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RESEARCH NEWS

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Researchers Discover New Source of Neural Stem Cells in Adult Brain

Researchers have found an unexpected source of stem cells in the adult human brain. They have demonstrated for the first time that human astrocytes—brain cells thought to play more of a secondary role by providing a supportive, nurturing environment for the neuron—can actually function as stem cells. The astrocytes can form new stem cells and are able to generate all three types of mature brain cells.

But these astrocytes are different: They form a novel ribbon-like structure in the brain's lateral ventricle. Stem cells from comparable areas in the rodent brain follow a distinct path from their place of origin to the olfactory bulb (a brain region that processes smells), where they create new neurons.

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> **— Nader Sanai**

The work, led by former HHMI medical student fellow Nader Sanai and Arturo Alvarez-Buylla, Heather and Melanie Muss Professor of Neurological Surgery at the University of California, San Francisco, opens the possibility that such stem cells could be harnessed and one day used to regenerate damaged areas in the central nervous system. The scientists reported their findings February 19, 2004, in the journal *Nature* .

“We've found a structure in the human brain that represents a significant departure from other species,” Sanai said. “The differences we see imply that this region in the human brain doesn't necessarily do the same things as its primate and rodent counterparts. This is a cell population that has the potential to regenerate parts of the brain, though it's not clear what regions those may be. Neurons generated in this area may migrate to other areas of the brain and potentially regenerate those areas.”

With millions of dollars invested in animal models of stem cells, he said, the team's findings might call into question the fidelity of those models in predicting the human brain.

Alvarez-Buylla had previously characterized neural stem cells in the subventricular zone of the adult rodent brain, showing that newly born neurons migrate to the olfactory bulb. Other studies had shown that human brain cells grown in the laboratory could form stem cell colonies.

The researchers wanted to see if a similar organization of stem cells existed in the adult human brain. They expected to find a population of human stem cells lining the lateral human brain ventricles, organized similarly to rodents and generating neurons for the human olfactory bulb.

They studied brain tissue from the lateral ventricles - two cerebrospinal fluid-filled cavities in the center of the brain - available from either surgery patients or from pathology samples after autopsy. The researchers first stained the tissue to locate astrocytes, and immediately saw the ribbon of astrocytes lining the ventricle walls. They subsequently determined that cells within the ribbon were dividing, implying that they were part of a region of proliferative stem cells.

Next, the scientists decided to look for the stem cells. They took representative sections of tissue from the lining of the lateral ventricles, and found that these specimens could generate neurospheres in a dish. Neurospheres contain all of the precursors for the major central nervous system cell types the stem cell produces: neurons, astrocytes, and oligodendrocytes. They result from a stem cell being put in a culture dish with various growth factors.

To make sure, they subsequently isolated individual human astrocytes and put each in a dish with growth factors, showing they could form neurospheres as well.

This was the first time anyone had shown that a single human astrocyte could function as a stem cell. Alvarez-Buylla, Sanai, and their co-workers then found that single astrocytes from the lateral ventricle could generate neurons without added growth factors—direct evidence that a single astrocyte could generate a neuron.

The findings are provocative because astrocytes have traditionally been considered simple helper cells, Sanai said.

“This speaks to the plasticity of the human brain,” he said. “Certain cell types may have hidden potential.” These subtypes of astrocytes appear no different from any other astrocytes, implying that “it's possible that other astrocytes in other regions of the body have the same potential.”

Other work by scientists at the Salk Institute in La Jolla has shown that neurons are generated in the adult human hippocampus, said HHMI investigator Sean Morrison at the University of Michigan. As a result, he said, there's at least the possibility that stem cells in the human subventricular zone “could well be giving rise to new neurons in the adult human brain, at least at a low rate, and the rate of neurogenesis by these stem cells could increase in response to injury.”

Still, the work brings up more questions than it has answered. “We know the cells are dividing, yet it leaves us with the question, what are these cells doing if they are not going to the olfactory bulb?” Alvarez-Buylla said. They now plan to better characterize this region of the human brain and investigate potential relationships between these stem cells and brain tumors.