Pediatric tumors traced to stem cells in developing brain

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Stem cells that come from a specific part of the developing brain help fuel the growth of brain tumors caused by an inherited condition, researchers at Washington University School of Medicine in St. Louis report.

Scientists showed in mice that disabling a gene linked to a common pediatric tumor disorder, neurofibromatosis type 1 (NF1), made stem cells from one part of the brain proliferate rapidly. But the same genetic deficit had no effect on stem cells from another brain region.

The results can be explained by differences in the way stem cells from these regions of the brain respond to cancer-causing genetic changes.

NF1 is among the world's most common genetic disorders, occurring in about one of every 3,000 births. It causes a wide range of symptoms, including brain tumors, learning disabilities and attention deficits.

Brain tumors in children with NF1 typically arise in the optic nerve and do not necessarily require treatment. If optic gliomas keep growing, though, they can threaten the child's vision. By learning more about the many factors that contribute to NF1 tumor formation, scientists hope to develop more effective treatments.

"To improve therapy, we need to develop better ways to identify and group tumors based not just on the way they look under the microscope, but also on innate properties of their stem cell progenitors," says David

H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology.

The study appears July 9 in *Cancer Cell*. Gutmann also is the director of the Washington University Neurofibromatosis Center.

In the new study, researchers compared brain stem cells from two primary sources: the third ventricle, located in the midbrain, and the nearby lateral ventricles. Before birth and for a time afterward, both of these areas in the brain are lined with growing stem cells.

First author Da Yong Lee, PhD, a postdoctoral research associate, showed that the cells lining both ventricles are true stem cells capable of becoming nerve and support cells (glia) in the brain. Next, she conducted a detailed analysis of gene expression in both stem cell types.

"There are night-and-day differences between these two groups of stem cells," Gutmann says. "These results show that stem cells are not the same everywhere in the brain, which has real consequences for human neurologic disease."

The third ventricle is close to the optic chiasm, the point where the optic nerves cross and optic gliomas develop in NF1 patients. Lee and Gutmann postulated that stem cells from this ventricle might be the source of progenitor cells that can become gliomas in children with NF1.

To test the theory, they disabled the Nf1 gene in neural stem cells from the third and lateral ventricles in the mice. This same gene is mutated in patients with NF1, increasing their risk of developing tumors.

Lee found that loss of Nf1 activity had little effect on stem cells from the lateral ventricle, but stem cells from the third ventricle began to divide rapidly, a change that puts them closer to becoming tumors.

The third ventricle usually stops supplying stem cells to the brain shortly after birth. When researchers inactivated the Nf1 gene before the third ventricle closed, the mice developed optic gliomas. When they waited until the third ventricle had closed to inactivate the Nf1 gene, gliomas did not develop.

Gutmann plans further studies to determine whether all NF1-related optic gliomas form in cells descended from the third ventricle. He suspects that additional factors are necessary for optic gliomas to form in cooperation with Nf1 gene loss in third-ventricle stem cells.

"We have to recognize that cancers which appear very similar actually represent a collection of quite different diseases," he says. "Tumors are like us — they're defined by where they live, what their families are like, the traumas they experience growing up, and a variety of other factors. If we can better understand the interplay of these factors, we'll be able to develop treatments that are much more likely to succeed, because they'll target what is unique about a specific patient's tumor."

Provided by Washington University School of Medicine