This Week in The Journal

New Genetic Mouse Line Validates GRIK2 Role in Neurodevelopmental Disorders

Toshihoro Nomura, Sakiko Taniguchi, Yi-Zhi Wang, Nai-Hsing Yeh, Anika P. Wilen, et al. (see pages 7913–7928)

Neurodevelopmental disorders (NDDs), such as autism spectrum disorder and attention-deficit/hyperactive disorder, affect the development of social, cognitive, and emotional functioning. Research has identified genes that encode proteins present in synapses that cause NDDs when they are mutated. However, the consequences of these genetic mutations at the cellular and circuit level remain unclear. In this issue, Nomura et al. investigated the cellular and circuit changes following a missense mutation in the glutamate ionotropic receptor kainate type subunit 2 (GRIK2) gene that alters the functioning of this glutamate receptor and causes NDDs. Kainate receptors modulate the afterhyperpolarizations of hippocampal neuron action potentials and their impact on cell excitability has been explored in vitro, but not in vivo. Thus, the authors generated a genetic knock-in mutant line of mice to mimic the missense mutation and analyzed hippocampal neurons. They ultimately found that the pathogenetic missense mutation reduced calcium-activated potassium channel activity on cell dendrites, which increased dendritic excitability and led to increased firing rates of neurons. Not only do these data demonstrate the translatability of the in vitro findings of the field, but the authors’ development of a new mouse model to investigate this mechanism underlying NDDs may help isolate new treatment targets.

Cell Adhesion Molecule Involvement in Glioblastoma Cell State Transitions

Arpan De, John M. Lattier, John E. Morales, Jack R. Kelly, Xiaofeng Zheng, et al. (see pages 8043–8057)

The most aggressive and common form of primary cancer in the adult brain is glioblastoma (GBM). GBM consists of heterogeneous cell populations that work together to drive rapid tumor progression and recurrence following treatment. One of the many reasons why cancers like GBM are difficult to treat is the quick rate at which cells change from being proliferative to invasive. The molecular mechanisms that enable GBM cells to exit the tumor core, inhabited by proliferative cells, and invade healthy brain tissue are not known. In this issue, De et al. used human tumor specimens and primary cancer cell cultures from both sexes to discover high expression of a type of cell adhesion molecule called GlialCAM in proliferative cells in the tumor core. Cells with lower levels of GlialCAM showed invasion into the surrounding brain tissue. They used quantitative RNA sequencing to determine that expression of GlialCAM as well as its associated signaling proteins can determine whether GBM cells are proliferative or invasive. These findings point to GlialCAM signaling as a potential mechanism for cancer cell state transitions. Future work may investigate whether this mechanism can be targeted by pharmacological treatments to manage cancer spread.

This Week in The Journal was written by Paige McKeon

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