# Study shows gene's role in developing and maintaining cells key for a lifetime of memories

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St. Jude Children's Research Hospital investigators showed a gene named Prox1 is a key player in normal development of a brain structure crucial for learning and memory and remains active throughout life, nurturing the cells vital for making new memories.

This study focused on a small region of the hippocampus known as the dentate gyrus, a brain structure needed for memory and learning that is home to the subgranular zone where the neural stem cells destined to become granule cells are housed. The dentate gyrus is one of two regions of the adult brain where neural stem cells continue to produce the precursor cells that ultimately differentiate into neurons.

Although investigators knew Prox1 was expressed during development of the dentate gyrus, this is the first report detailing the gene's function in this region of the brain. Prox1 is a transcription factor that functions like an on-off switch for genes.

Researchers showed that by removing Prox1 at different stages of mouse development, the dentate gyrus fails to develop properly. Investigators also demonstrated that Prox1 remains important throughout mammalian life to ensure production of new granule cells, which are needed to form new memories. The work appears in the August 17 edition of *PloS Biology*.

The findings raise the possibility that subtle mutations in Prox1 might be linked to memory and learning problems, said the paper's senior author Guillermo Oliver, Ph.D., member of the St. Jude Department of Genetics. "The more we understand about how signaling pathways work in the brain, the more we will eventually be able to manipulate the system to promote or block the differentiation process," he said.

Although this is the first detailed report of the role Prox1 plays in normal brain development, earlier studies suggest the gene is central to normal development in a wide range of organs and cell types. Prox1 also plays a role in several types of cancers.

In this study, investigators determined that in the adult mammalian brain, Prox1 is active during a particular stage of differentiation when neural stem cells change from cells of unlimited potential to more specialized granule cells. The scientists reported that in the dentate gyrus Prox1 is produced by intermediate progenitor cells and that the lack of Prox1 results in death of these intermediate cells. Without these intermediate progenitor cells, new adult granule cells do not develop.

Researchers also linked Prox1 to a feedback mechanism that signals stem cells to stop differentiating. "When we switched off the expression of the Prox1 gene in mice and the intermediate progenitor cells disappeared, the adult neural stem cells continued differentiating into granule cells until the supply of stem cells was exhausted. When we switched on Prox1 in these adult neural stem cells, we observed a similar depletion of stem cells caused by their premature differentiation," Oliver said. Investigators are still studying the signaling pathways involved.

The paper's first author, Alfonso Lavado, Ph.D., a postdoctoral fellow in Oliver's laboratory, added: "It was surprising to find out that the loss of Prox1 in intermediate progenitors impacted neural stem cells. Without the intermediate progenitors, their mother cells, the neural stem cells,

also disappear. That shows the progeny is somehow needed to maintain the mother cells when new neuronal cells develop."

These findings indicate that during dentate gyrus development and adult neurogenesis, Prox1 is necessary for the differentiation of granule cells and reveals a regulatory mechanism that links the production of the proper number of new granule cells to the maintenance of adult stem cells.

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