Investigators discover a new hot spot for the genesis of signaling neurons in the adult brain

September 9 2010

In an unanticipated finding, researchers at the UC Davis School of Medicine have discovered that, during early adulthood, the brain produces new excitatory neurons, and that these neurons arise from non-neuronal support cells in an area of the brain that processes smell.

The study, conducted in mice, is the first to demonstrate that pyramidal neurons in the mature brain stem are generated by precursors of glial cells — non-neuronal support cells — and that these new neurons likely are capable of transmitting information to widespread regions of the brain, said David Pleasure, a professor of neurology and pediatrics at the UC Davis School of Medicine and the study's author.

"Pyramidal Neurons are Generated from Oligodendroglial Progenitor Cells in Adult Piriform Cortex," is published online this week in the *Journal of Neuroscience*.

"We used to think that the sole destiny of oligodendroglial progenitor cells was to become myelin-forming oligodendroglia," Pleasure said. "Later it was shown that they also can generate other kinds of glial cells as well. We now have demonstrated that these oligodendroglial progenitor cells, which are widely distributed in the brain, and persist throughout life, also give rise to a group of large cerebral cortical neurons. Thus, oligodendroglial progenitor cells are truly multipotent."

The researchers found that precursors of glial cells, called proteolipid promoter-expressing NG2 progenitors (PPEPs, pronounced Pee-peps), give rise to glutamatergic pyramidal neurons, an important type of brain cell that sends long-range excitatory signals. PPEPs belong to a class of glial precursor cells called oligodendroglial progenitor cells (OPCs). These cells have been discovered only recently, and they hold tremendous promise for stem-cell regenerative medicine. They are the largest proliferating population of cells in the mammalian brain and spinal cord, and they could replace or repair injured cells.

"This study shows very definitively that PPEPs generate new neurons, that these new neurons have all the morphological and structural features which suggest that they are functionally integrated into the existing circuitry," said Fuzheng Guo, the study's lead author and a postdoctoral fellow in the Department of Neurology in the UC Davis School of Medicine.

"For the past two decades, we have known that there are two small regions that continue to give rise to newborn neurons," said study co-author Joyce Ma, a student at the UC Davis School of Medicine and doctoral candidate in neuroscience. "The new neurons in those known regions are small interneurons or small granule neurons that modulate existing circuitry or relay signals generated by other neurons, respectively. Unlike these neurons, the new pyramidal neurons are likely the main players in processing and integrating olfactory memories."

The study identified the new pyramidal neurons in a part of the brain not typically associated with neurogenesis, the piriform cortex. The piriform cortex receives not only olfactory information, but also inputs from regions of the brain that are involved in emotion regulation and memory formation. Because of its privileged access to diverse brain regions, the piriform cortex is capable of tying odor representations to other types of information that are important for a wide range of behaviors. In animals

and humans, activation in the piriform cortex is linked to odor memory and the emotional qualities of odors. In rodents, activity in this region is related to sexual behavior.

Earlier studies have found that precursors to neural cells can give rise to neurons in two mature brain regions: the subventricular zone and the subgranular zone in the hippocampus, a structure crucial for memory formation. The new neurons in those regions were only capable of influencing neuronal activity within localized areas of the brain rather than sending far-reaching signals, said Pleasure, who also is the research director at Shriners Hospitals for Children - Northern California and the director of the UC Davis-Shriners Institute for Pediatric Regenerative Cures.

The current study follows findings published in 2009 that PPEPs in the immature mouse brain generate neurons in multiple regions, including the hippocampus and piriform cortex, and that these neurons survive into adulthood. They also found that PPEPs produced GABA-ergic interneurons in the immature brain. Prior to that study, scientists had assumed that the general class of glial precursor cells, called oligodendroglial progenitor cells (OPCs), could produce only glial cells, which create insulating sheets that wrap around neuronal projections and ensure speedy and reliable signal transmission. Instead, their results showed that these cells generate all three major cell types in the brain and spinal cord.

"Whether or not OPCs could form new neurons was not at all clear until our prior study," Pleasure said.

The researchers focused on the piriform cortex in the current study because it was found to be a "hot spot" for PPEPs in the earlier study. The study was conducted using a genetic fate-mapping technique to track the lineage, or cell fates, of OPCs in the young adult brains of

genetically-engineered mice. These cells and their progeny glow fluorescent yellow after being injected with the drug tamoxifen. The scientists then extracted tissue samples from their piriform cortex and analyzed the data using a confocal microscope at different time points for six months.

Their initial results, which led to the current findings, suggested that neurons could derive from OPCs. The team found that almost all PPEPs expressed high levels of a marker for neuronal progenitor cells called Sox2, and cells which expressed low levels of a marker for immature neurons also expressed markers for OPCs. Additionally, the study authors found that PPEPs expressed markers for precursors of glutamatergic neurons, those that transmit excitatory signals throughout the brain. To their surprise, the authors found that large, excitatory pyramidal neurons were generated from PPEPs in young adult mice.

"We didn't expect that PPEPs would create signaling neurons this late in life," Ma said.

After 17 days, OPCs began showing markers for mature neurons in piriform cortex. Additionally, cells derived from OPCs showed characteristic features of neurons, such branches called dendrites and axons. And the size of the dendrites continued to increase between one and five months after tamoxifen treatment. The team identified these cells as glutamatergic pyramidal neurons because of their distinct shape and size, as well as their characteristic surface proteins and internally expressed enzymes.

The neurons arose from PPEPs within the piriform cortex rather than neural stem cells in the subventricular zone, another hot spot for neurogenesis. The researchers did not detect the fluorescent marker for OPCs in neural stem cells from the subventricular zone.

Taken together, the results suggest that PPEPs continued to generate mature neurons during young adulthood. The number of OPC-derived neurons gradually increased by 20-fold for the duration of the experiment. After six months, about 6 percent of OPCs became mature neurons, and were concentrated in the layer of piriform cortex that receives incoming signals from a brain structure responsible for distinguishing odors. The authors estimate that the OPCs generated about 10 new neurons per day in the piriform cortex.

Several lines of evidence suggest that the new cells became integrated into existing neuronal networks. The neurons survived up to 300 days, and their branches were found next to proteins that mark junctions between neurons. They also expressed genes that characterize neurons that function in circuits.

"The study opens up many questions," Pleasure said. "The next big question is, 'What are these neurons doing?'"

Because piriform cortex receives olfactory input and interacts with the hippocampus, the authors speculate that the neurons contribute to the formation of new odor memories, particularly those with emotional meaning. The researchers currently are recording electrical activity from the cells to elucidate their functional role in the young adult brain. They also are investigating whether other classes of OPCs form new neurons in later stages of the adult lifespan and genetically modifying OPCs to identify factors important for their differentiation. In addition, they plan to test the regenerative potential of OPCs in animal models of neurological injury and disease, such as multiple sclerosis and Parkinson's and Alzheimer's diseases.

Provided by University of California - Davis