Protein found to control the early migration of neurons

July 27 2010

Long before a baby can flash her first smile, sprout a first tooth or speak a first word, the neurons that will form her central nervous system must take their first, crucial steps. And these steps must be careful to take the right neurons to the right places and avert developmental disasters that could thwart those other baby firsts from ever coming to pass. Now new research promises a deeper understanding of how this essential form of cell migration occurs, finding a gene that works behind the scenes to control a closely related adhesion gene that helps keep young neurons on the right track.

The findings could revive interest in an aspect of early neuron migration that was first discovered by Mary E. Hatten in the 1980s, and also may provide clues about diseases such as schizophrenia and autism that have been linked to mutations in the newly characterized gene.

The protein in question is astrotactin, a cell receptor that the Hatten Lab showed to function in binding young neurons to the glial fibers, which guide them to their proper location in the developing layers of vertebrate brains.

In the 1990s, after moving to Rockefeller, Hatten, now the Frederick P. Rose Professor and head of the Laboratory of Developmental Neurobiology, and colleagues cloned the gene *Astn1*, which produces the protein that provides a neuron-glial adhesion receptor. The new findings are about a second member of the Astrotactin gene family called *Astn2*, which they now show regulates *Astn1*, by controlling the amount of

ASTN1 receptor that is expressed on the surface of migrating neurons.

The experiments, published last month in the *Journal of Neuroscience*, suggest that migrating neurons attach to their glial guides via ASTN1 and that interactions with ASTN2 promote the intracellular trafficking of ASTN1, effectively removing it from the cell surface and allowing the neuron to glide forward until a new adhesion site forms. A critical new idea in the paper is that receptor trafficking of an adhesion receptor regulates movement. “It is very exciting to have new insights into a protein we have studied over so long a period, insights that explain new aspects of how neurons migrate on glial fibers,” Hatten says.

By treating the cells with a molecule that prevents them from being able to internalize the ASTN1 receptor, the researchers were able to halt the cells’ migration. The cells were effectively stuck in place. The team was then able to re-initiate movement by simply washing out the molecule. Imaging experiments revealed that unlike its close relative ASTN1, the adhesion protein exposed on the cell surface, ASTN2 was not expressed on the cell surface but rather interacted with ASTN1 to control the amount of ASTN1 protein on the neurons’ surface that is available for binding to glial fibers.

While *Astn1* has not been directly implicated in developmental disorders, a number of recent human genetic studies have associated mutations in the *Astn2* gene with developmental diseases such as attention deficit disorder, autism and schizophrenia. Both *Astn1* and *Astn2* are very active early in development and continue to be expressed at low levels in adulthood. Hatten believes *Astn2* may be important for several different types of receptor trafficking, including at the synapse. Defects in receptor recycling could affect fundamental aspects of the neuronal circuitry important for autism or schizophrenia.

The findings add to an evolving picture of cell migration that builds on

Hatten and colleagues' recent work on other key players, including the role of conserved polarity proteins in controlling the rhythmic assembly of motor proteins that provide the force to move the neuron forward along the glial guide.

"It is very satisfying to be able to understand how neuronal migration works and especially the features that distinguish this specialized form of directed migration that is essential to form the basic neuronal layers of the developing brain," Hatten says. "We are particularly excited about understanding how conserved polarity proteins control the tempo of adhesion and de-adhesion, as there is the possibility of forming a unified model for the control of this critical form of CNS migration.

"There's good reason to think that understanding this better will give us insight into some devastating developmental diseases."

More information: The Journal of Neuroscience 30: 8529-8540 (June 23, 2010) *Astn2*, A Novel Member of the Astrotactin Gene Family, Regulates the Trafficking of ASTN1 during Glial-Guided Neuronal Migration. Perrin M. Wilson, Robert H. Fryer, Yin Fang and Mary E. Hatten

Provided by Rockefeller University