Scientists discover a new mechanism controlling neuronal migration

July 15 2009

The molecular machinery that helps brain cells migrate to their correct place in the developing brain has been identified by scientists at St. Jude Children's Research Hospital. The finding offers new insight into the forces that drive brain organization in developing fetuses and children during their first years. Disruption of this brain-patterning machinery can cause epilepsy and mental retardation and understanding its function could give new insight into such disorders.

Led by David Solecki, Ph.D., an assistant member in the St. Jude Department of Developmental Neurobiology, the researchers published their findings in the July 16 issue of the journal *Neuron*.

In the experiments, the researchers sought to understand the biological machinery powering a process called glial-guided neuronal migration. Glial cells in the brain support and guide neurons, which make up the brain's wiring. During brain development, neurons are born in germinal zones at some distance from where they must ultimately land in order to form brain structures and integrate into the brain's circuitry.

"Glial cells produce very thin fibers, and neurons in essence walk a tightrope along these fibers in moving from these germinal zones to their final position," Solecki said. In earlier work, Solecki and his colleagues identified a control molecule called Par6 alpha that regulates this migration. Other researchers had produced evidence that a molecular motor called Myosin II might power the migration. Myosins are proteins that use chemical energy to create contractions by moving along

filamental proteins called actins—like a train moves along a railroad track.

The researchers used a technique of microscopic time-lapse imaging to establish that Myosin II and actin made up the machinery of neuronal migration. Working with cultures of migrating neurons, the investigators used fluorescent dyes to label Myosin II and actin proteins, as well as key cell structures. The scientists then illuminated the cultures with rapid-fire pulses of laser light measured in thousandths of a second, taking an image with each flash. The result was a series of micromovies that revealed how the Myosin II and actin proteins and cell structures behaved during migration.

These micromovies showed that the Myosin II-actin machinery powers neuronal migration. As part of a step-wise migration process, the machinery pulls the internal cell structures of the neuron forward during migration to allow those structures to build the scaffolding that enables the neuron to move the main cell body forward. The researchers demonstrated that both Myosin II and actin are necessary for the process, because they could completely shut it down by using drugs that inhibited either molecule.

"No one had actually looked in living cells to see the configuration of actin in migrating neurons to show how it positions the machinery that will eventually elicit movement of the cell," Solecki said. "We also found that contraction of Myosin II in the leading portion of a neuron powers movement."

Critical to the researchers' success was the development of a computer analysis technique for the massive number of time-lapse images, Solecki said. The analysis program was developed by study co-authors Ryan Kerekes, Ph.D., and Shaun Gleason, Ph.D., of Oak Ridge National Laboratories in Tennessee.

"Our time-lapse microscopy could image hundreds of cells in a single afternoon, but analyzing that mass of data by hand would have taken months," Solecki said. "However, the automated analysis enabled those data to be analyzed in a matter of hours. Also, the automated analysis was free of the kind of natural bias that can occur when humans analyze such images."

In further experiments, the researchers also showed that Par6 alpha regulates Myosin II motor activity, shedding light on how the machinery is regulated. Additional studies will explore that regulation mechanism further.

Basic understanding of the migration machinery could have important clinical implications.

"If we more clearly understand how neurons migrate in neural development, we will have a better framework to explain the basis of neuronal migration defects in children," Solecki said. "Also, cell migrations may contribute towards the spread of brain tumors in children. If we can understand how normal neurons migrate, we might be able to dissect the machinery of the migration of brain tumor cells."

Source: St. Jude Children's Research Hospital