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Astrocytes Trigger Maturation of Neural Stem Cells

Researchers have discovered that astrocytes — brain cells once thought to be little more than a component of the supportive scaffold for neurons — may actually play a starring role in triggering the maturation and proliferation of adult neural stem cells. The studies also suggest that growth factors produced by astrocytes may be critical in regenerating brain or spinal tissue that has been damaged by trauma or disease.

The discovery that astrocytes are important for neuronal maturation, or neurogenesis, was reported in the May 2, 2002, issue of the journal *Nature* by Howard Hughes Medical Institute investigator Charles F. Stevens and colleagues Fred H. Gage and HHMI research associate Hong-jun Song at The Salk Institute.

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— Charles F. Stevens

Neurons are the key information-carrying cells in the central nervous system. All neurons, as well as other types of brain cells, arise from immature neural stem cells, which have the potential to develop into any kind of cell in the central nervous system.

According to Stevens, astrocytes have not traditionally been thought to be involved in neurogenesis. "Astrocytes, so-named because of their starlike shape, are glial cells, a term which is derived from the Latin word for 'glue,'" explained Stevens. "They fill in the space between neurons, and they have long been known to have a supportive role, which includes taking up neurotransmitters released by neurons. They also maintain the extracellular environment with the right concentrations of chemicals to support neurons."

Recently, however, evidence emerged that astrocytes might actually be "instructing" stem cells about which developmental pathway to select, said Stevens. For example, Stevens and his colleagues reported in a previous

research article that adult neuronal stem cells proliferated more readily when they were cultured with astrocytes rather than on a layer of fibroblast cells.

Stevens said that at first it seemed likely that the astrocytes might be keeping the stem cells alive longer or encouraging proliferation. In other words, they might be merely supporting the cells in becoming functional neurons, Stevens said.

"Another possibility was that the astrocytes were somehow actually instructing the stem cells to divide and adopt a neuronal fate," he said. "This seemed least likely because when the embryonic brain is growing, most of the neurons are born before the glia, so one wouldn't have thought glia were instructing stem cells."

To define the astrocytes' contribution to neuronal development, Song, Stevens and Gage tagged adult neural stem cells with a green fluorescent marker so they could follow the development of those cells. When they grew the tagged stem cells in cell culture with both astrocytes and other neurons, the stem cells readily developed into mature neurons. However, when the scientists grew the tagged stem cells in cultures enriched with astrocytes, they found that the astrocytes supported the growth of many more neurons from the stem cells.

A big question, said Stevens, was whether the astrocytes influenced neuronal growth by releasing chemicals or by direct contact with the stem cells. So, the scientists cultured neural stem cells so that they could not touch the astrocytes, or so that the astrocytes were gently killed and could not release regulatory chemicals. The experiments showed that in both cases, the astrocytes triggered stem cell development. This suggests that astrocytes trigger neuronal growth both by releasing chemicals and through a contact-related signal, Stevens said.

Mathematical analysis of the cells in culture revealed that astrocytes encouraged both stem cell proliferation and their maturation into neurons. "We found that stem cells grown on glia divided about twice as fast as they did when grown on fibroblasts," said Stevens. "Glia make a good environment to instruct them to divide.

"But the big surprise was that the stem cells were adopting a neuronal fate at about six times the rate they were on fibroblasts," said Stevens. "The astrocytes either instruct the progenitors to adopt a neuronal fate or form an environment that induces or permits that fate. We're not exactly sure what word to use, because we don't know what the mechanism is," he said.

In additional experiments, the researchers found that adult astrocytes were about half as effective as embryonic astrocytes in promoting neurogenesis in adult neural stem cells.

One intriguing implication of the experiments, said Stevens, is that astrocytes' involvement in neuronal growth regulation might explain why neural stem cells can regenerate neurons in areas of the brain such as the

hippocampus, but not in the spinal cord, where they mature into glial cells.

"It was surprising to us that the stained stem cells from the hippocampus would only produce neurons when grown on glia from the hippocampus, but they hardly made any neurons at all when we grew them on glia from the spinal cord," said Stevens.

"While it is only speculation at this point, it may be that spinal cords fail to regenerate not because the stem cells aren't there, but because there is something missing in their glial cells. Thus, developing spinal cord regeneration therapies might mean supplying some factor produced by glial cells," said Stevens.