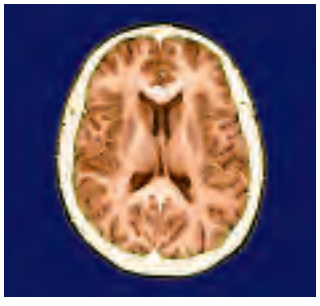
Nourishing Neural Stem Cells

CEREBROSPINAL FLUID DOES MORE THAN PROTECT THE BRAIN.



Cerebrospinal fluid surrounds the brain and fills its central cavities, like those shown here in the darkest brown.

Inside your skull, your brain is floating in a clear liquid. This *liquor cerebrospinalis*, or cerebrospinal fluid (CSF), until recently was considered simply cushioning for the brain. It maintains a constant pressure in the skull, keeps the brain protected when it's jolted, and carries waste away from the vital organ. Now, HHMI investigator Christopher A. Walsh has revealed that CSF does much more—it holds proteins that play irreplaceable roles in controlling brain development, growth, and health.

Walsh and his colleagues at Children's Hospital Boston suspected that CSF has such important roles when they identified, in 2007, hundreds of proteins suspended in the fluid. In their latest work, they looked at how these proteins might affect the brain's neural stem cells—the precursors to brain cells. They took bits of brain tissue from embryonic rats and bathed them in CSF from old and young rats. When exposed to the CSF from young animals, neural stem cells divided quickly. When soaked in older CSF, stem cells divided more slowly, and they more often differentiated into adult brain cells rather than renewing the population of stem cells.

"What we showed for the first time is that CSF's role changes with time," says Walsh.

The research team went on to determine that one particular CSF protein—called insulin-like growth factor 2 (Igf2)—largely controls neural stem cells. Knowing this, the scientists suspected that Igf2 could play a role in glioblastoma, a type of brain tumor in which neural stem cells are misdirected. So, in collaboration with another group, they analyzed a collection of CSF samples taken from glioblastoma patients. Indeed, they reported in *Neuron* on March 10, 2011, that more advanced cases of the cancer are associated with higher levels of Igf2 in the CSF. Whether this is a cause or an effect, they can't yet conclude, but it ushers in a new mindset about CSF.

"This really changes how we think about a lot of things," says Walsh. "The CSF clearly carries many different proteins that have active, and changing, roles in modulating the brain. There may be many other processes—potentially learning or behavioral states—that are modulated by CSF." ■ –SARAH C.P. WILLIAMS

IN BRIEF

Elledge and his colleagues found that when PTPN12 is mutated, deleted, or turned off, the kinases initiate tumor growth.

The good news, says Elledge, is that existing drugs inhibit the activity of many of these kinases, which have also been implicated in some head, lung, pancreatic, and colorectal cancers. The researchers reported in *Cell* on March 4, 2011, that a combination of two of these kinase inhibitors slowed and reversed tumor growth in mice with triple-negative breast cancers. The scientists are working to identify all the kinases affected by changes in PTPN12 and are investigating whether different phosphatases may explain other cases of triple-negative breast cancer.

THE NATURE OF ASYMMETRY

Most of the time when cells divide, their goal is to divide evenly, producing two equal daughter cells. But sometimes, a dividing cell needs to send daughters down different paths. In developing mammalian skin, for example, asymmetric cell divisions of skin stem cells are required to turn a single layer of skin into the many layers that protect an organism. In this process, known as stratification, asymmetric divisions leave one daughter cell in the innermost layer of skin and push the other to an outer layer.

HHMI investigator Elaine Fuchs and her colleagues at the Rockefeller University knew of a regulatory pathway that regulates asymmetric cell divisions in flies and wondered whether this pathway also operates in mice. After they found mouse versions of three proteins in the pathway—LGN, NuMA, and DCTN1—they blocked the RNAs that code for them by using a new technique that allows them to turn off genes when the skin is only a single layer. The skin cells failed to orient correctly and the skin failed to stratify.

Moreover, by blocking the three proteins, the team reported in *Nature* on February 17, 2011, they inhibited part of another developmental pathway, called Notch. Next, the researchers hope to work out the rest of the biochemical pathway involved in asymmetrical cell division and skin stratification.

SHUTTING OFF ANXIETY

Anxiety isn't a hard-wired state of the brain but a continuously adapting condition that can be altered instantaneously, according to new research. The flip of a neural switch can make an anxious mouse more apt to explore its cage, the latest study by HHMI early career scientist Karl Deisseroth shows.

Over the past six years, Deisseroth and his colleagues at Stanford University have pioneered the field of "optogenetics," the use of light to manipulate neuron behavior in the brain. Now, they've used their optogenetic techniques to explore an area of the brain called the basolateral amygdala. But rather than activate all the neurons in this area—which has a broad, and hard to tease apart, effect—the researchers activated only a subset of the neural projections.

They focused on the neurons that connect the basolateral amygdala to a neighboring area called the central amygdala and found that when these neurons are turned on, mice showed fewer signs of anxiety. When the same neurons are shut off, the mice become more nervous. Activating all the cells in the basolateral amygdala, rather than just those leading to the central amygdala, had little effect on anxiety, presumably because the light switch activated pathways that both trigger and stifle anxiety, canceling one another out, says Deisseroth. The results appear in the March 17, 2011, issue of *Nature*.

"Most thinking [in the field] had suggested that anxiety was a very stable state in the brain," he adds. "What we found is that it's really something that's under real-time, continuous control."

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