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Neuronal Activity in the Glioma Microenvironment

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Abstract

Gliomas are the most common primary brain tumor and high-grade gliomas the leading cause of brain tumor-related death in both children and adults. An appreciation for the crucial role of the nervous system in the tumor microenvironment is emerging for cancers in general, and the neural regulation of glioma progression has come into sharp focus. Here, we review what is known about the influence of active neurons on glioma pathobiology.

Gliomas, central nervous system cancers that resemble glial cells molecularly and morphologically, are among the most common primary brain tumors in adults and children. High-grade gliomas, a histopathologic class that encompasses devastating tumors such as glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma and midline H3K27M mutant gliomas of childhood (Louis et al., 2016) such as diffuse intrinsic pontine glioma (DIPG), have a particularly poor prognosis and remain the primary cause of mortality from brain tumors in patients of all ages. Distinctive properties of the central nervous system during the periods of both postnatal neurodevelopment and adult neural plasticity establish a unique tumor microenvironment for these cancers. Understanding microenvironmental determinants of glioma growth and progression is thus a focus of current lines of research that aim to uncover new targets and strategies for treating the disease and addressing its high burden of morbidity and mortality. Prior work has endeavored to describe interactions of glioma cells with astrocytes, immune cells, and cells of the vascular system (Charles et al., 2011; Pyonteck et al., 2013; Quail and Joyce, 2017; Silver et al., 2013). Emerging research now suggests that interactions with neurons, and the direct and indirect consequences of

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Conflict of Interest Statement

Stanford University has filed a patent application relevant to our work on the neuronal regulation of glioma growth. We have no other conflicts of interest to report.

neuronal activity, represent critically important determinants of glioma cell behavior, as well.

The concept of active neurons as important components of the tumor microenvironment recalls our understanding of neuronal activity as a key regulator of central nervous system development and plasticity. While the glioma cell of origin remains unconfirmed and openly debated, accumulating research suggests that glioma may arise from neural stem or precursor cells of the oligodendroglial lineage, specifically oligodendrocyte precursor cells (OPCs), pre-OPCs or earlier neural precursor cells (NPCs) (Galvao et al., 2014; Liu et al., 2011; Monje et al., 2011; Wang et al., 2009; Nagaraja et al., 2017). The known influence of active neurons on the proliferation, differentiation, and/or function of the cells from which glioma is thought to arise suggest that parallel mechanisms could play a role in glial cancers if co-opted for the promotion of tumor growth and progression.

Activity-Dependent Glioma Growth

Electrical activity of neurons is known to locally and specifically influence the proliferation of myelinating cell precursors, as well as the promotion of circuit myelination by functionally mature oligodendrocytes generated downstream. This was first suggested by early studies demonstrating that OPC proliferation could be suppressed by silencing neuronal activity in the rat optic nerve, either surgically via nerve transection or chemically via exposure to tetrodotoxin (Barres and Raff, 1993). Using optogenetic control of premotor cortical neural activity in awake, behaving mammalian models, NPCs, pre-OPCs and OPCs were found to exhibit a brisk mitogenic response to optogenetically increased cortical activity, leading to downstream differentiation to functionally mature oligodendrocytes and myelination of the active circuit in an adaptive manner (Gibson et al., 2014). Similarly, optogenetic manipulation of cortical neuronal activity also leads to an increased rate of proliferation of primary patient-derived pediatric cortical glioblastoma cells xenografted into the cortex of a mammalian model (Venkatesh et al., 2015). This occurs in a specific manner proximal to the stimulated circuit, and leads to increased tumor burden when optogenetic stimulation is performed repeatedly over time.

