Targeting stem-like cells shrinks medulloblastoma tumors in preclinical study

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Graphical abstract. Credit: Cell (2024). DOI: 10.1016/j.cell.2024.06.011

A team of researchers at Baylor College of Medicine, Texas Children's Hospital, the Hospital for Sick Children in Toronto and collaborating institutions has identified and located a population of stem-like cells that
initiates and maintains Group 3 medulloblastoma (Gr3-MB) in the developing brain. Gr3-MB is one of the most aggressive forms of brain cancer in children and is associated with metastatic spread and poor survival.

The researchers showed that eliminating the small population of stem-like cells present in Gr3-MB tumors led to tumor shrinkage in preclinical models. Although more research is needed, this novel approach may lead to new ways to treat children with Gr3-MB. The study appears in *Cell*.

"We believe that as Gr3-MB develops, it retains characteristics present in embryonic development, resulting in rapid tumor growth," said corresponding author Dr. Michael D. Taylor, professor of pediatrics, hematology—oncology and neurosurgery at Baylor and Texas Children’s. He also is the Cyvia and Melvyn Wolff Chair of Pediatric Neuro-Oncology at Texas Children's Cancer and Hematology Center.

"Our goal was to identify embryonic cells that would give rise to tumors, as well as their location and factors that drive their growth."

The researchers compared the genes expressed by Gr3-MB cells from six tumors with those expressed by human fetal hindbrain cells during the first trimester of pregnancy.

"We found traces of a lineage of embryonic stem-like cells in Gr3-MB tumors," said first author Dr. Abhirami Visvanathan, a postdoctoral fellow in the Taylor lab. "These cells express a protein called protogenin that is present only in these high risk Gr3-MB but absent in normal postnatal cerebellum."

The researchers located the cancer stem-like cells in a specific brain region in the developing cerebellum called the rhombic lip. The cells are embedded in a structure unique to humans that is known as the
interposed vascular plexus. When Gr3-MB tumors develop, they recreate the vascular plexus. Other types of medulloblastoma do not have this unique vascular structure.

"Stem-like cells in the tumor live in this immature blood vessel nest. Both tumor and vascular cells talk to each other and maintain a symbiotic niche benefiting both cells," Visvanathan said.

**A novel idea to treat Gr3-MB**

The finding that the tumors have a small population of protogenin-expressing stem-like cancer cells that sustains their growth inspired the researchers to test a novel approach to treating GR3-MBs.

"Instead of attacking the entire tumor, we hypothesized that eliminating the small population of cancer stem-like cells that sustains the tumor would be therapeutic, which is analogous to triggering the dissolution of an army by removing the leader," Taylor said.

As predicted by the hypothesis, therapies directed at eliminating the cancer stem-like cells produced effective results in animal models.

"We targeted the protogenin-expressing cells that sustain tumor growth with CAR T-cell immunotherapy. CAR T-cell therapy is a promising strategy in which immune T-cells are modified to attack a specific target—protogenin in this case—enabling them to kill the cancer. This exciting finding supports conducting further investigations to determine whether this strategy is effective in treating human Gr3-MB," added Taylor.

The study also shows that targeting the vascular niche that supports tumor cell growth is another potential therapeutic option. Further studies are needed to explore this possibility.
More information: Abhirami Visvanathan et al, Early rhombic lip Protogenin\textsuperscript{+ve} stem cells in a human-specific neurovascular niche initiate and maintain group 3 medulloblastoma, *Cell* (2024). DOI: 10.1016/j.cell.2024.06.011

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