding that neuron–glioma cell interactions regulate malignancy and that neuronal activity is a critical determinant of glioma growth and progression. Elucidation of the interplay between normal and malignant neural circuitry is critical to realizing the promise of effective therapies for these seemingly intractable diseases. Here, we review current knowledge regarding the role of neuronal activity in the glioma microenvironment and highlight critical knowledge gaps in this burgeoning research space.

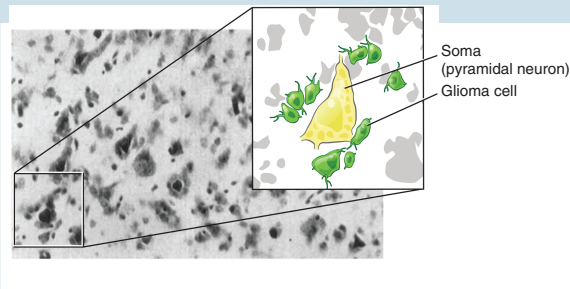
### Keywords

glioma | tumor microenvironment | neurons | neuronal activity.

Over 80 years ago, a neuropathologist working in Belgium painstakingly described the structures and cytological features of a class of brain tumors known as gliomas. Dr. H. J. Scherer noted the predilection of glioma cells to grow along and around normal neurons, referring to the phenomenon as “precocious perineuronal growth” (Fig. 1).<sup>1</sup> Were the glioma cells under Scherer's microscope simply clustering around abundant neuronal soma, an observation now referred to as “perineuronal satellitosis,” and following paths of least resistance along axons as they invaded distant brain regions, or were they actively engaged in a signaling relationship with normal neural circuitry? Our conceptual understanding of cancer has evolved a great deal in 80 years and now includes an appreciation for the importance of microenvironmental influences on cancer cell behavior. Neuronal regulation of cancer cells has recently emerged as a fundamentally important aspect of brain tumor biology. Here, we discuss new insights and evolving concepts regarding the relationship between glioma cells and neurons in tumor growth and progression.

### Electrical Activity as a Component of the Tumor Microenvironment

Among the most common primary brain tumors in adults and children, gliomas are so named because their constituent cells are morphologically and molecularly reminiscent of normal macroglial cells. A subset of these neoplasms, the high-grade gliomas, carry the worst prognoses and are the principal cause of death among patients with brain tumors. These tumors include adult glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, pediatric glioblastoma, and H3K27M-mutant diffuse midline gliomas of childhood<sup>2</sup> such as diffuse intrinsic pontine glioma (DIPG). The growth of gliomas around and along neurons is not a unique trait of neoplastic cells, but rather reflects a shared behavior with normal neural cell types such as oligodendrocytes and their precursors. Ample evidence from the literature illustrates that healthy glial cells and glial precursors participate in bidirectional and mutually beneficial relationships with nearby neurons. Accumulating data



**Fig. 1** An image from Dr. Scherer's 1938<sup>1</sup> analysis depicts clusters of glioma cells around neuronal soma. Magnified and schematized inset added for clarity. Neuronal soma, yellow. Glioma cells, green.

support a model in which glioma cells utilize and exploit normal neuronal signaling mechanisms to promote their own survival and growth. Here, we review our current knowledge of the mechanisms by which neurons in the microenvironment regulate glioma growth, and discuss the emerging therapeutic avenues to target newly understood microenvironmental dependencies in these devastating cancers.

Gliomas exist within and are regulated by a unique and dynamic microenvironment, the properties of which change throughout postnatal neurodevelopment and during adult neural plasticity. As one example, diffuse midline gliomas chiefly arise during a temporally restricted window in early to middle childhood and within the signaling environment of developing midline (diencephalic, rhombencephalic, and lower neural tube-derived) structures. In contrast, glioblastomas of adulthood chiefly grow within the (telencephalic) cerebrum. The differences between these two brain ecosystems are many and include cell type composition, signaling molecules, developmental state, and profiles of axonal myelination. Understanding microenvironmental determinants of glioma growth and progression is therefore a focus of current research efforts aimed at uncovering new targets and strategies for treating these seemingly intractable diseases. There has been a recent accumulation of knowledge regarding interactions of glioma cells with astrocytes, endothelial cells, immune cells, and neural precursor cells.<sup>3-8</sup> While these relationships are no doubt integral to glioma pathobiology, emerging research now suggests that interactions with neurons and the direct and indirect consequences of neuronal activity represent critically important determinants of glioma cell behavior.