Activity-Regulated Secretion of Neuroligin-3

While the mechanism by which neuronal activity leads to increased proliferation of OPCs remains to be determined, an unexpected mechanism was implicated in the observed mitogenic effect of neuronal activity on glioma *in vivo*. Optogenetic stimulation of cortical slices resulted in the activity-dependent secretion of factors into conditioned medium that, when exposed to glioma cells, demonstrated a broad mitogenic effect on a nine out of ten patient-derived high-grade glioma cultures tested, including diffuse intrinsic pontine glioma, adult and pediatric glioblastoma, and anaplastic oligodendroglioma (Venkatesh et al., 2015). Biochemical and proteomic analyses revealed that the synaptic protein neuroligin-3 (NLGN3), secreted in an activity-regulated manner, was the primary factor responsible for the observed mitogenic effect, along with lesser contributions from known glioma mitogens, the neurotrophin BDNF (brain-derived neurotrophic factor) and GRP78 (78-kDa glucose-regulated protein) (Venkatesh et al., 2015). Secreted NLGN3 activates the PI3K-mTOR

signaling pathway to increase glioma cell proliferation, and also leads to the expression of NLGN3 by glioma cells in a feed-forward, potentially autocrine/paracrine loop. Furthermore, NLGN3 expression was found to correlate inversely with overall survival in adult patients with glioblastoma, emphasizing the clinical significance of this mechanism in the human disease. This study provided compelling evidence that active neurons are an important component of the glioma microenvironment, introducing a new potential approach to glioma therapeutics.

Given the diversity of microenvironmental and cell-intrinsic mechanisms that may promote glioma growth, what is the relative contribution of activity-regulated NLGN3? To answer this question, patient-derived high-grade glioma cells were orthotopically xenografted to neuroligin-3 knock out mice or littermate neuroligin-3 WT controls. Strikingly, glioma xenografts fail to grow in the neuroligin-3 deficient brain, indicating an unexpected dependency on this molecule. Neuroligin-3 dependency is conserved across molecularly and clinically distinct glioma types including adult glioblastoma, pediatric glioblastoma and DIPG (Venkatesh et al, 2017). Detailed phosphoproteomic studies reveal that neuroligin-3 stimulates numerous oncogenic signaling cascades in the glioma cell, with early activation of focal adhesion kinase and downstream activation not only of PI3K-mTOR but also SRC and RAS pathways (Venkatesh et al, 2017). In addition to these signaling consequences, neuroligin-3 also induces numerous gene expression changes in the glioma cell. The most intriguing changes include up-regulated expression of numerous synapse-associated genes. In addition to the previously described feed-forward expression of *NLGN3*, several glutamate receptor subunit genes and the BDNF receptor gene *NTRK2* increase expression following NLGN3 exposure in glioma (Venkatesh et al, 2017). As well, NLGN3 induces tweety homologue-1 (*TTHY1*) expression, a protein that regulates tumor microtube network formation in glioma (Osswald et al., 2015; Jung et al, 2017). While the functional significance of these gene expression changes remain to be clarified, the complex downstream consequences of activity-regulated neuroligin-3 release in the tumor microenvironment indicate that our understanding is still nascent regarding this crucial molecule and its pathological roles in glioma.

Although there is much to learn about the mechanisms that account for the observed neuroligin-3 dependency in glioma, this activity-regulated molecule represents an important therapeutic target. Neuroligin-3 is cleaved at the membrane by the ADAM10 protease resulting in ectodomain release into the microenvironment (Venkatesh et al., 2017). Inhibiting ADAM10 prevents neuroligin-3 release and dramatically reduces the growth of patient-derived high-grade glioma orthotopic xenografts (Venkatesh et al., 2017), suggesting a new therapeutic strategy targeting this key neuron-glioma interaction.

Neurotrophins in the Glioma Microenvironment

The identification of BDNF as a contributor to activity-dependent glioma proliferation (Venkatesh et al., 2015) is consistent with prior work suggesting a role for neurotrophins in glioma cell survival and growth. Neurotrophins are a family of growth factor molecules in the nervous system that act as major regulators of neuronal function, survival, and maturation, both in development and plasticity; they also govern the proliferation,

