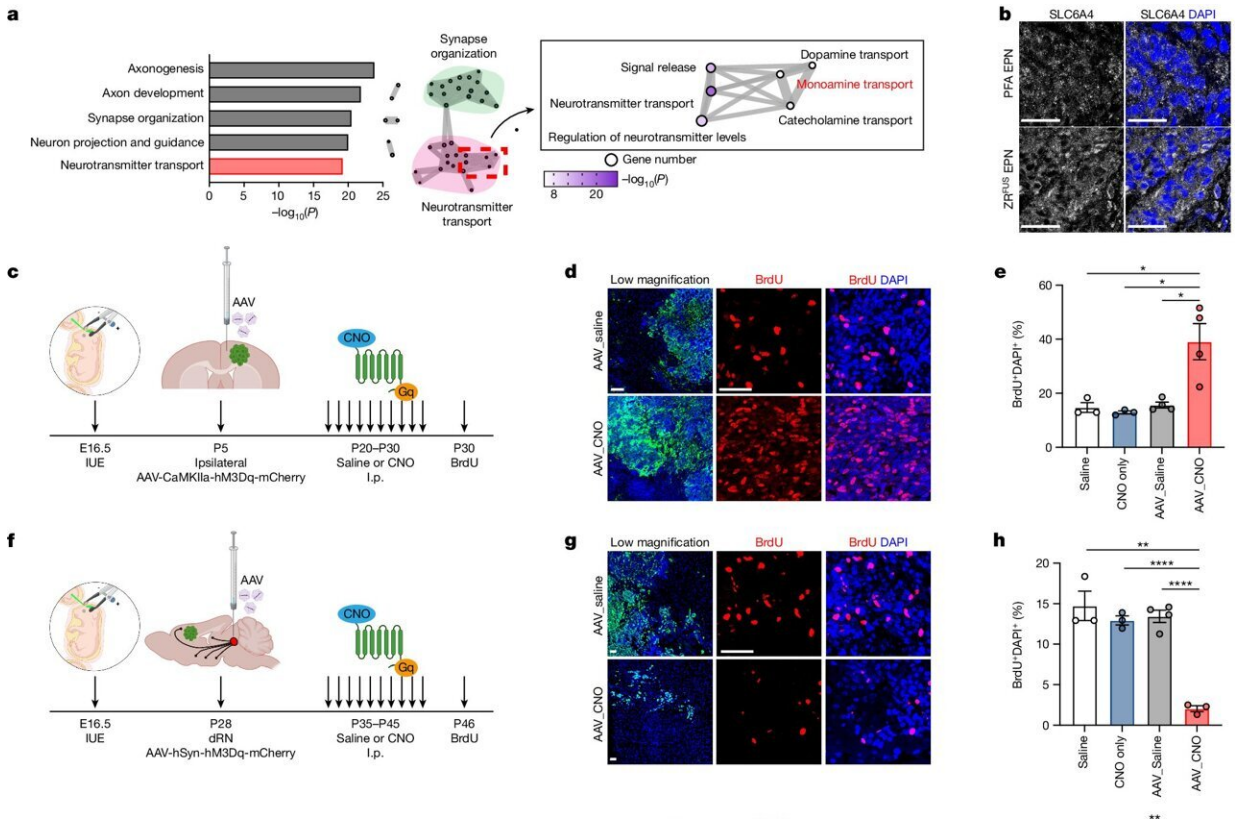
Serotonin-producing neurons regulate malignancy in ependymoma brain tumors

July 31 2024



Stimulation of serotonergic neurons suppresses EPN tumorigenesis. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07751-z

A study published in *Nature* reveals the functional relevance of tumor-neuron interactions that regulate the growth of ependymoma brain

tumors. The study, conducted by researchers at Baylor College of Medicine and St. Jude Children's Research Hospital, highlights how neuronal signaling, modifications in DNA-associated proteins and developmental programs are intertwined to drive malignancy in brain cancer.

"Ependymomas are the third most common type of pediatric brain tumors," said co-corresponding author, Dr. Benjamin Deneen professor and Dr. Russell J. and Marian K. Blattner Chair in the Department of Neurosurgery, director of the Center for Cancer Neuroscience and a member of the Dan L Duncan Comprehensive Cancer Center at Baylor.

