Study offers clues to cause of kids' brain tumors

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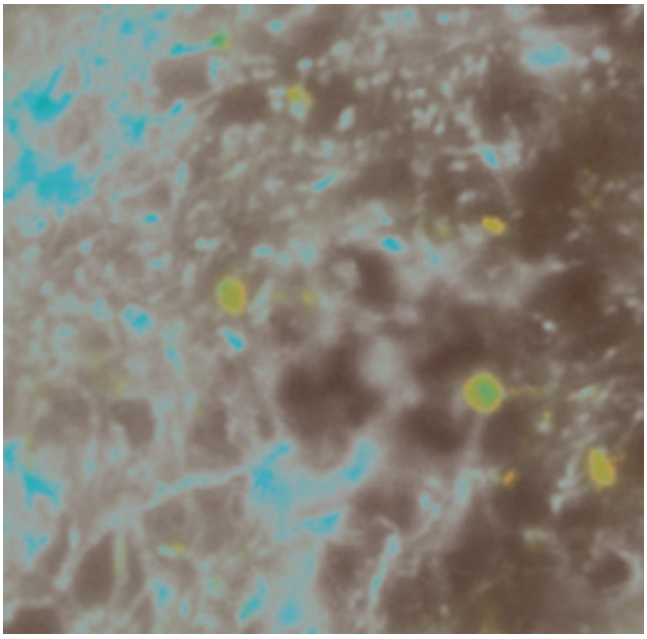

An abnormal version of the BRAF protein (shown in red) from a mouse brain with a low-grade brain tumor. Scientists have shown that in certain cells, this protein can cause the cells to proliferate rapidly, leading to tumor formation. Credit: David Gutmann, MD, PhD

(Medical Xpress)—Insights from a genetic condition that causes brain cancer are helping scientists better understand the most common type of brain tumor in children.

In new research, scientists at Washington University School of Medicine

in St. Louis have identified a cell growth pathway that is unusually active in pediatric brain tumors known as gliomas. They previously identified the same growth pathway as a critical contributor to brain tumor formation and growth in neurofibromatosis-1 (NF1), an inherited cancer predisposition syndrome.

"This suggests that the tools we've been developing to diagnose and treat NF1 may also be helpful for sporadic brain tumors," says senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology.

The findings appear Dec. 1 in Genes and Development.

NF1 is among the most common tumor predisposition syndromes, but it accounts for only about 15 percent of pediatric low-grade gliomas known as pilocytic astrocytomas. The majority of these brain tumors occur sporadically in people without NF1.

Earlier research showed that most sporadic pilocytic astrocytomas possess an abnormal form of a signaling protein known as BRAF. In tumor cells, a piece of another protein is erroneously fused to the business end of BRAF.

Scientists suspected that the odd protein fusion spurred cells to grow and divide more often, leading to tumors. However, when they gave mice the same aberrant form of BRAF, they observed a variety of results. Sometimes gliomas formed, but in other cases, there was no discernible effect or a brief period of increased growth and cell division. In other studies, the cells grew old and died prematurely.

Gutmann, director of the Washington University Neurofibromatosis Center, previously showed that mouse NF1-associated gliomas arise from certain brain cells.

According to Gutmann, the impact of abnormal NF1 gene function on particular cell types helps explain why gliomas are most often found in the optic nerves and brainstem of children with NF1—these areas are where the susceptible cell types reside.

With that in mind, Gutmann and his colleagues tested the effects of the unusual fusion BRAF protein in neural stem cells from the cerebellum, where sporadic pilocytic astrocytomas often form, and in cells from the cortex, where the tumors almost never develop.

"Abnormal BRAF only results in increased growth when it is placed in neural stem cells from the cerebellum, but not the cortex," Gutmann says. "We also found that putting fusion BRAF into mature glial cells from the cerebellum had no effect."

When fusion BRAF causes increased cell proliferation, postdoctoral fellows Aparna Kaul, PhD and Yi-Hsien Chen, PhD, showed that it activates the same cellular growth pathway, called mammalian target of rapamycin (mTOR), that is normally also controlled by the NF1 protein. An extensive body of research into the mTOR pathway already exists, including potential treatments to suppress its function in other forms of cancer.

"We may be able to leverage these insights and our previous work in NF1 to improve the treatment of these common pediatric brain tumors, and that's very exciting," Gutmann says.

Gutmann and his colleagues are now working to identify more of the factors that make particular brain cells vulnerable to the tumor-promoting effects of the NF1 gene mutation and fusion BRAF. They are also developing animal models of sporadic pilocytic astrocytoma for drug discovery and testing.

More information: Kaul, A. et al., Pediatric glioma-associated KIAA1549:BRAF expression regulates neuroglial cell growth in a cell type-specific and mTOR-dependent manner. *Genes & Development*, Dec. 1, 2012.

Provided by Washington University School of Medicine in St. Louis