differentiation and function of OPCs (Tsiperson et al.; VonDran et al.; Wong et al.). This role is coupled to neuronal activity, as BDNF is synthesized in an activity-dependent manner (Hong et al., 2008; Lindholm et al., 1994) and secreted in response to depolarization (Androutsellis-Theotokis et al., 1996; Goggi et al., 2003). BDNF mediates its effects by signaling via the high-affinity TrkB (NTRK2) receptor (Chao et al., 2003; Klein et al., 1991) and indeed, this pathway is also implicated in the mechanism by which BDNF promotes proliferation, survival, and migration of high-grade glioma cells in studies *in vitro* (Lawn et al., 2015; Xiong et al., 2013). In further support of a role of BDNF-TrkB signaling in the glioma microenvironment, many human glioma cells, particularly astrocytomas, express neurotrophins and their receptors (Assimakopoulou et al., 2007; Lawn et al., 2015; Wadhwa et al., 2003; Wang et al., 1998) and exhibit mutations in Trk genes, including frequently activating fusions of NTRK1, NTRK2, and NTRK3 in pediatric high-grade glioma (Wu et al., 2014), pilocytic astrocytoma (Jones et al., 2013) and less commonly in adult glioblastoma (Frattini et al., 2013), as well as NTRK1 and/or NTRK2 amplifications in about half of diffuse intrinsic pontine gliomas (DIPG) (Grasso et al., 2015). Whether gliomas exhibiting NTRK fusions or amplifications are differentially dependent on or responsive to activity-regulated neurotophins in the microenvironment is unknown and represents an area for further research. These early findings certainly suggest a potentially targetable role of activity-regulated neurotrophin signaling in glioma progression, although the therapeutic potential of disrupting BDNF-TrkB signaling in glioma remains to defined in the literature.

Neurotransmitters and Glioma Growth and Progression

Neuronal activity could potentially also influence glioma growth and progression via neurotransmitter release. Several studies to date have begun to investigate glioma cell response to neurotransmitters in order to identify potential new therapeutic targets. Glioma incidence is reduced in patients with history of long-term therapy with tricyclic antidepressants, which have broad neurotransmitter effects and are thought to act primarily via reuptake inhibition of serotonin and norepinephrine (Walker et al., 2011). Low-grade glioma-bearing mice treated with the tricyclic antidepressant imipramine exhibited prolonged survival, with decreased rate of tumor cell proliferation and reduced progression to high grade lesions; the mechanism of action appears to involve induction of autophagy, leading to apoptosis (Shchors et al., 2015). Glioblastoma cells express dopamine receptors (Dolma et al., 2016; Li et al., 2014), and in a proliferation screen performed on three patient-derived glioma cell cultures exposed to a panel of neurotransmitter agonists, antagonists, and reuptake inhibitors, pharmacologic blockade of dopamine receptor D4 emerged as an effective and selective inhibitor of glioma cell proliferation via disruption of autophagy and downstream induction of apoptosis (Dolma et al., 2016). Glioma cells also express functional serotonin receptors (Mahe et al., 2004), but whether serotonergic signaling influences glioma growth or progression is less clear, as increased serotonin levels as a result of selective serotonin reuptake inhibitor (SSRI) therapy have not been shown to have a survival benefit in retrospective studies of patients with glioblastoma and comorbid depression (Caudill et al., 2011). It should be noted in all glioma studies pharmacologically manipulating neurotransmitter signaling *in vivo* that it is difficult to de-convolute the cell

autonomous effects on glioma from the non-cell autonomous effects on neuronal activity, and these dissecting the various possible effects of neurotransmitter signaling blockade in the glioma ecosystem should be an area of dedicated study.

It also remains to be seen whether GABA, the primary inhibitory neurotransmitter in the mature CNS, regulates glioma growth; low-grade astrocytomas and oligodendrogliomas cells do express functional $GABA_A$ receptors, and while the function of such signaling is largely unclear, it is notable that higher grade gliomas did not express GABA receptors, and glioma cell lines without GABA receptor expression exhibited unlimited proliferation in culture (Labrakakis et al., 1998). Indeed, GABAergic signaling to OPCs inhibits their proliferation and promotes differentiation to mature oligodendrocytes (Zonouzi et al., 2015), but it is yet unclear whether glioma cells respond to GABA in a similar manner. This raises the interesting unanswered question regarding the influence GABAergic interneurons may exert on glioma. Understanding the direct role that GABA signaling plays in glioma growth may elucidate additional therapeutic avenues to control disease progression.

