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# Neuronal activity promotes glioma progression by inducing proneural-to-mesenchymal transition in glioma stem cells

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## Abstract

Neuronal activity can drive progression of high-grade glioma by mediating mitogen production and neuron-glioma synaptic communications. Glioma stem cells (GSCs) also play a significant role in progression, therapy resistance, and recurrence in glioma, which implicates potential crosstalk between neuronal activity and GSC biology. Here, we manipulated neuronal activity using chemogenetics in vitro and in vivo to study how it influences GSCs. Neuronal activity supported glioblastoma progression and radioresistance through exosome-induced proneural-to-mesenchymal transition (PMT) of GSCs. Molecularly, neuronal activation led to elevated miR-184-3p in neuron-derived exosomes that were taken up by GSCs and reduced the mRNA N6-methyladenosine (m6A) levels by inhibiting RBM15 expression. RBM15 deficiency decreased m6A modification of DLG3 mRNA and subsequently induced GSC PMT by activating the STAT3 pathway. Loss of miR-184-3p in cortical neurons reduced GSC xenograft growth, even when neurons were activated. Levetiracetam, an antiepileptic drug, reduced the neuronal production of miR-184-3p-enriched exosomes, inhibited GSC PMT, and increased radiosensitivity of tumors to prolong survival in xenograft mouse models. Together, these findings indicate that exosomes derived from active neurons promote glioblastoma progression and radioresistance by inducing PMT of GSCs.