UCSD Researchers Describe Cell Activity Leading To Disruption Of Neuron Migration

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An interaction between two brain proteins that leads to abnormal brain development has been identified by researchers at the University of California, San Diego (UCSD) School of Medicine in a study published in the January 22, 2004 issue of the journal *Neuron*.

The studies in mice, conducted in the lab of Joseph G. Gleeson, M.D., UCSD assistant professor of neurosciences, combines work in both humans and mice to identify a protein kinase called Cdk5 as the "off" switch for a crucial neuronal migration protein called doublecortin. When Cdk5 adds a phosphate molecule to doublecortin, the doublecortin is inactivated and neuronal migration is arrested.

In the normal brain, neurons are born deep within fluid filled cavities of the brain during the third and fourth month of gestation. Then, they must migrate hundreds of cell-body distances to reach their proper position within the six-layered cortex. When this migration is defective and neurons are stopped short of their destination, there is an absence of the normal grooves and ridges that characterize the brain in higher mammals.

A severe brain disorder in newborns, called lissencephaly, or "smooth brain," is a result of abnormal neuronal migration where only four, instead of six layers of cortex are formed. Those children who survive the mutation suffer from profound mental retardation, epilepsy and cerebral palsy. Gleeson and colleagues previously showed that mutations in the doublecortin gene account for approximately 20 percent of the cases of lissencephaly in humans.

The study concluded that Cdk5 phosphorylation and inactivation of doublecortin takes place normally in the developing brain, but that it is balanced by reactivation of doublecortin by an as-yet-unidentified "on" switch. It appears that the regulation of this phosphorylation is critical for migration, and that both inactivation and reactivation are required for the normal functioning of the protein. Gleeson's laboratory is currently searching for the signals that serve as the "on" switch to reactivate doublecortin.

"Neuron migration is poorly understood by scientists," he noted. "With the discovery of Cdk5 as a factor that regulates doublecortin, we are learning more about this vital developmental process. Eventually, discoveries such as this will contribute to therapies to prevent abnormal brain development."

In back-to-back published articles in 1998, Gleeson and a team led by Christopher A. Walsh at Harvard*, and a group of French scientists co-discovered doublecortin as one of the genes that causes lissencephaly when it is mutated. Further studies in 1999 by Gleeson and colleagues determined that doublecortin directly binds to microtubules, part of the cellular cytoskeleton that acts like a railroad track for the contents of neurons that move in the brain. However, researchers still didn't know how doublecortin worked or what regulated its function.

In the current study, the Gleeson team used sophisticated molecular technology to determine that Cdk5 interacts with doublecortin to add a phosphate molecule to a precise site on the protein. Next, the team inactivated Cdk5 in one group of neurons, thus preventing its phosphorylation of doublecortin. When these

neurons, or neurons containing mutant doublecortin, were pitted in a race with normal neurons, they stopped short of their goal, indicating that this regulation by Cdk5 was critical for the function of doublecortin on the cells' ability to move.

In the January 22 issue of Neuron is commentary about the Gleeson discovery by Joseph Lo Turco, Ph.D., University of Connecticut, who notes that doublecortin may "sit at the center of a general cellular program of morphological change engaged as neurons migrate through developing neocortex."

Additional authors of the UCSD paper included first author Teruyuki Tanaka, M.D., UCSD Department of Neurosciences; Finley F. Serneo, M.D., UCSD Department of Neurosciences; Huang-Chun Tseng, Ph.D., and Li-Huei Tsai, Ph.D., Department of Pathology, Harvard Medical School and the Howard Hughes Medical Institute; and Ashok B. Kulkarni, Ph.D., Functional Genomics Unit, National Institute of Dental and Craniofacial Research, National Institutes of Health.

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