Both glial progenitor cells and glioma cells express glutamate receptors (Gallo et al., 1994; Ishiuchi et al., 2002; Labrakakis et al., 1998), and furthermore, non-synaptic secretion of glutamate by glioblastoma cells has been directly observed *in vitro* (Ye and Sontheimer, 1999) and supported by *in vivo* studies describing increased extracellular glutamate levels in brain tissue proximal to glioblastomas (Behrens et al., 2000). Glutamate has been found to promote glioblastoma cell survival, growth and migration via calcium influx-mediated activation of PI3K-Akt signaling through AMPA receptors (Ishiuchi et al., 2002; Ishiuchi et al., 2007; Takano et al., 2001). Accordingly, gliomas that secrete greater levels of glutamate also exhibit increased tumor growth in mammalian models (Takano et al., 2001). Thus, nonsynaptic secretion of glutamate by glioma cells appears to have an autocrine/paracrine function in enhancing the tumor growth, survival and progression. Neuronal glutamate release could further contribute to glioma progression, although the extent to which neuronal glutamate release contributes to glioma progression – and whether neuronal glutamate release would signal in the same way as glutamate secreted form glioma cells - has not yet been explored.

Influence of Glioma on Cortical Excitability

Emerging work also suggests that the influence of active neurons on glioma cells may actually represent one facet of a bidirectional relationship (Figure 1). Of note, glutamate secretion by glioma cells contributes to hyperexcitability of neural circuits in the glioma microenvironment, including promotion of seizure activity (Buckingham et al., 2011; Campbell et al., 2012). This suggests that gliomas may actually enhance their own growth and progression not only via direct autocrine/paracrine effects of nonsynaptic secreted glutamate, but also by enhancing local neural activity, inducing an increase in subsequent release of activity-dependent mitogens by other cell types in the microenvironment. This may be a factor underlying the well-known clinical feature of seizure activity among human glioma patients, particularly in those with glioblastoma. Increased cortical excitability may also occur as gliomas progress and tumor cell behavior evolves. A recent study identified functionally diverse subgroups of astrocytes whose gene expression profiles match with

those of apparently analogous populations in glioma (John Lin et al., 2017). In a transgenic mouse model of glioma, the emergence of a subpopulation of glioma cells with particularly synaptogenic properties was observed as tumors progressed, which correlated with the onset of clinical seizure activity in the tumor-bearing mice, suggesting that increased and/or altered synaptogenesis due to shifting predominance of tumor cell phenotypes may underlie the cortical hyperexcitability seen in later-stage glioma in this model (John Lin et al., 2017). Interestingly, this increased excitability also correlated with enhanced migratory behavior of the glioma cells, suggesting a possible link between synaptic neuronal activity and promotion of infiltration, though this association has yet to be directly tested. Additional work is also needed to demonstrate whether seizure activity as well as physiologic cortical activity similarly promotes glioma growth. Furthermore, as clinically apparent seizures are more common in individuals with low-grade gliomas and oligodendrogliomas than those with astrocytomas, it will be important to determine if these glioma types promote cortical hyperexcitability via similar mechanisms.

Conclusion

Gliomas thus join an ever-increasing number of cancers for which neural regulation of the tumor microenvironment plays a key role in malignancy (for review, please see (Venkatesh and Monje, 2017). A fascinating model is emerging from the literature to date, suggesting multiple mechanisms by which active neurons may promote the growth and progression of glioma, including activity-regulated neurotransmitter, growth factor, and NLGN3 release into the glioma microenvironment. Furthermore, as glioma remodels its microenvironment in order to promote hyperexcitability of local circuits, the resultant increase in neuronal activity may contribute even further to various activity-dependent mechanisms of tumor growth and progression. While additional work is needed to elucidate the nature of many of these mechanisms, the important influence of neuronal activity on glial precursor cell growth and behavior during development and plasticity may suggest parallel interactions between active neurons and glioma cells. A better understanding of this underrecognized aspect of the glioma microenvironment, and the degree to which glioma cells may co-opt or diverge from physiological activity-dependent processes, may reveal promising new approaches to developing therapeutics for the treatment of this devastating group of neural cancers.

