Newborn brain cells modulate learning and memory

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Boosted by physical and mental exercise, neural stem cells continue to sprout new neurons throughout life, but the exact function of these newcomers has been the topic of much debate. Removing a genetic master switch that maintains neural stem cells in their proliferative state finally gave researchers at the Salk Institute for Biological Studies some definitive answers.

Without adult neurogenesis — literally the “birth of neurons” —genetically engineered mice turned into “slow learners” that had trouble navigating a water maze and remembering the location of a submerged platform, the Salk investigators report in the Jan. 30 Advance Online Edition of *Nature*. The findings suggest that, one day, researchers might be able to stimulate neurogenesis with orally active drugs to influence memory function, the researchers say.

“Our study directly establishes that neurogenesis plays an important role in a defined process, the acquisition and storage of spatial memory,” says Howard Hughes Medical Investigator Ronald M. Evans, Ph.D., a professor in the Salk Institute’s Gene Expression Laboratory, who, together with his Salk colleague Fred H. Gage, Ph.D., a professor in the Laboratory of Genetics, directed the study.

“This finding puts us in a new and important position to exploit the potential of stem cell-based therapies to improve brain function in neurodegenerative diseases such as Alzheimer’s that are accompanied by a loss of memory,” Evans says.

In an earlier collaboration, Evans and Gage had discovered that TLX, a so-called orphan receptor is crucial for maintaining adult neural stem cell in an undifferentiated, proliferative state. Orphan receptors are structurally related to the well-known hormone receptors that mediate steroid and thyroid signaling. In contrast, a TLX regulatory molecule has not yet been identified.

Now, the Salk team wanted to learn more about TLX's biology and function. However, the global deletion of TLX leads to a variety of developmental problems, so postdoctoral fellow and first author Chun-Li Zhang, Ph.D., had to devise a strategy that would allow them to control when to shut off the gene coding for TLX in neural stem cells kept in Petri dishes as well as in live animals. When he cultured mouse neural stem cells without the gene encoding TLX, the proliferation rate of these cells plummeted and the activity of hundreds of genes changed.

Explains Zhang, "This experiment confirmed that TLX specifically induces the genetic program necessary for maintaining neural stem cells in their stem-like state," handing the Salk researchers the perfect tool to track the contribution of newborn neurons to normal brain function — a question Gage is particularly interested in.

"In the past, methods to knock out neurogenesis, such as radiation and mitotic inhibitors that block all cell division have been rather crude," he says. "So, maybe not surprisingly the literature is riddled with contradictory results."

Adult neural stem cells continually generate new brain cells or neurons in two small areas of mammalian brains: the olfactory bulb, which processes odors, and the central part of the hippocampus, which is involved in the formation of memories and learning. Some of these newborn cells die shortly after they are born but many of them become functionally integrated into the surrounding brain tissue. Whether they

live or die is regulated by the animals' experience.

Combining mouse genetics and gene transfer techniques, Zhang genetically engineered mice that allowed him to specifically delete TLX in the brains of adult mice and thus shut down neurogenesis. He then put the mice through a battery of standard behavioral tests.

The mice passed with flying colors in all but one test: the Morris water maze, a common behavioral test in which mice have to rely on visual cues on the surrounding walls to find and remember the location of a submerged platform hidden in a pool of milky water. This task draws on many cognitive abilities, including analytical skills, learning and memory, and the ability to form strategies.

The more challenging Zhang made the test, the more difficult the altered mice found it to navigate the maze and remember the location of the platform. "The mice showed both learning and memory deficits," he says. "It's not that they didn't learn, they were just slower at learning the task and didn't retain as much as their normal counterparts," observes Zhang.

"Whatever these new neurons are doing it is not controlling whether or not these animals learn," explains Gage. "But these new cells are regulating the efficiency and the strategy that they using to solve the problem."

Source: Salk Institute