Gliomas are named for their morphological similarity to normal macroglial cells. While the cell of origin for gliomas remains an open point of debate and may differ between glioma subtypes, mounting evidence supports the idea that many glioma types originate from neural stem or precursor cells of the oligodendroglial lineage.<sup>9-18</sup> Identifying a cell of origin for glioma has important implications for understanding the pathophysiology of the disease. As discussed below, neurons regulate the proliferation, differentiation, and function of normal glial cells in

an activity-dependent manner, suggesting that these regulatory mechanisms may be co-opted for the promotion of tumor growth and progression.

## Activity-Dependent Regulation of Neural Development, Plasticity, and Cancer

Activity of the nervous system is a powerful regulator of numerous aspects of neurodevelopment and ongoing neural plasticity, from neural stem cell proliferation, survival, and differentiation in the developing and mature nervous system to refinement and plasticity of synaptic connectivity.<sup>19-23</sup> It has been known for some time that early in neurodevelopment, neurotransmitters regulate neural precursor cell proliferation and differentiation through nonsynaptic depolarization.<sup>24</sup> A more recent report demonstrated that the orderly transition from multipolar-to-bipolar migration of neocortical neuroblasts is instructed by transient glutamatergic synaptic communication from subplate neurons to neuroblasts.<sup>25</sup> In the adult brain, proliferation and differentiation of stem cells in the subgranular zone of the dentate gyrus is coupled to excitation of neighboring neurons.<sup>19</sup> Neurogenesis in the postnatal subventricular zone, another stem cell niche in the brain, is regulated by the activity of a population of cholinergic neurons that project to the subventricular zone.<sup>26</sup> In the peripheral nervous system, axons regulate Schwann cell proliferation and survival and influence peripheral nerve myelination.<sup>27,28</sup>

We now recognize that neuronal activity also robustly regulates central nervous system glial precursor proliferation as part of a process known as myelin plasticity: activity-regulated, adaptive changes to myelination that represent a newly recognized dimension along which experience modulates brain structure and thus function. Researchers in the early 1990s first studied the rat optic nerve as a model system to identify an influence of electrical activity on normal oligodendrocyte progenitor cells (OPCs).<sup>29</sup> In this landmark study, silencing neuronal activity surgically by transection of the optic nerve or chemically with sodium channel blockade effectively and specifically inhibited local proliferation of OPCs. Since OPCs terminally differentiate into myelinating oligodendrocytes, it was reasonable to extrapolate from these studies that neuronal activity may allow for dynamic and adaptive modulation of circuit myelination, a concept supported by numerous *in vitro* studies<sup>30,31</sup> and studies correlating experience with changes in myelin-forming cells.<sup>32-34</sup> Direct *in vivo* evidence for this concept was enabled by the recent advent of optogenetic techniques that allow for minimally invasive, cell type-specific experimental manipulation of neuronal activity in awake, behaving mice.<sup>35-37</sup> These *in vivo* optogenetic studies revealed that neuronal activity of glutamatergic projection neurons in the premotor cortex elicit circuit-specific mitogenic responses from NPCs, pre-OPCs, and OPCs, ultimately resulting in differentiation of some progeny to functionally mature oligodendrocytes and adaptive changes to myelin microstructure of the involved circuit.<sup>38</sup> The influences of neuronal activity on

OPC proliferation, oligodendrogenesis, and adaptive myelin changes have now been replicated in additional model systems, including volitional motor behavior during motor learning<sup>39</sup> and elevation of neuronal activity in the somatosensory cortex by chemogenetic means.<sup>40</sup>

If neuronal activity promotes the proliferation of normal glial precursor cells that represent candidate cells of origin for high-grade glioma, do high-grade glioma cells similarly respond to neuronal activity? Indeed, *in vivo* optogenetic stimulation of premotor cortex neuronal activity also leads to increased proliferation of patient-derived pediatric cortical glioblastoma xenografts in the premotor circuit.<sup>41</sup> The proliferative response of glioma cells in this study was restricted to the stimulated premotor circuit, indicating circuit specificity of the growth-promoting effects of neuronal activity. Collectively, these data demonstrate that the parallels between human glioma cells and normal glial precursor cells extend to their proliferative responses to neuronal activity in the brain and define neurons as an important component of the glioma microenvironment.<sup>41</sup>