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Highlights

- Neuronal activity promotes glioma growth
- Gliomas increase neuronal excitability and promote seizures
- Bidirectional communication between gliomas and neurons in the tumor microenvironment drives a cycle of malignancy

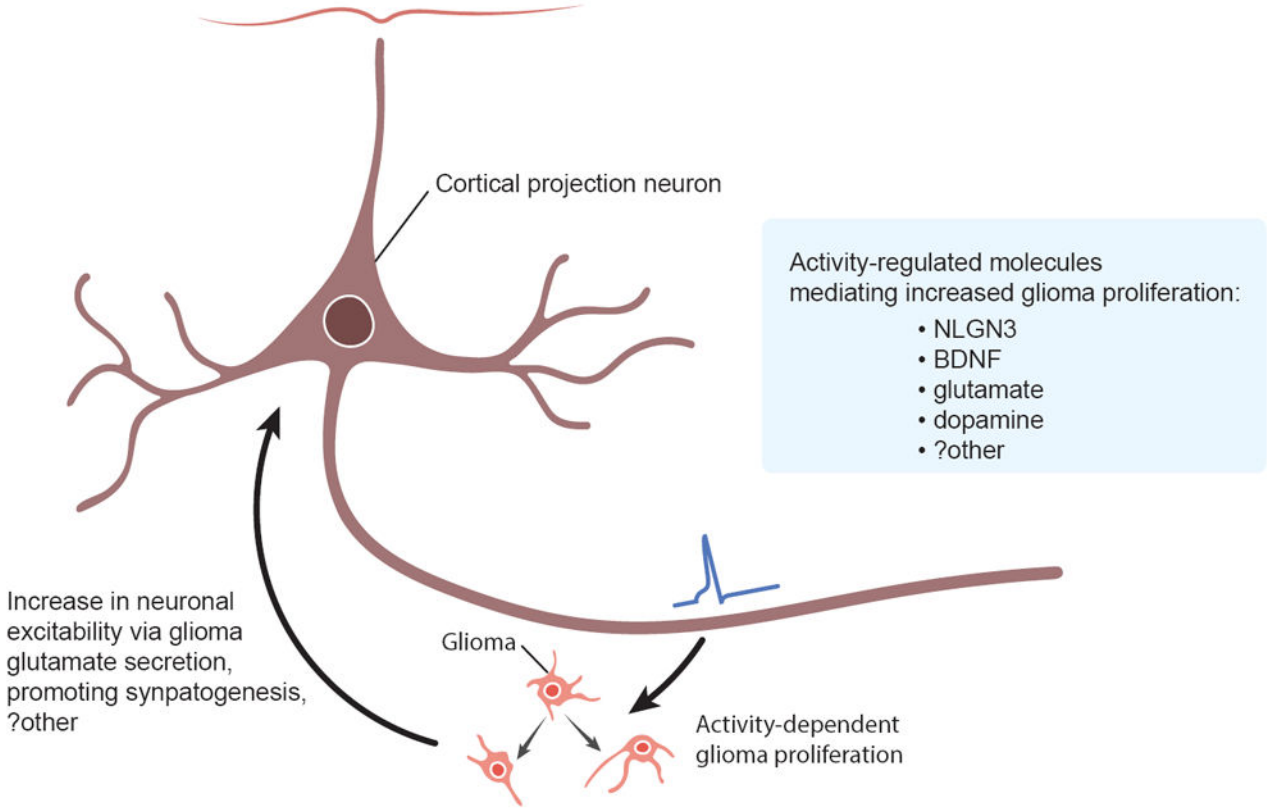

Figure 1. Bidirectional signaling between neurons and gliomas promote glioma growth

Neuronal activity promotes glioma proliferation and growth through activity-regulated secretion of brain-derived neurotrophic factor (BDNF), soluble neuroligin-3 (NLGN3), glutamate, dopamine and likely other factors. In turn, gliomas encourage neuronal activity through glutamate release, promoting synaptogenesis, and possibly additional mechanisms.