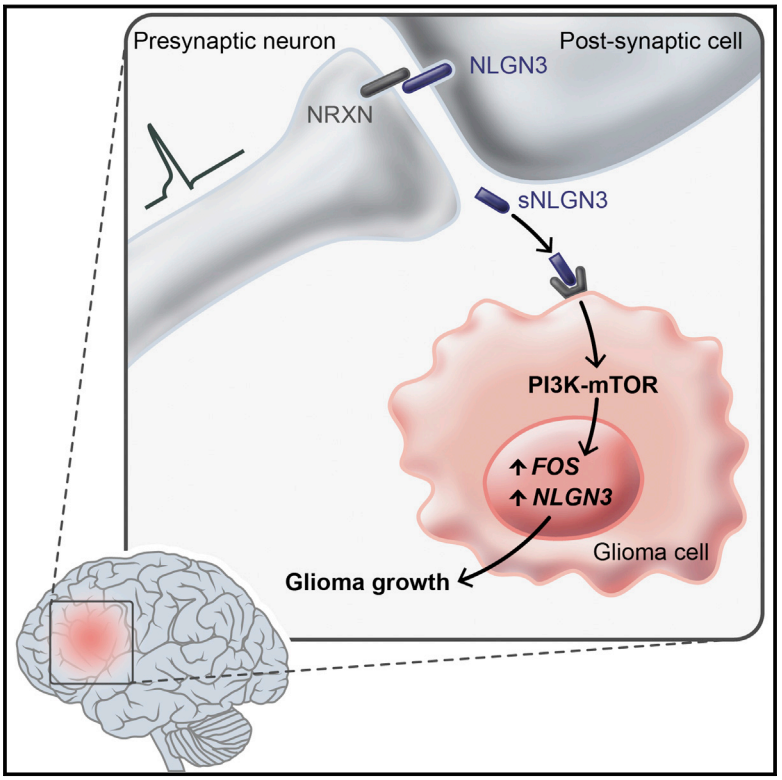
Article

Cell

Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion

Graphical Abstract



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In Brief

Neuronal activity promotes the growth of malignant glioma through activity-regulated secretion of the synaptic protein neuroligin-3, which acts as a mitogen, recruiting the PI3K-mTOR pathway to induce glioma cell proliferation.

Highlights

- Neuronal activity promotes high-grade glioma (HGG) proliferation and growth
- Neuroligin-3 is an activity-regulated secreted glioma mitogen
- Neuroligin-3 induces PI3K-mTOR signaling in HGG cells
- Neuroligin-3 expression is inversely correlated with survival in human HGG

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Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion

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SUMMARY

Active neurons exert a mitogenic effect on normal neural precursor and oligodendroglial precursor cells, the putative cellular origins of high-grade glioma (HGG). By using optogenetic control of cortical neuronal activity in a patient-derived pediatric glioblastoma xenograft model, we demonstrate that active neurons similarly promote HGG proliferation and growth in vivo. Conditioned medium from optogenetically stimulated cortical slices promoted proliferation of pediatric and adult patient-derived HGG cultures, indicating secretion of activity-regulated mitogen(s). The synaptic protein neuroligin-3 (NLGN3) was identified as the leading candidate mitogen, and soluble NLGN3 was sufficient and necessary to promote robust HGG cell proliferation. NLGN3 induced PI3K-mTOR pathway activity and feedforward expression of *NLGN3* in glioma cells. *NLGN3* expression levels in human HGG negatively correlated with patient overall survival. These findings indicate the important role of active neurons in the brain tumor microenvironment and identify secreted NLGN3 as an unexpected mechanism promoting neuronal activity-regulated cancer growth.

INTRODUCTION

High-grade gliomas (HGG), the leading cause of brain tumor death in both children and adults, occur in a striking spatiotemporal pattern highlighting the critical importance of the tumor microenvironment. Molecularly defined subtypes of HGG parse by neuroanatomical site of origin and patient age, with pontine and thalamic HGGs typically occurring in mid-childhood, cortical gliomas of childhood occurring in older children and young adults, and HGG of later adulthood occurring chiefly in the frontotemporal lobes (Khuong-Quang et al., 2012; Schwartzentruber et al., 2012; Sturm et al., 2012; Wu et al., 2012). These age and neuroanatomical predilections of gliomagenesis point to interactions between cell of origin and microenvironment, suggesting dysregulation of neurodevelopment and/or plasticity.

Microenvironmental determinants of glioma cell behavior are incompletely understood, although important relationships between glioma cells and neighboring microglia, astrocytes, and vascular cells have recently come to light (Charles et al., 2011; Pyonteck et al., 2013; Silver et al., 2013). While cellular origins of HGG remain unclear, converging evidence implicates oligodendroglial precursor cells (OPCs) and earlier neural precursor cells (NPCs) as putative cells of origin for many forms of HGG (Galvao et al., 2014; Liu et al., 2011; Monje et al., 2011; Wang et al., 2009). Clues to microenvironmental influences driving HGG growth may thus be inferred from mechanisms governing the proliferation of normal NPCs and OPCs in the postnatal brain. We recently demonstrated that neuronal activity exerts a strong mitogenic effect on normal NPCs and OPCs in juvenile and adult mammalian brains (Gibson et al., 2014), raising the possibility that neuronal activity could promote proliferation in HGG.

RESULTS

Optogenetic Control of Cortical Neuronal Activity in a Patient-Derived Pediatric Cortical HGG Orthotopic Xenograft Model

To test the role of neuronal activity in HGG growth, we employed in vivo optogenetic stimulation of premotor cortex in freely behaving mice bearing patient-derived orthotopic xenografts of pediatric cortical glioblastoma (GBM; Figure 1A–1C). The well-characterized Thy1::ChR2 mouse model expressing the excitatory opsin channelrhodopsin-2 (ChR2) in deep cortical