## Molecular Mechanisms of Neural Regulation of Glioma Growth

### An Unexpected Dependency on Neuroligin-3

While the molecular mechanism by which neuronal activity induces proliferation of normal OPCs remains an open question, several have been proposed and include activity-regulated neurotransmitters and neurotrophic factors.<sup>42</sup> In contrast, the mechanisms regulating glioma cell response to elevated neuronal activity are better understood. Glioma cell proliferation assays using conditioned medium from mouse brain slices with varying levels of neuronal activity demonstrated a robust proliferative effect of activity-regulated secreted factors in a range of clinically and molecularly distinct high-grade glioma types, including pediatric glioblastoma, DIPG, adult glioblastoma, and adult anaplastic oligodendroglioma.<sup>41</sup> Biochemical and proteomic analyses of this conditioned medium followed by candidate sufficiency testing revealed 3 activity-regulated glioma mitogens: brain-derived neurotrophic factor (BDNF), 78-kDa glucose-regulated protein (GRP78), and the synaptic cell adhesion protein neuroligin-3 (NLGN3).<sup>41</sup> Neuroligin-3, which classically binds presynaptic neu-rexin proteins, plays important roles in the maturation and proper functioning of synapses.<sup>43</sup> However, this interesting synaptic protein was not previously known to regulate cell cycle progression in any context.

In addition to uncovering an unexpected role for NLGN3 in glioma proliferation, these studies elucidated previously unknown proteolytic processing of this protein. A type 1 membrane protein, NLGN3 straddles the cell membrane with an N-terminal ectodomain and a C-terminal cytoplasmic domain. In the course of identifying proteins responsible for the mitogenic response observed in glioma cells, it became evident that despite abundant spectral counts for the N-terminal portion of NLGN3 by mass spectrometry, peptides corresponding to the C-terminus were notably absent. This discrepancy in peptide coverage suggested

that NLGN3 could be proteolytically cleaved at the cell surface, releasing the N-terminal ectodomain into the extracellular space and, in the context of glioma, into the tumor microenvironment. Bioinformatic analysis of peptide sequences near the transmembrane domain of NLGN3 pointed toward the metalloprotease family of proteins as likely cleavage enzymes. Subsequent pharmacological and genetic mouse modeling assays identified a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) as the enzyme primarily responsible for cleavage of NLGN3, a result that is logically consistent with previous research implicating the same enzyme in activity-dependent cleavage of NLGN1.<sup>44</sup> Given the position of NLGN3 within postsynaptic specializations, it is perhaps not surprising that neurons were found to be one cellular source of cleaved NLGN3. Intriguingly, another postsynaptic cell type in the brain, the OPC, was also found to contribute substantially to the production of cleaved NLGN3 in the brain.<sup>45</sup> Once cleaved by ADAM10 and released into the extracellular space, soluble NLGN3 engages an unidentified glioma cell surface receptor, activates numerous oncogenic signaling pathways (discussed below), and promotes proliferation.<sup>41,45</sup>

Seeking to isolate and clarify the relative contribution of activity-regulated NLGN3 secretion into the glioma microenvironment toward tumor growth and progression, the NLGN3 knockout mouse was crossed onto an immunodeficient background amenable to orthotopic xenografting of human patient-derived high-grade glioma cells.<sup>45</sup> Given the mitogenic influence of NLGN3 *in vitro*, some growth defects were expected in the human glioma cells implanted in the NLGN3 knockout brain microenvironment. Unexpectedly, while human glioma cells engrafted and survived, xenografts in the NLGN3-deficient brain did not expand over the course of several months in many cases. In other words, the ability of glioma cells to thrive in the brain is unexpectedly reliant on microenvironmental NLGN3. This dependency on NLGN3 was conserved across molecularly and clinically distinct glioma subtypes, including adult and pediatric glioblastoma and DIPG, suggesting a fundamental characteristic of gliomas that may supersede specific genetic mutations in regulating survival and growth. The importance of this observation for glioma cell biology is underscored by the fact that this dependency was not shared by patient-derived breast cancer brain metastasis xenografts, which grew equivalently in the brains of NLGN3<sup>-/-</sup> and wild-type mice.<sup>45</sup> Collectively, these data support a model in which gliomas are uniquely dependent on NLGN3 exposure in the brain microenvironment.

