

Neuron-glia Interactions in Health and Disease: from Cognition to Cancer

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Zoom Only

SPEAKER:



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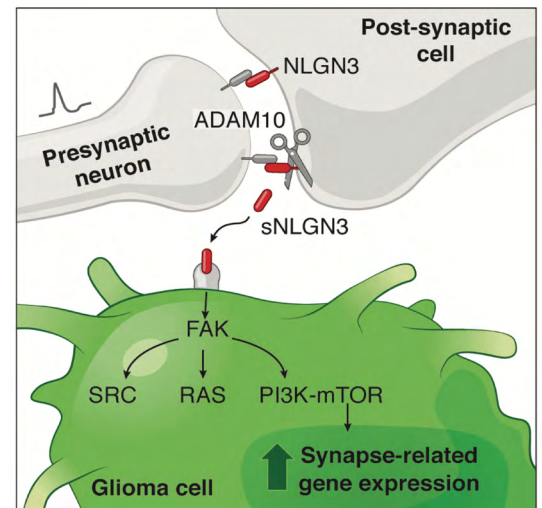
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Abstract

The nervous system regulates stem and precursor cell behavior across a range of tissues. In the central nervous system, neuronal activity is a critical regulator of development and plasticity. Activity-dependent proliferation of healthy glial progenitors, oligodendrocyte precursor cells (OPCs), and the consequent generation of new oligodendrocytes contributes to adaptive myelination. This plasticity of myelin tunes neural circuit function and contributes to healthy cognition. The robust mitogenic effect of neuronal activity on normal oligodendroglial precursor cells, a putative cellular origin for many forms of glioma, suggests that dysregulated or “hijacked” mechanisms of myelin plasticity might similarly promote malignant cell proliferation in this devastating group of brain cancers. Indeed, neuronal activity regulates initiation and promotes progression of gliomas in preclinical models. Crucial mechanisms mediating activity-regulated glioma progression include secretion of BDNF and the synaptic protein neuroligin-3 (NLGN3). NLGN3 induces multiple oncogenic signaling pathways in the cancer cell, and also promotes glutamatergic synapse formation between neurons and glioma cells. This synaptic and electrical integration of glioma into neural circuits is central to tumor progression in preclinical models. NLGN3 is necessary for the growth of gliomas in a range of preclinical models, and therapeutic targeting of NLGN3 is presently under clinical investigation. Thus, neuron-glia interactions not only modulate neural circuit structure and function in the healthy brain, but paracrine and synaptic neuron-glioma interactions also play important roles in the pathogenesis of glial cancers. The mechanistic parallels between normal and malignant neuron-glia interactions underscores the extent to which mechanisms of neurodevelopment and plasticity are subverted by malignant gliomas, and the importance of understanding the neuroscience of cancer.



Publications:

Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Inema I, Miller SE, Bieri G, Zuchero JB, Barres BA, Woo PJ, Vogel H, Monje M (2014) *Neuronal activity promotes adaptive oligodendrogenesis and myelination in the mammalian brain*. Science, 344 (6183):487; 344:1252304.

Venkatesh HS, Johung T, Caretti V, Noll A, Tang Y, Nagaraja S, Gibson EM, Mount CW, Polle palli J, Mitra SS, Woo PJ, Malenka RM, Vogel H, Bredel M, Mallick P, Monje M (2015) *Neuronal activity promotes glioma growth through neuroligin-3 secretion*, Cell, 161(4):803-16

Venkatesh HS, Tam LT, Woo PJ, Nagaraja S, Gillespe SM, Lennon J, Ni J, Duveau DY, Morris PJ, Zhao JJ, Thomas CJ, Monje M (2017) *Targeting neuronal activity-regulated neuroligin-3 dependency for high-grade glioma*, Nature 549: 533-537