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'Housekeeping' mechanism for brain stem cells discovered

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Researchers at Columbia University Medical Center (CUMC) have identified a molecular pathway that controls the retention and release of the brain's stem cells. The discovery offers new insights into normal and abnormal neurologic development and could eventually lead to regenerative therapies for neurologic disease and injury. The findings, from a collaborative effort of the laboratories of Drs. Anna Lasorella and Antonio Iavarone, were published in the online edition of *Nature Cell Biology*.

The research builds on recent studies, which showed that stem cells reside in specialized niches, or microenvironments, that support and maintain them.

"From this research, we knew that when stem cells detach from their niche, they lose their identity as stem cells and begin to differentiate into specific cell types," said co-senior author Antonio Iavarone, MD, professor of Pathology and Neurology at CUMC.

"However, the pathways that regulate the interaction of stem cells with their niche were obscure," said co-senior author Anna Lasorella, MD, associate professor of Pathology and Pediatrics at CUMC and a member of the Columbia Stem Cell Initiative.

In the brain, the stem cell niche is located in an area adjacent to the ventricles, the fluid-filled spaces within the brain. Neural stem cells (NSCs) within the niche are carefully regulated, so that enough cells are

released to populate specific brain areas, while a sufficient supply is kept in reserve.

In previous studies, Drs. Iavarone and Lasorella focused on molecules called Id (inhibitor of differentiation) proteins, which regulate various stem cell properties. They undertook the present study to determine how Id proteins maintain stem cell identity.

The team developed a genetically altered strain of mice in which Id proteins were silenced, or knocked down, in NSCs. In the absence of Id proteins, mice died within 24 hours of birth. Their brains showed markedly lowered NSC proliferative capacity, and their stem cell populations were reduced.

Studies of NSCs from this strain of mice revealed that Id proteins directly regulate the production of a protein called Rap1GAP, which in turn controls Rap1, one of the master regulators of cell adhesion. The researchers found that the Id-Rap1GAP-Rap1 pathway is critical for the adhesion of NSCs to their niche and for NSC maintenance. "There may be other pathways involved, but we believe this is the key pathway," said Dr. Iavarone. "There is good reason to believe that it operates in other kinds of stem cells, and our labs are investigating this question now."

"This is a new idea," added Dr. Lasorella. "Before this study, the prevailing wisdom was that NSCs are regulated by the niche components, conceivably through the release of chemical attractants such as cytokines. However, our findings suggest that stem cell identity relies on this mechanism."

More research needs to be done before the findings can be applied therapeutically, Dr. Iavarone said. "Multiple studies show that NSCs respond to insults such as ischemic stroke or neurodegenerative diseases. If we can understand how to manipulate the pathways that determine

stem cell fate, in the future we may be able to control NSC properties for therapeutic purposes."

"Another aspect," added Dr. Lasorella, "is to determine whether Id proteins also maintain stem cell properties in cancer stem cells in the brain. In fact, normal stem cells and cancer stem cells share properties and functions. Since cancer stem cells are difficult to treat, identifying these pathways may lead to more effective therapies for malignant brain tumors."

Stephen G. Emerson, MD, PhD, director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, added that, "Understanding the pathway that allows stem cells to develop into mature cells could eventually lead to more effective, less toxic cancer treatments. This beautiful study opens up a wholly unanticipated way to think about treating brain tumors."

Provided by Columbia University Medical Center