Mechanistic insight into the consequences of NLGN3 binding to glioma cells was garnered by detailed phosphoproteomic studies which demonstrated that NLGN3 stimulates numerous oncogenic signaling cascades in the glioma cell, with early activation of focal adhesion kinase and downstream activation not only of phosphatidylinositol-3 kinase (PI3K)—mammalian target of rapamycin but also the Src and Ras pathways. In addition to these signaling events, transient NLGN3 exposure also induces numerous gene expression changes in the glioma cell. Perhaps the most intriguing changes include upregulated expression of numerous synapse-associated genes. NLGN3 exposure strongly increases NLGN3 mRNA and protein

expression by glioma cells in a feed-forward, potentially autocrine/paracrine loop.<sup>41</sup> Of note, NLGN3 expression was inversely correlated with overall survival in adult glioblastoma patients, emphasizing the clinical significance of this mechanism in human disease. In addition to this feed-forward expression of NLGN3, several glutamate receptor subunit genes and the BDNF receptor gene neurotrophin receptor tyrosine kinase 1 (NTRK2) are upregulated following NLGN3 exposure in glioma.<sup>45</sup> Alongside increases in synapse-related genes, NLGN3 also leads to increased expression of tweety homologue 1, a protein that was reported to regulate tumor microtubule network formation in adult high-grade astrocytomas.<sup>46,47</sup> While the functional implications of these transcriptional changes require further clarification, the complex downstream consequences of activity-regulated NLGN3 release into the tumor microenvironment highlight our nascent molecular understanding of the roles played by this crucial molecule. Altogether, these findings further the concept that neuronal activity represents an integral component of the glioma microenvironment, highlighting an understudied topic that is ripe for investigation.

While there is much to learn about the mechanisms that account for the observed NLGN3 dependency in glioma, this activity-regulated molecule nevertheless represents an important therapeutic target. Leveraging the new insight that the ADAM10 metalloprotease mediates release of soluble NLGN3 into the tumor microenvironment, recent work has demonstrated that inhibiting ADAM10 prevents NLGN3 release and dramatically reduces the growth of patient-derived high-grade glioma orthotopic xenografts, suggesting a new therapeutic strategy targeting this key neuron–glioma interaction.<sup>45</sup>

## Neurotrophins

As mentioned previously, BDNF was implicated alongside NLGN3 as contributing to activity-dependent glioma proliferation, suggesting a role for neurotrophins in glioma cell survival and growth.<sup>41</sup> Neurotrophins, a family of growth factor proteins expressed in the nervous system, promote broad aspects of neural function, survival, and maturation.<sup>48</sup> Accordingly, the diverse activities of neurotrophins are engaged throughout development and during adult neural plasticity. Of particular relevance to the present discussion, neurotrophins also influence the proliferation, differentiation, and function of OPCs during development.<sup>49–51</sup> This particular role is linked to neuronal activity, as BDNF expression is regulated in an activity-dependent manner<sup>52,53</sup> and can be secreted in response to depolarization.<sup>54,55</sup> Mechanistically, BDNF initiates a signaling cascade upon binding to the high affinity tropomyosin-related kinase B (TrkB) (NTRK2) receptor on the cell surface.<sup>56</sup> *In vitro* evidence supports the idea that BDNF-TrkB signaling is involved in promoting proliferation, survival, and migration of high-grade glioma cells.<sup>57,58</sup> In further support of a role for BDNF-TrkB signaling in the glioma microenvironment, many human gliomas, particularly astrocytomas, express neurotrophin genes and their receptors<sup>31,57,59,60</sup> and exhibit mutations in Trk genes. Among Trk gene alterations in brain

tumors are fusion proteins involving NTRK1, NTRK2, and NTRK3 in pediatric high-grade glioma,<sup>61</sup> pilocytic astrocytoma,<sup>62</sup> and less commonly in adult glioblastoma.<sup>63</sup> In one study, these chimeric proteins were identified as fusions between the C-terminal kinase domains of NTRK1–3 and domains from 5 N-terminal partners, a pattern that appeared to activate oncogenic BDNF signaling cascades in these cells.<sup>61</sup> In addition to Trk fusions, about half of DIPGs in one sample cohort harbor genomic amplifications of NTRK1 and/or NTRK2, implying increased gene expression and therefore pathway activity in these cells.<sup>64</sup> This early research highlights the need to clarify whether gliomas harboring NTRK fusions or amplifications are dependent upon or differentially responsive to activity-regulated neurotrophins in the microenvironment. Collectively, these data suggest that activity-regulated neurotrophin signaling in glioma is potentially targetable, although the efficacy of disrupting this particular signaling network for glioma therapy remains to be defined experimentally.

