Researchers identify possible approach to block medulloblastoma growth

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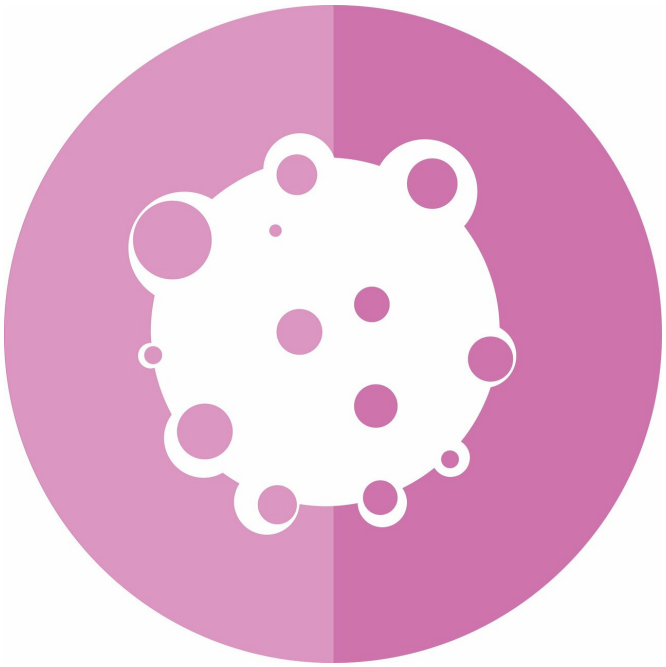

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University of North Carolina Lineberger Comprehensive Cancer Center researchers have identified a potential approach to stop the growth of the most common type of brain tumor in children.

UNC Lineberger's Timothy Gerson, MD, Ph.D., and colleagues reported in the journal *Development* that by blocking a signal called GSK-3, they could control tumor growth in a subtype of medulloblastoma. Their preclinical findings may provide clues to a possible new targeted treatment strategy.

"This work could lead to new insights into developmental brain malformations and also to new treatments for medulloblastoma that may spare the severe side effects of radiation and typical chemotherapy," said Gerson, who is an associate professor in the UNC School of Medicine Department of Neurology.

While as many as 80 percent of children with medulloblastoma survive long-term with radiation and chemotherapy, researchers said there is a need to improve therapies in order to limit debilitating side effects from those treatments, as well as to develop treatments that work for children whose cancer don't respond to treatment.

"For one of the more common subtypes of medulloblastoma, we found we can target a signaling pathway to block tumor growth," said Jennifer Ocasio, Ph.D., the study's first author and a former graduate student in the UNC School of Medicine Neuroscience Curriculum. "By targeting this pathway, we think this would be a way to sidestep effects of radiation and chemotherapy that have a lot of side effects because we are blocking growth rather than killing these cells."

In laboratory studies using mice and cells, the researchers focused on a tumor subtype that accounts for about one-third of medulloblastoma cases. In this type of brain tumor, the Sonic Hedgehog cellular signal helps trigger a series of signals in developing brain cells that lead to an overgrowth of neurons in the cerebellum, which controls balance, speech and other activities.

When researchers used genetic engineering to remove GSK-3 before tumors form in laboratory models of medulloblastoma, they discovered upregulation of other signals, including an important one called WNT that instructed the cells that form tumors to stop dividing. The result was that by genetically inactivating GSK-3 in mice, they could prevent tumor growth. Then they tested a drug called CHIR98 that also blocks GSK-3, and found that it stops tumor cells from growing.

The researchers said their findings were surprising because other studies have shown that blocking

GSK-3 actually stimulates growth in other parts of the brain. They cautioned while this treatment might be promising for a specific subtype of medulloblastoma, it could drive growth in other brain cancers, including other medulloblastoma subtypes.

"In other areas of the brain, parts of this signaling pathway are important to promoting growth," said Ocasio, who is now a postdoctoral fellow at St. Jude Children's Research Hospital. "We think this has to do with the cell types in medulloblastoma; progenitor cells are not exactly the same. These cells in the cerebellum have different regulators than cells in the forebrain, and they respond differently to the same signals."

Researchers have already begun work to evaluate this treatment type further in laboratory models. Ultimately, Gershon said their goal is to find therapies to increase survival rates for medulloblastoma, and to make therapy less toxic.

"While we can now allow most patients with medulloblastoma to survive long-term, almost everybody comes through treatment changed. Our goal would be to find ways to treat the disease that would provide fewer side effects," he said.

More information: Jennifer K. Ocasio et al, GSK-3 modulates SHH-driven proliferation in postnatal cerebellar neurogenesis and medulloblastoma, *Development* (2019). DOI: 10.1242/dev.177550

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