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New imaging studies reveal mechanics of neuron migration

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(PhysOrg.com) -- The development of the brain proceeds a little like the European settlement of North America. The earliest pioneers settled on the east coast with subsequent waves of settlers forming communities further and further westward. In cortical regions of the developing brain, generations of young neurons undergo a staged migration as well, with the earliest-born cells staying relatively close to their birthplace and subsequent generations traveling further, ultimately stratifying into six neuronal layers in the mature brain. Now, for the first time, imaging studies have identified the “motors” that propel a unique form of cell migration that creates these layers that underlie the formation of synaptic circuitry.

“The complexity of the cell types is so much greater in the brain than in other parts of the body, nothing else compares,” says Mary E. Hatten, head of the Laboratory of Developmental Neurobiology at The Rockefeller University. “Since different classes of neurons are born at different times in the brain’s development, neuronal migration is responsible for patterning specific types of cells into particular layers. The normal development of the brain depends critically on this specialized form of motility, which places the neurons in the right layer.”

Hatten and former postdoctoral associate David Solecki, now at St. Jude Children’s Research Hospital, focused on the mechanism of neuronal migration in cortical regions of the brain, including the cerebellum, hippocampus and cerebral cortex. With colleagues, they developed techniques to fluorescently label the motor proteins inside the tiny

neurons and watch their dynamics as the cells migrate along what Hatten calls a monorail system — glial fibers — toward their destinations. The researchers used a spinning-disk, confocal microscope, equipped with a CCD camera to image the migration in real time at extremely high resolution, allowing them to examine the motor proteins in great detail.

The Hatten lab had already discovered in 2004 that a conserved polarity protein, par6α, controls the migration of neurons along glial guides. The new research, published July 16 in Neuron, identifies the motors regulated by par6α. The researchers found that par6α localizes in a key organelle called the centrosome directly in front of the cell nucleus, and effects the phosphorylation of an enzyme called the myosin light chain kinase, needed to activate actomyosin motors. These motors appear to pull the cell forward in discrete steps: They first assemble in front of the nucleus, pull the cell forward, disperse as the cell pauses and then assemble again as the neuron takes another step along the glial guide. The researchers demonstrated that any significant change in the dynamics of actomyosin assembly or par6α activity stops neuron migration in its tracks.

The mechanics of this specialized form of neuron migration seen in the developing brain are distinct from those that direct the classical migration of epithelial cells and fibroblasts, as actomyosin motors in the latter are at the tip of the migrating cell in a “leading edge” that is relatively far removed from the cell nucleus.

“Neuronal migration is a very delicate process. The model we’re suggesting is that the actomyosin dynamics are pulling the system forward, but they’re close to the nucleus to control this very regulated and precise kind of motility,” Hatten says. “This specialized motility is essential to the formation of neuronal layers in brain. Defects in the process can result in all of the major brain malformations such as lissencephaly as well as a misfiring of the neuronal circuitry as occurs in

epilepsy."

More information: *Neuron* 63(1): 63-80 (July 16, 2009) Myosin II motors and F-actin dynamics drive the coordinated movement of the centrosome and soma during CNS glial-guided neuronal migration, David J. Solecki, Niraj Trivedi, Eve-Ellen Govek, Ryan A. Kerekes, Shaun S. Gleason and Mary E. Hatten -- www.cell.com/neuron/abstract/S0896-6273(09)00435-8

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