Discovery of stem cell illuminates human brain evolution, points to therapies

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UCSF scientists have discovered a new stem cell in the developing human brain. The cell produces nerve cells that help form the neocortex - the site of higher cognitive function -- and likely accounts for the dramatic expansion of the region in the lineages that lead to man, the researchers say.

Future studies of these cells are expected to shed light on developmental diseases such as autism and schizophrenia and malformations of brain development, including microcephaly, lissencephaly and neuronal migration disorders, they say, as well as age-related illnesses, such as Alzheimer's disease.

Studies also will allow scientists to track the molecular steps that the cell goes through as it evolves into the nerve cell, or neuron, it produces. This information could then be used to prompt embryonic stem cells to differentiate in the culture dish into neurons for potential use in cell-replacement therapy.

The study is reported in a recent issue of the journal *Nature*, (vol. no. 464, 554-561; issue 7288).

"This discovery has the potential to transform our understanding of the development and evolution of the human neocortex, the most uniquely human part of the central nervous system," says the senior author of the study, neurologist Arnold Kriegstein, MD, PhD, director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research

at UCSF.

"It also should inform our understanding of developmental diseases and advance the creation of cell-based therapies. Many neurological diseases develop in neurons or the neural circuits between them. If we're going to understand how these disorders develop, we have to better understand how the human and primate cerebral cortex develops."

In rodents and humans, the developing cortex contains a layer of neural stem cells called radial glial cells that resides near the fluid-filled ventricles and produces cells that are precursors to neurons. These precursor neurons further proliferate in a region known as the subventricular zone (SVZ), to increase their numbers, and then differentiate into newborn neurons. The neurons then migrate along radial glial fibers up to the neocortex, where they help form the tissue that is the site of sensory perception, motor commands, spatial reasoning, conscious thought and language.

In human and nonhuman primates, however, the SVZ has a massively expanded outer region, known as the outer subventricular zone (OSVZ). About 20 years ago, scientists presumed that the OSVZ also contained stem cells, but until now they have lacked evidence.

In the current study, lead authors David V. Hansen, PhD, a postdoctoral fellow, and Jan H. Lui, a graduate student in the Kriegstein lab, examined the OSVZ, using new labeling and tracking techniques to follow individual cells and their progeny over time in cultured tissue slices from fetal cortex tissue that had been donated for research.

They characterized two kinds of cells within the region -- both the novel neural stem cell and its daughter cell, known as the transit amplifying cell. The stem cell closely resembles the radial glial cell in structure and behavior and, like the radial glia, has radial fibers which newborn

neurons migrate along up to the neocortex.

The region is a busy hub of cell proliferation. The stem cell undergoes asymmetrical cell division, giving rise to two distinct daughter cells -- one a copy of the original stem cell, the other a transit amplifying cell. The transit amplifying cell undergoes multiple rounds of symmetrical divisions before all of its daughter cells begin the process of differentiating into neurons.

"We are very interested in understanding how these modes of division are regulated," says Kriegstein. "We suspect that faults in cell-cycle regulation account for a variety of developmental brain diseases."

More broadly, he says the team wants to understand how the new stem cells compare to radial glial cells and how the two sets of neurons they produce integrate in the neocortex. "Neurons are probably being generated in both the SVZ and OSVZ at once," he says. "They likely end up in the same layer of the neocortex as they migrate into position and start forming circuits.

"This suggests to us that there may be a mosaic of cell types in the human neocortex, in which there are cells that originate in the traditional zone and cells produced in the newer zone that intermix in the cortex. The complexity of primate neocortex may be significantly increased by the interaction of the evolutionarily-speaking 'younger' neurons with those originating in the more primitive zone."

The massive number of cells within the OSVZ of humans "tells us we have to be careful when modeling human brain diseases in mice," says Kriegstein. "Especially in the neocortex -- the most highly developed part of the brain in primates and humans - there are going to be important differences between rodents and humans."

More information: Nature paper: www.nature.com/nature/journal/ … ull/nature08845.html

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