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Neuroscientists find brain stem cells that may be responsible for higher functions, bigger brains

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Scientists from The Scripps Research Institute have identified a new stem cell population that may be responsible for giving birth to the neurons responsible for higher thinking. The finding also paves the way for scientists to produce these neurons in culture—a first step in developing better treatments for cognitive disorders, such as schizophrenia and autism, which result from disrupted connections among these brain cells.

Published in the August 10, 2012 issue of the journal *Science*, the new research reveals how neurons in the uppermost layers of the cerebral cortex form during embryonic brain development.

"The cerebral cortex is the seat of higher brain function, where information gets integrated and where we form memories and consciousness," said the study's senior author Ulrich Mueller, a professor and director of the Dorris Neuroscience Center at Scripps Research. "If we want to understand who we are, we need to understand this area where everything comes together and forms our impression of the world."

In the new study, Mueller's team identified a neural stem cell in mice that specifically gives rise to the neurons that make up the upper layers of the cerebral cortex. Previously, it was thought that all cortical neurons—those making up both the lower and upper layers—came from

the same type of stem cell, called a radial glial cell, or RGC. A neuron's fate was thought to be determined by the timing of its birth date. The Scripps Research team, however, showed that there is a distinct stem cell progenitor that gives rise to upper layer neurons, regardless of birth date or place.

"Advanced functions like consciousness, thought, and creativity require a lot of different neuronal cell types and a central question has been how all this diversity is produced in the cortex," said Santos Franco, a senior research associate in Mueller's laboratory and first author of the paper. "Our study shows this diversity already exists in the progenitor cells."

Peeling Back the Onion Layers

In mammals, the cortex is made up of six distinct anatomic layers holding different types of excitatory neurons. They are not the uniform layers of a cake, but rather, they are more like the layers wrapped around an onion. The smaller lower layers, on the inside, host neurons that connect to the brain stem and spinal cord to help regulate essential functions such as breathing and movement. The larger upper layers, closer to the outer surface of the brain, contain neurons that integrate information coming in from the senses and connect across the two halves of the brain.

The upper layers are a "relatively young invention," evolutionarily speaking, having been greatly expanded during primate evolution, said Mueller. They give humans in particular the unique abilities to think abstractly, plan for the future and problem-solve.

For the last two decades, scientists have believed that the fate of cerebral cortex neurons was determined by their birth date because each layer is formed in a time-dependent manner. The lower layer neurons form in the center of the "ball" first, and then the cells that will become the

upper layers form last, migrating through the lower layers.

"So the model was that there is a stem cell in the center of the ball that generates the different types of neurons in successive waves," said Mueller. "What we now show is that there are at least two different populations of RGCs and potentially more."

Following Fate

Franco first created a line of mice in which he could track upper-layer neurons as they were born and migrated. The team followed a marker gene called Cux2, which was previously reported to be expressed only by upper-layer neurons. By linking a gene for an enzyme called Cre to the Cux2 gene, the scientists could watch any cell expressing Cux2 under the microscope, because the Cre enzyme flips on another gene that glows fluorescent red.

Surprisingly, the team observed Cux2 already turned on in some of the RGCs, even at the earliest points in brain development—embryonic day nine or ten—before any upper-layer neurons exist. Following this population of glowing stem cells through development, the team showed that the cells almost exclusively generated upper-layer neurons. In contrast, the subgroup of RGCs not expressing Cux2 became lower-layer neurons.

Next, the team removed these Cux2-positive precursor cells from their niche in the embryonic brain to see how they would develop in a lab dish. When they cultured both types of RGCs, again only Cux2-expressing RGCs developed into upper-layer neurons.

In developing brains, these Cux2-positive stem cells first self-renew and proliferate before differentiating later into neurons. So, the team wanted to know if a neuron's birth date determined its fate. To test this, the

researchers delivered a TCF4 molecule in utero that forced the Cux2-positive RGCs to prematurely differentiate. Even though it was too early in normal development, the Cux2-positive RGCs still produced upper-layer neurons.

In other words, regardless of position or timing, the Cux2-positive RGCs are destined to become upper-layer neurons. Mueller and colleagues concluded that these stem cells have some intrinsic property that determines their fate from the start.

The work also shows that this RGC subset is responsible for the huge proliferation of cells necessary to create the larger upper-layer cortex found in primate brains. "If we want to understand how the human brain evolved, how we are different from an amphibian, then this one precursor cell may have been important," said Mueller.

But, bigger brains came with a risk, making humans more prone to disorders when upper-layer neurons don't form connections properly. Up until now, researchers trying to reproduce human cortical neurons in the lab from stem cells have only generated lower-layer-type neurons. "This opens a door now to try to make the upper-layer neurons, which are frequently affected in psychiatric disorders," said Mueller.

More information: "Fate-restricted neural progenitors in the mammalian cerebral cortex," *Science*, August 10, 2012.

Provided by Scripps Research Institute

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