Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion.

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Public Summary:
In our CIRM-funded work, we had previously found that neuronal activity - the firing of signals between neurons in the brain- promotes the proliferation of myelin-forming precursor cells (oligodendrocyte precursor cells and earlier neural stem cells). It is thought that many forms of brain cancer, including glioblastoma and pediatric high-grade gliomas, arise from such neural precursor cells. In this paper, we tested the hypothesis that brain activity may similarly promote the proliferation of brain cancer cells and cause tumors such as glioblastoma to grow more aggressively. We found this to be the case, and also identified the molecules responsible for the growth-promoting effects of brain activity on brain cancer. Ultimately, these findings may provide new therapies for deadly brain cancers affecting both children and adults as well as elucidate potential neuro-regenerative strategies.

Scientific Abstract:
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.

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