Researchers uncover unanticipated aspects of the genetic regulation of different brain tumors

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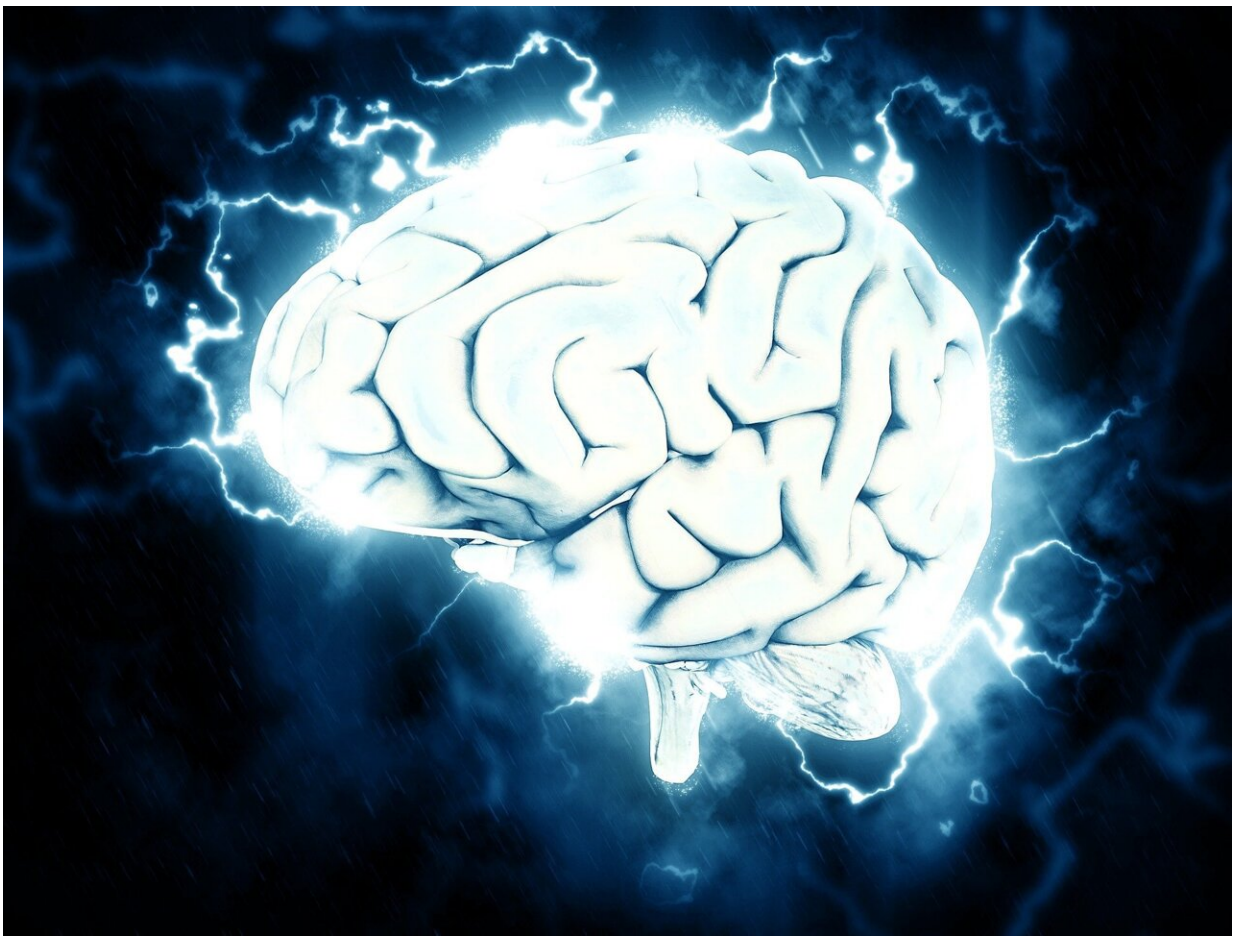

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A team led by researchers at Baylor College of Medicine has shed new light on the genetic regulation of brain tumor behavior. Published in the *Proceedings of the National Academy of Sciences*, the study reveals that, contrary to what is expected, gene expression regulator Sox9, a well-known transcription factor, influences brain tumor behavior in dissimilar ways in different tumor types. The findings bring to the table the importance of considering the mechanisms of gene regulation involved in different tumors when planning therapies.

Cancer cells express different genes than normal cells, and these new gene expression patterns are key to cancer behavior. One way cells can alter gene expression is by adding small chemical modifications to the DNA or associated proteins called epigenetic markers that determine which genes are turned on or off.

"Sox9 has emerged as a key regulator of epigenetic modifications and gene expression programs that contribute to brain tumor growth; however, how Sox9 achieves this is not well known," said co-first author Dr. Debosmita Sardar, postdoctoral associate in the lab of Dr. Benjamin Deneen at Baylor. "In this study we investigated Sox9-mediated mechanisms of epigenetic dysregulation in two mouse models of human brain tumors: high-grade glioma (HGG) and ependymoma (EPN)."

"We knew that Sox9 is elevated in both HGG and EPN. Also, we knew that these tumors have different epigenetic profiles," said co-first author Hsiao-Chi Chen, graduate student in the Deneen lab. "We wanted to know whether Sox9 was involved in shaping these distinct profiles and the mechanism that led to them."

"We expected that Sox9's contribution to set up the tumors' epigenetic patterns would be the same," said Deneen, professor and Dr. Russell J. and Marian K. Blattner Chair of neurosurgery and the Center for Cancer Neuroscience at Baylor. Deneen also is the corresponding author of the

work. "The function of a gene, in this case Sox9, is assumed to be the same regardless of the cell type in which the gene is expressed. We found something unexpected in that Sox9 function was dramatically different in these two different tumors."

The researchers manipulated Sox9 expression in the mouse models and found that increasing Sox9 suppressed tumor growth in HGG but promoted it in EPN. Surprisingly, Sox9 regulated the epigenetic patterns of HGG and EPN in different ways. In HGG, Sox9 mediated its effect by interacting with a group of proteins called histone deacetylation complex, while in EPN Sox9 interacted with oncofusion proteins. Sox9 has different protein-protein interactions in different tumors.

"This is what is really driving the different ways Sox9 regulates epigenetic patterns in these tumors," Sardar said. "Its actions are tumor-specific and we essentially took advantage of state-of-the art proteomic technologies to uncover these distinct mechanisms."

"Importantly, we also see these distinct Sox9 protein-protein interactions in human HGG tumor samples graciously provided by Dr. Ganesh Rao, Marc J. Shapiro professor and chair of neurosurgery at Baylor," Chen said. "Also, our collaboration with Dr. Stephen Mack at St. Jude Children's Research Hospital was crucial for comparing epigenetic datasets of our mouse models with clinical tumor samples from human patients. This revealed a strong overlap between epigenetic profiles in our mouse models and human tumors, establishing these mouse models as powerful tools to understand clinically relevant tumor behaviors. These findings suggest new possibilities for developing novel therapies directed at epigenetic mechanisms."

More information: Debosmita Sardar et al, Sox9 directs divergent epigenomic states in brain tumor subtypes, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2202015119

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