Cerebral spinal fluid guides stem cell development in the brain

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Cerebrospinal fluid -- the clear and watery substance that bathes the brain and spinal cord -- is much more important to brain development than previously realized.

Howard Hughes Medical Institute investigator Christopher Walsh, his postdoctoral fellow Maria Lehtinen, former student Mauro Zappaterra, and their colleagues have discovered that cerebrospinal fluid (CSF) contains a complex mix of proteins that changes dramatically with age. In the lab, CSF by itself is enough to support the growth of neural stem cells, and this effect is particularly robust in young brains.

What's more, the protein make-up of CSF in people with malignant brain cancer is different from that of healthy people, the researchers found. "This suggests that the CSF can make a more supportive or less supportive environment for tumor growth," notes Walsh, Chief of Genetics at Children's Hospital Boston. The work is published in the March 10, 2011, issue of the journal *Neuron*.

Centuries ago, philosophers thought spinal fluid held particular importance for health. The French philosopher and mathematician René Descartes, for example, described the brain as a simple hydraulic machine, pumping fluid—pneuma anima, or 'animal spirits'—through the body's nerves like a Parisian water fountain.

"Recent history has not been so kind to CSF," Walsh notes. Today, most researchers think of it as a relatively simple salt solution that gives the brain buoyancy and helps protect it from knocking against the skull.

Several years ago, Walsh's work on brain development led him to suspect that there is much more to the unassuming fluid. He noticed that neural stem cells tend to line up around the brain's inner chambers, where CSF is stored, and stick cellular fingers, called cilia, into the pool of CSF. "That made us think, there's got to be something in CSF that's binding to cilia and controlling how the cell divides," Walsh says.

In 2007, Zappaterra and Walsh performed the first comprehensive analysis of embryonic human CSF. They found it holds hundreds of different proteins that are involved in a variety of tasks, including cell growth, transport, support, and signaling. "We were amazed at the diversity of substances that we identified in there, many of which people had no clue would be there," Walsh says.

In the new study, the researchers took small pieces of embryonic rat brain tissue and, using a thin platinum wire, deftly moved them onto culture plates made up of CSF from rats of different ages. They found that when brain stem cells bathe in CSF from young rats, they furiously divide. In contrast, when grown on CSF from older rats, there is less cell division, but CSF from all ages contains all that is needed to maintain brain stem cells in a dish. Subsequent analysis of the fluid showed that the amount of a protein called Insulin-like growth factor 2 (Igf2) strongly correlates with the level of cell division.

The researchers then teamed up with a group of scientists from Beth Israel Deaconess Medical Center that has a unique collection of CSF samples isolated from people with various stages of glioblastoma, a type of brain cancer in which tumors infiltrate the whole brain. The Beth Israel Deaconess group, led by Eric Wong, found that people with more advanced cancer have higher levels of Igf2 in CSF than do those with less severe forms of the disease.

The scientists don't know whether the increase in Igf2 levels is partly causing the cancer, or is instead a consequence of living with the disease. "We certainly don't think Igf2 is the only contributor to the pathology, because glioblastomas are very complex. But it may be an interesting biomarker to consider," says Maria Lehtinen, who is a joint first author of the study, along with Zappaterra.

Taking a closer look at CSF could be helpful in other brain diseases as well. Some researchers are investigating whether the levels of certain proteins, like Tau and Beta amyloid, might be used as predictors of Alzheimer's disease, for example.

Because CSF is made in the choroid plexus—the tiny knob in the brain's chambers that forms the interface between the bloodstream and the brain—it could explain part of the mystery of how changes in the body link up to the brain. For example, if you exercise a lot, you form more brain cells, but no one knows exactly how this works.

"We sometimes get very spiritual about this," Walsh says, laughing. "It presents mechanisms about how different parts of the body are talking to each other in ways that I hadn't really conceived of before."

Provided by Howard Hughes Medical Institute

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