Children's Hospital Boston
Public release date: 9-Mar-2011

Study illuminates role of cerebrospinal fluid in brain stem cell development

CSF holds potential clues to brain tumors

Cerebrospinal fluid (CSF), the fluid found in and around the brain and spinal cord, may play a larger role in the developing brain than previously thought, according to researchers at Children's Hospital Boston. A paper published online March 10th by the journal *Neuron* sheds light on how signals from the CSF help drive neural development. The paper also identifies a CSF protein whose levels are elevated in patients with glioblastoma, a common malignant brain tumor, suggesting a potential link between CSF signaling and brain tumor growth and regulation.

The study, led by senior investigator Christopher Walsh, MD, PhD, chief of the Division of Genetics at Children's, adds to a very small body of literature on the normal physiological roles of CSF in neural development. It harkens back to ancient and medieval thinking about CSF – not the brain itself -- as the locus of the mind.

Walsh and colleagues became aware of the role of the CSF while studying how stem cells in the brain establish polarity -- distinct regions within a cell. All stem cells in the brain contain groups of proteins, known as apical protein complexes, that work together to establish polarity. They also play a role in telling stem cells whether to continue dividing or to become neurons.

The researchers noticed that these apical proteins are expressed on the parts of the stem cell that are in contact with the CSF, and that stem cells actually send tiny protruding processes called cilia, that act almost like antennae, directly into the CSF. They suspected that signals to initiate or curb stem cell growth were coming from the CSF. But how?

They found that two proteins within the apical complex, Pals1 and Pten, were interacting with the Igf1 receptors in the stem cells, relocating the receptors to the boundary between the stem cells and the CSF. This allowed the receptors to be stimulated by the CSF protein Igf2. When Pals1 or Pten were disrupted, the cell's ability to receive signals from the CSF was impaired, and stem cell growth was altered.

"When we deleted Pals1 in mice, we disrupted the normal assembly of the apical complexes, which then led to loss of polarity in the stem cells," said Maria Lehtinen, PhD, in Walsh's laboratory, one of the study's first authors. "This disruption of polarity impaired the stem cells' ability to divide appropriately."

This, in turn, dramatically curtailed brain development. "These mice essentially have no cortex," Lehtinen said.

Pten, they found, has the opposite effect: its disruption caused the creation of too many stem cells, an effect previously associated with tumor formation.

When the Children's team interbred the mutant Pals1-deficient mice with Pten-deficient mice, they were able to reactivate stem cell growth in the brain artificially. "We saw a nearly complete restoration of brain size," said Lehtinen.

The team then focused its attention on the CSF, showing that the Igf2

concentration in CSF regulates the rate of stem-cell proliferation. Moreover, they found that the concentrations of Igf2 and hundreds of other CSF proteins change over time, peaking near birth in rats and mice. The Igf2 peak occurs at the time when the cortex is most actively developing.

The researchers explored these dynamic fluctuations by floating young brains in old CSF and old brains in young CSF.

"We found that the stem cells really behaved according to what CSF they were in," said Walsh. "The CSF is really telling the brain what to do. It's telling the stem cells to either divide a lot if you're in the embryonic brain, or if you're in the adult brain, just rest, and we'll tell you if we need you."

A better understanding of the Igf2 signaling pathway, the stem cell's apical complex proteins that interact with it, and the temporally-driven changes in the CSF could lead to increased understanding of some brain tumors, including glioblastoma.

"It may be that too much Igf2 in the CSF sets up an environment that promotes tumorigenesis, adding to genetic changes in the brain tumor stem cells themselves," said Walsh.

In principle, the CSF is accessible for treatment purposes, so it could potentially be altered to inhibit brain tumorigenesis. This study did not explore direct clinical applications, however.

"One insight we found is that the CSF seems to have all the stuff in it that you need to regulate stem cells – to keep them alive and to tell them whether to proliferate or rest," said Walsh. "That gives us the potential to really understand much more clearly how we want to regulate those stem cells, acting through this medium. Hopefully we can soon get a better understanding of how to control brain stem cells so we can use them for many experimental or therapeutic applications."

###

Mauro W. Zappaterra of Children's Hospital Boston and Harvard Medical School was co-first author of the paper. The study was supported by a Sigrid Jusélius Fellowship, an Ellison/AFAR Postdoctoral Fellowship, grants from the National Institutes of Health, a Stuart H.Q. & Victoria Quan Fellowship, an NIH MSTP grant, the Child Neurology Foundation, the A Reason To Ride research fund, a UNC-CH Reynolds Faculty Fellowship, the Manton Center for Orphan Disease Research, Simons Foundation, the NLM Family Foundation, the Intellectual and Developmental Disabilities Research Centers and the Howard Hughes Medical Institute.

Children's Hospital Boston is home to the world's largest research enterprise based at a pediatric medical center, where its discoveries have benefited both children and adults since 1869. More than 1,100 scientists, including nine members of the National Academy of Sciences, 12 members of the Institute of Medicine and 13 members of the Howard Hughes Medical Institute comprise Children's research community. Founded as a 20-bed hospital for children, Children's Hospital Boston today is a 392-bed comprehensive center for pediatric and adolescent health care grounded in the values of excellence in patient care and sensitivity to the complex needs and diversity of children and families. Children's also is the primary pediatric teaching affiliate of Harvard Medical School. For more information about research and clinical innovation at Children's visit: Vector Blog

http://www.eurekalert.org/pub_releases/2011-03/chb-sir030711.php