Findings reveal unexpected role of protein OTX2 that drives aggressive medulloblastoma

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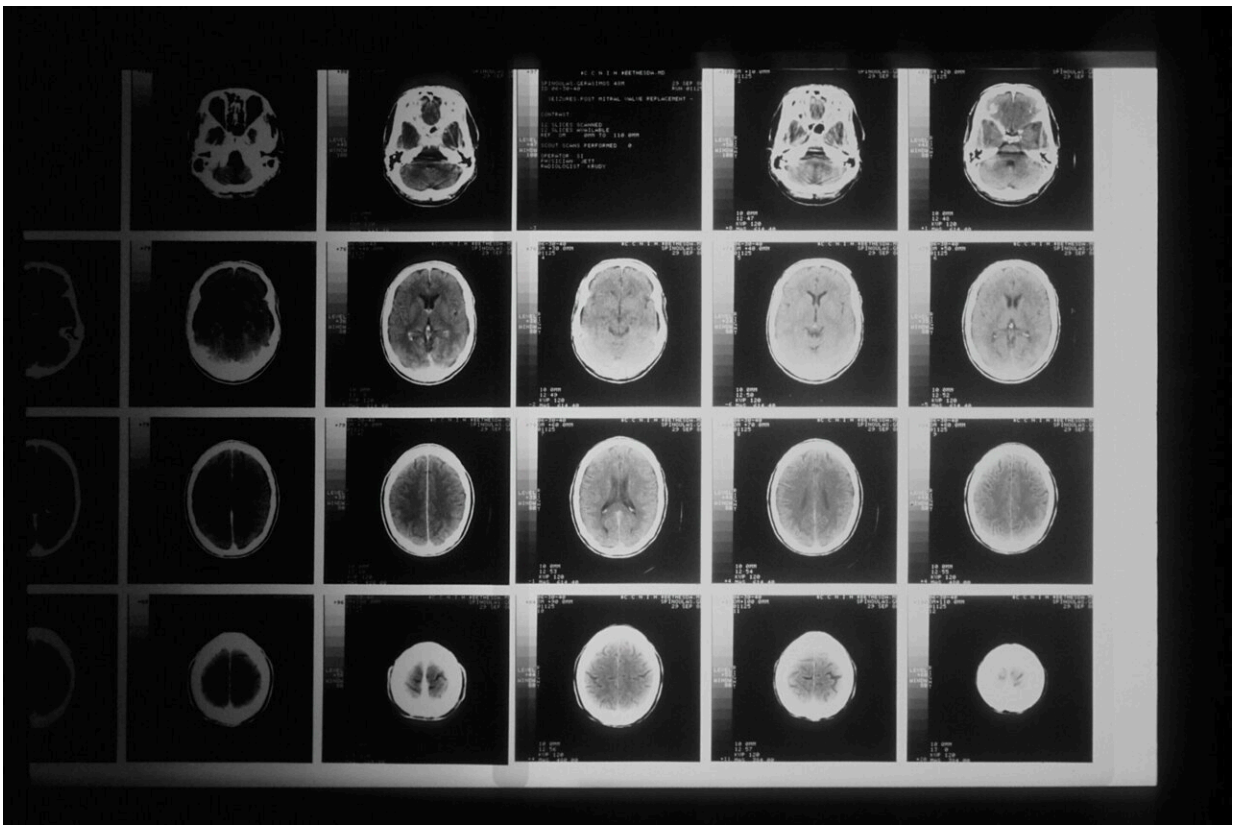

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In a report published in *Nature Cell Biology*, researchers at Baylor College of Medicine, Texas Children's Hospital, the University of

Manitoba and collaborating institutions have revealed an unexpected way in which the protein OTX2 drives the progression of medulloblastoma—the most common aggressive childhood brain cancer. The findings suggest that targeting OTX2 or its effects can have therapeutic relevance.

"We see medulloblastoma stem cells as the root of the disease. The tumors develop from these cells early during development of the cerebellum, the brain region located at the back of the head," said co-corresponding author Dr. Tamra Werbowetski-Ogilvie, professor of pediatrics, hematology-oncology at Baylor, Texas Children's and adjunct professor at the University of Manitoba.

"We already knew that OTX2 is a transcription factor in these stem cells—it helps the cells transcribe the instructions in the genes into functional proteins. Here, we investigated what other roles OTX2 could play to generate medulloblastoma."

The researchers conducted a comprehensive screening of the proteins that interact with OTX2 in the cell.

"We confirmed the usual suspects, proteins involved in transcription, but unexpectedly, we discovered that OTX2 also interacts with other proteins called splicing factors," they state.

Splicing factors are involved in alternative splicing, a cellular process that allows cells to produce different proteins from the instructions encoded in a single gene.

"Imagine that three cooks meet in the kitchen to bake a cake," Werbowetski-Ogilvie said. "They all begin with the same instructions, but each cook adds a different twist to the cake. One cook uses more chocolate than the others, another cook substitutes yogurt for butter and

the third one adds shredded carrots to the cake. In the end, different versions of the cake emerge from the same recipe, and some may taste better than the others."

Alternative splicing is similar. A cell can combine the different components of a transcribed gene (the ingredients in the cake recipe analogy) in different ways, giving rise to different proteins. Some versions of the protein will promote normal stem cell development, others might not work, and other proteins might take the cells on a path to disease.

"We found that OTX2 is like the cook that makes an unpalatable cake," Werbowetski-Ogilvie said. "OTX2 plays several roles in controlling alternative splicing of genes that fuel medulloblastoma development. For example, a specific version of the gene PPHLN1 promotes medulloblastoma stem cell growth and survival instead of normal growth. This is the first time that alternative splicing has been shown to play a functional role in the development of the most aggressive kind of medulloblastoma."

Importantly, the researchers discovered that disturbing PPHLN1 gene splicing with an anti-PPHLN1 drug called a morpholino reduces tumor growth, opening new possibilities for the development of improved treatments.

"This research demonstrates the effectiveness of unbiased multi-level studies, combined with collaboration between teams with diverse skills, in advancing our knowledge of how OTX2 drives medulloblastoma," said co-senior author Dr. Brad Doble, associate professor and Bihler Chair in Stem Cell Research in the Departments of Pediatrics and Child Health & Biochemistry and Medical Genetics at the University of Manitoba.

The findings have implications beyond cancer. "It is fascinating that a transcription factor would be moonlighting to control splicing, and that this differential splicing should be important in both childhood brain cancer and the normal development of the human fetal hindbrain," said co-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.

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More information: Alternative splicing mediated by OTX2 maintains a Group 3 medulloblastoma stem cell program, *Nature Cell Biology* (2024). DOI: 10.1038/s41556-024-01460-5

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