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Brain-wide neuronal circuit connectome of human glioblastoma

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Abstract

Glioblastoma (GBM) infiltrates the brain and can be synaptically innervated by neurons, which drives tumor progression[1,2]. Synaptic inputs onto GBM cells identified so far are largely short-range and glutamatergic[3,4]. The extent of GBM integration into the brain-wide neuronal circuitry remains unclear. Here we applied rabies virus- and herpes simplex virus-mediated trans-monosynaptic tracing[5,6] to systematically investigate circuit integration of human GBM organoids transplanted into adult mice. We found that GBM cells from multiple patients rapidly integrate into diverse local and long-range neural circuits across the brain. Beyond glutamatergic inputs, we identified various neuromodulatory inputs, including synapses between basal forebrain cholinergic neurons and GBM cells. Acute acetylcholine stimulation induces long-lasting elevation of calcium oscillations and transcriptional reprogramming of GBM cells into a more motile state via the metabotropic CHRM3 receptor. CHRM3 activation promotes GBM cell motility, whereas its downregulation suppresses GBM cell motility and prolongs mouse survival. Together, these results reveal the striking capacity for human GBM cells to rapidly and robustly integrate into anatomically diverse neuronal networks of different neurotransmitter systems. Our findings further support a model wherein rapid connectivity and transient activation of upstream neurons may lead to a long-lasting increase in tumor fitness.

Update of

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Sun Y, Wang X, Zhang DY, Zhang Z, Bhattarai JP, Wang Y, Dong W, Zhang F, Park KH, Galanaugh J, Sambangi A, Yang Q, Kim SH, Wheeler G, Goncalves T, Wang Q, Geschwind D, Kawaguchi R, Wang H, Xu F, Binder ZA, Chen IH, Pai EL,

Stone S, Nasrallah M, Christian KM, Fuccillo M, O'Rourke DM, Ma M, Ming GL, Song H.

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