## Neurotransmitters

Given that glioma growth and progression are impacted by neuronal activity-regulated release of protein factors into the microenvironment, it is reasonable to speculate that neurotransmitters may also regulate aspects of glioma cell behavior. This supposition has recently gained traction as several reports have begun to interrogate glioma cell responses to neurotransmitter exposure. One curious and potentially illuminating observation comes from a retrospective analysis demonstrating that patients with a history of long-term therapy with tricyclic antidepressants also display a reduced incidence of glioma. These drugs are known to have broad effects, but are thought to act primarily via reuptake inhibition of serotonin and norepinephrine.<sup>65</sup> Although a correlative study, this phenomenon may nevertheless indicate an unappreciated causal link between neurotransmitters and glioma cell behavior. One group provided experimental support for this concept by treating low-grade glioma-bearing mice with the tricyclic antidepressant imipramine, resulting in prolonged survival, reduced tumor cell proliferation, and a lower rate of progression to high-grade lesions.<sup>66</sup> Although apparently initiated by blockade of neurotransmitter reuptake, the mechanism of action in these studies also appeared to involve downstream regulation of autophagy, ultimately leading to programmed cell death of glioma cells.

Evidence for the importance of neurotransmitters to glioma biology extends to high-grade lesions such as glioblastoma, the cells of which are known to express dopamine receptors.<sup>67,68</sup> To test the functional relevance of these receptors, one group performed a proliferation screen across 3 patient-derived glioma cell cultures that were exposed to a panel of neurotransmitter agonists, antagonists, and reuptake inhibitors. The screen revealed that pharmacologic blockade of dopamine receptor D4 selectively and effectively inhibited glioma cell proliferation via disruption of autophagy and downstream induction of apoptosis,<sup>67</sup> a mechanism reminiscent of but distinct from that observed in the low-grade glioma imipramine study.

The results described above highlight the relevance of specific molecules to glioma biology, but it is unclear whether this trend will expand to include other neurotransmitters. For instance, glioma cells also express functional serotonin receptors, but whether serotonergic signaling impacts glioma cell behavior is less clear.<sup>69</sup> One retrospective study found that increased serotonin levels as a result of selective serotonin reuptake inhibitor therapy did not impact survival in patients with glioblastoma and comorbid depression.<sup>70</sup> One important caveat from such studies is that *in vivo* pharmacologic manipulation of neurotransmitter signaling is likely to alter both cell autonomous effects on glioma and non-cell autonomous effects on neuronal activity. Therefore, careful interrogation and dissection of neurotransmitter signaling in the glioma microenvironment should be an area of concerted research effort.

The functional relevance of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the mature CNS, to glioma regulation is also an area in need of investigation. One study demonstrated that primary low-grade astrocytomas and oligodendrogliomas express functional GABA<sub>A</sub> receptors, and though the function of such signaling is largely unclear, it is notable that higher-grade gliomas did not express GABA<sub>A</sub> receptors in that study. In addition, the authors found that glioma-derived cell culture lines failed to exhibit functional GABA<sub>A</sub> receptor activity *in vitro*.<sup>71</sup>

Normally, GABAergic inputs to OPCs inhibit their proliferation and promote differentiation to mature oligodendrocytes,<sup>72</sup> but it is unknown whether glioma cells respond to GABA in a similar manner. This raises an interesting and unanswered question regarding the role that GABAergic interneurons may play in regulating glioma. Elucidating the activity of GABA signaling in glioma growth and progression may therefore reveal additional therapeutic targets for these incurable diseases.

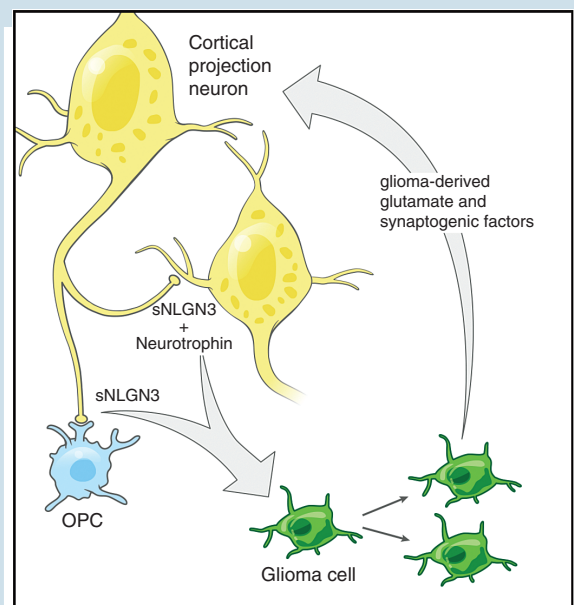
Both normal glial precursors and glioma cells express glutamate receptors.<sup>73,74</sup> In addition, nonsynaptic secretion of glutamate by glioblastoma cells has been reported *in vitro*<sup>75</sup> and further supported by *in vivo* studies describing increased extracellular glutamate levels in brain tissue in physical proximity to glioblastomas.<sup>76</sup> Glutamate has been shown to augment glioblastoma cell survival, growth, and migration via calcium influx-mediated activation of PI3K-Akt signaling through AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors.<sup>74,77,78</sup> In line with these observations, elevated glutamate secretion from gliomas is positively correlated with tumor growth in mammalian models.<sup>78</sup> Collectively, nonsynaptic glutamate secretion by glioma cells appears to function in an auto-crine/paracrine fashion in promoting tumor growth, survival, and progression. Neuronal glutamate release could further augment glioma progression, although the extent to which neuron-derived glutamate contributes to glioma progression—and whether neuronal glutamate release would signal in the same way as glioma-derived glutamate—has not yet been tested.

