# Novel Pathway Regulates Timing of Brain-Cell Development

5 October 2006

Brain formation involves the carefully timed production of different types of nerve cells by neural stem cells: neurons are produced first, then astrocytes. Making too much of one kind of cell and too little of another at a given time could lead to brain malformations. In the October 6 issue of *Cell*, researchers in the Neurobiology Program at Children's Hospital Boston report discovering a new molecular pathway that influences the timing of nerve-cell production.

The pathway—which acts through a novel and unexpected mechanism—inhibits production of astrocytes during the early stages of brain development, thereby favoring the production of neurons. (Astrocytes provide structural and functional support to neurons, but can also regulate their differentiation.) Children's neurobiologist Gabriel Corfas, PhD, senior investigator on the study, says the discovery could have implications for diseases such as Alzheimer's disease, schizophrenia and autism.

One key component of the pathway is a protein called erbB4 that straddles the outer membrane of the neural stem cell. Corfas's team showed that mice lacking erbB4 produced astrocytes earlier in embryonic development than normal. ErbB4 is activated by another protein called neuregulin 1 (NRG1), and then is cut in two by a third critical protein called presenilin, the researchers showed. The half of erbB4 that resides inside the cell—a protein called E4ICD—then joins with other proteins in the cell and travels to the cell nucleus. "Once in the nucleus, E4ICD represses genes that trigger astrocyte production, and thereby inhibits astrocyte formation," explains S. Pablo Sardi, PhD, a postdoctoral fellow at Children's and the study's first author.

Previous studies have found presenilin activity to be altered in Alzheimer's disease, and that erbB4 is abundant around the plaques found in Alzheimer's patients' brains. Taken together, the evidence suggests that presenilin's role in Alzheimer's may have to do, in part, with its effects on erbB4 activity—an effect that was previously unrecognized. ErbB4 signaling also regulates neuronal function and survival, processes that have been implicated in Alzheimer's pathology, the researchers note.

"Our findings raise the intriguing possibility that defects in presenilin-mediated erbB4 signaling could be implicated in the early stages of Alzheimer's disease," Corfas says. "Further studies of erbB4 nuclear signaling could provide important insights into the causes of neurodegeneration."

In addition, the genes for both NRG1 and erbB4 have been linked to schizophrenia. Corfas speculates that premature formation of astrocytes resulting from altered functioning of these genes causes subtle malformations in the brain's circuitry. "Changes in the timing in which different neural cells are produced could lead to alterations in brain wiring," he says. "This would lead to alterations in cognitive function such as those seen in schizophrenia—which is now considered to be a developmental disorder—and potentially in other diseases such as autism."

Source: Children's Hospital Boston