"These tumors are aggressive, resistant to chemotherapy and lack tumor-specific therapies, leading to poor survival."

"We have not made an impact on patient survival in the last three decades. A major factor has been a poor understanding of the disease. The motivation of our collaborative work with the Deneen lab is to dissect the biology of these tumors as a basis for developing new therapies," said co-corresponding author Dr. Stephen Mack, associate member at St. Jude Children's Research Hospital and member of the Department of Neurobiology, Neurobiology and Brain Tumor Program and Center of Excellence in Neuro-Oncology Sciences.

Previous studies have shown in other types of brain tumors that brain activity surrounding the tumor can influence its growth.

"In the current study, we investigated whether brain activity played a role in ependymoma growth, specifically in a very aggressive type driven by a protein called ZFTA-RELA," said first author Hsiao-Chi Chen, a graduate student in the Deneen lab. "In collaboration with the Mack lab, we developed an animal model to study this rare pediatric brain tumor and validated these findings in human tumor samples."

The researchers discovered evidence of abnormal neuronal activity in ependymoma's environment and investigated whether it affected ependymoma growth. They found that while hyperactivity of some neural circuits promoted tumor growth, hyperactivity of other neural circuits surprisingly reduced tumor growth, which had not been described before. Their study revealed a novel chain of events at play that regulates tumor growth, which may hold therapeutic applications.

"First, we found that normal neurons located in the brain region called dorsa raphe nucleus (dRN) project towards the cortex, where ependymoma grows. These neurons secrete serotonin, a brain chemical that carries messages between nerve cells, which surprisingly slows tumor growth," Chen said.

Interestingly, ependymoma cells carry a serotonin transporter, a molecule that imports serotonin within the cell.

"We were surprised to discover that serotonin enters ependymoma cells and binds to histone H3, a protein that is tightly associated with DNA," Chen said. "Histone serotonylation, the addition of serotonin to histone, regulated tumor growth. Promoting it enhanced tumor growth while preventing it slowed down ependymoma growth in animal models."

"Discovering histone serotonylation in ependymoma piqued our interest because a previous study from our lab had revealed that adding serotonin to histones affects which genes the cell turns on," Deneen said.

The team discovered that histone serotonylation in ependymoma increases the expression of transcription factors, genes that regulate the expression of other genes," Chen said. "We focused on transcription factor ETV5 whose overexpression accelerated tumor growth. But how does it do it?"

The next experiments showed that ETV5 expression triggers changes in the 3D structure of chromatin, the combination of DNA and proteins that forms chromosomes. The 3D changes prevent the activation of genes encoding neurotransmitters, molecules that mediate neural activity.

The team focused on a neurotransmitter called neuropeptide Y (NPY) and found that growing tumors have little NPY. Restoring the levels of NPY in tumors slowed down tumor progression and tumor-associated neural hyperactivity through the remodeling of surrounding synapses or neuron-to-neuron communication.

"We knew that brain tumors release factors that remodel synapses towards hyperactivity. Here we found the opposite also can happen, that ependymoma tumors can release factors that suppress excitatory synaptic remodeling and that repressing this mechanism is essential for tumor progression," Deneen said.

"I am excited that this work has redefined our understanding of how brain tumor cells grow, and how they take advantage of factors in their surrounding environment to initiate tumors," Mack said. "I am equally excited that this work has revealed many new avenues for research that may in the future lead to new therapies, which is desperately needed for this devastating disease."

Other contributors to this work include Peihao He, Malcolm McDonald, Michael R. Williamson, Srinidhi Varadharajan, Brittney Lozzi, Junsung Woo, Dong-Joo Choi, Debosmita Sardar, Emmet Huang-Hobbs, Hua Sun, Siri Ippagunta, Antrix Jain, Ganesh Rao, Thomas E. Merchant, David W. Ellison, Jeffrey L. Noebels and Kelsey C. Bertrand. The authors are affiliated with Baylor College of Medicine or St. Jude Children's Research Hospital.

More information: Benjamin Deneen, Histone serotonylation regulates ependymoma tumorigenesis, *Nature* (2024). DOI: 10.1038/s41586-024-07751-z.
www.nature.com/articles/s41586-024-07751-z

Provided by Baylor College of Medicine