Scientists find nerve cell activity drains stem cell pool in developing brain

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As babies grow, their brain cells develop from a pool of stem cells—some stem cells continuously divide, replenishing the pool, whereas others morph into mature functioning nerve cells. Now researchers at The Scripps Research Institute have shown that as the newly formed nerve cells start firing electrical signals, this activity slows down stem cell division, emptying out the stem cell pool in favor of nerve cell formation.

The study, published in the November 4 issue of the journal *Neuron*, shows that brain activity controls the balance between stem cells and mature nerve cells and suggests that abnormal brain activity, as it occurs during seizures, may have long-lasting effects on brain development. The results also have implications for replacing brain cells that are damaged or lost through diseases such as Alzheimer's or Parkinson's disease.

"One implication is that to get brain cells to form you need a period in which brain activity is low followed by a period of higher activity," said Scripps Research Professor Hollis Cline, Ph.D., senior author of the study. "Just having high or low brain activity won't have the same outcome."

Nerve Cell Development 101

During development, stem cells give rise to nerve cells in the central nervous system. During the first stages of development, stem cells

divide, each generating two identical daughter stem cells. This process, called proliferation, serves to increase the pool of stem cells. In later stages, stem cell division generates two different types of cells: a daughter stem cell plus a cell that changes into a mature, functioning nerve cell through a process known as differentiation. And once the nervous system approaches the final stages of development, all divisions give rise to nerve cells, leaving only a few stem cells behind.

So how is the switch from mainly stem cell proliferation to mainly nerve cell differentiation controlled in the developing brain?

It is known that in adult brains, brain activity helps new nerve cells form and existing ones survive. That is why older people are often told to keep their brains active by doing crossword puzzles and other exercises. But no one had looked at the connection between brain activity and nerve cell formation in the developing brain.

Activity is the Switch

To look for a possible link, Cline turned to the frog Xenopus laevis. In tadpoles, stem cells in the visual system—the part of the brain that receives and interprets signals from the eyes—continue to proliferate for several days even as brain circuits are starting to form and become functional. The researchers wanted to ask whether the activity by the newly formed circuits had any effect on stem cell proliferation and nerve cell differentiation. "We chose the visual system because we can control the amount of activity in pretty precise ways," noted Cline.

First, Cline and her colleague Research Associate Pranav Sharma, Ph.D., determined that the amount of stem cell proliferation in the visual system decreases as the visual circuits are laid out and become active (from about days 7 to 13 in a tadpole's life). But when the scientists shut off activity in the visual system by keeping some of the tadpoles in

darkness for two days, cell proliferation increased and nerve cell differentiation decreased.

These observations suggest that brain activity regulates both stem cell proliferation and nerve cell differentiation, but in opposite ways. As circuits are laid out during development, their activity influences the fate of cells generated through stem cell division, making them stop dividing and mature into nerve cells.

"We have found that a key reason why proliferation slows down during development is that brain activity turns it off," said Cline.

Identifying a Key Regulator

Cline and Sharma also discovered a protein that may hold the key to how brain activity slows down stem cell proliferation.

During visual system development, as stem cell proliferation decreases, they found that the amount of a protein called Musashi1, which is produced by stem cells, also decreases. On the other hand, the tadpoles kept in the dark for two days, whose visual system was not active, had an increase in both stem cell proliferation and an increase in Musashi1 protein levels in the stem cells.

In a series of experiments, Cline and Sharma either shut down or boosted the production of musashi1 in the tadpoles' stem cells. They showed that, in the absence of Musashi1, stem cell proliferation slows down. On the other hand, boosting the amounts of Musashi1 increases stem cell proliferation, even in the later stages of development.

"We knew that musashi1 was a marker for stem cells but no one knew that it was controlled by brain activity," said Cline. The findings suggest that this protein might be used as a way of expanding the stem cell pool

in developing brains, and possibly even adult brains.

New Avenues for Therapy

The study by Cline and Sharma shows that proliferation and differentiation are regulated differently by brain activity during development. It is not yet known whether these results apply to the adult brain, which contains a small number of stem cells. If they do, however, one implication is that to promote nerve cell formation, both brain activity and inactivity are necessary.

"You might say do a lot of brain exercises, but if you do not include periods of lower activity you will not have an expanded stem cell pool," noted Cline. "You have to keep the pool replenished."

Another question these findings raise is whether abnormal brain activity, as occurs in seizures, has long-lasting effects on developing brains. "Several studies have shown that there are changes in the brain due to seizures but the results are not consistent," she said. "It's possible that abnormal brain activity would affect differentiation or proliferation."

Cline and Sharma plan to pursue these questions in future studies.

More information: For more information on the paper, see www.cell.com/neuron/abstract/S0896-6273(10)00770-1

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