### Gliomas Increase Neuronal Activity

Accumulating research now suggests that the influence of active neurons on glioma cells may actually represent

one facet of a bidirectional relationship. For example, glutamate secretion by glioma cells contributes to hyperexcitability of neural circuits in the glioma microenvironment, including promotion of seizure activity.<sup>79,80</sup> This suggests that gliomas may enhance their own growth and progression not only via direct autocrine/paracrine effects of nonsynaptic secreted glutamate, but also by enhancing local neuronal activity, thereby resulting in greater release of activity-dependent mitogens by other cell types in the microenvironment (Fig. 2). This may play a role in the common, yet functionally enigmatic clinical feature of seizure activity among human glioma patients.

Increased cortical excitability may also manifest as gliomas progress and cancer cells evolve to promote synaptogenesis. A recent elegant study leveraged fluorescence activated cell sorting screening of cell-surface markers to separate astrocytes into 5 functionally diverse subgroups. One of these populations was particularly proficient in supporting synaptogenesis between neurons in a co-culture system. The authors then interrogated human gliomas for correlates of these astrocyte subgroups and found that the synaptogenic signature was represented among malignant cells.<sup>81</sup> Using 2 autochthonous mouse models of glioblastoma, the authors showed that the subpopulation of glioma cells exhibiting synaptogenic properties emerged as tumors progressed. This phenomenon correlated with the onset of clinical seizure activity



**Fig. 2** Schematic illustrating a bidirectional relationship between normal neural cells and their malignant glioma counterparts. Activity-regulated factors including a secreted form of neuroligin-3 (sNLGN3) from normal OPCs (blue) and neurons (yellow) and neurotrophins such as BDNF fuel the growth of glioma. Glioma cells (green), in turn, secrete glutamate and synaptogenic factors that increase neuronal excitability and probability of firing action potentials.

in the tumor-bearing mice, suggesting that increased and/or altered synaptogenesis due to shifting composition of tumor cell phenotypes may underlie the cortical hyperexcitability seen in later-stage gliomas in this model.<sup>81</sup> In addition, this increased excitability was positively associated with migratory behavior of the glioma cells, suggesting a possible link between neuronal activity and promotion of infiltration, though this association has yet to be formally tested. Thus, more work is needed to determine the extent to which seizure activity promotes glioma growth. In addition, as clinically apparent seizures are more common in individuals with low-grade astrocytomas and oligodendrogliomas than those with high-grade gliomas, it remains to be determined whether low-grade gliomas promote cortical hyperexcitability via similar mechanisms. The influence of neuronal activity on low-grade gliomas also remains to be demonstrated.

## Conclusion

The neural regulation of gliomas is now coming into focus and fits a developing paradigm in which neuronal activity promotes the growth and progression of several cancer types, including colon, gastric, prostate, pancreas, and skin,<sup>82–87</sup> as previously reviewed.<sup>88</sup> Furthermore, as glioma cells induce remodeling of the microenvironment to promote hyperexcitability of local circuits, the resultant increase in neuronal activity may in turn contribute to various activity-dependent mechanisms of tumor growth and progression. While research is needed to elucidate the nature and details of many of these mechanisms, the regulation of normal glial precursor cells by neuronal activity during development and plasticity suggests parallel interactions between neurons and glioma cells. A better understanding of the degree to which glioma cells may co-opt or diverge from physiological activity-dependent processes may elucidate promising new therapeutic approaches for these devastating cancers.

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